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ACTA Obstetricia et Gynecologica Scandinavica

AOGS REVIEW ARTICLE

# Efficacy of tranexamic acid in the treatment of idiopathic and non-functional heavy menstrual bleeding: a systematic review

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**Key words**
Tranexamic acid, idiopathic and non-functional heavy menstrual bleeding, menstrual blood loss

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**Conflict of interest**
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Please cite this article as: Naoulou B, Tsai MC. Efficacy of tranexamic acid in the treatment of idiopathic and non-functional heavy menstrual bleeding: a systematic review. Acta Obstet Gynecol Scand 2012; 91:529–537.

Received: 24 August 2011
Accepted: 28 December 2011

DOI: 10.1111/j.1600-0412.2012.01361.x

## Abstract

*Objective.* To evaluate the efficacy of tranexamic acid in the treatment of idiopathic and non-functional heavy menstrual bleeding. *Design.* Systematic review. *Population.* Women with a diagnosis of idiopathic and non-functional heavy menstrual bleeding treated with tranexamic acid. *Methods.* Electronic searches were conducted in literature databases up to February 2011 by two independent reviewers. We included all trials involving the efficacy of tranexamic acid for the treatment of heavy uterine bleeding. Pregnant, postmenopausal and cancer patients were excluded. *Main outcome measures.* Effect of tranexamic acid treatment on objective reduction of menstrual bleeding and improvement in patient quality of life. *Results.* A total of 10 studies met our inclusion criteria. Available evidence indicates that tranexamic acid therapy in women with idiopathic menorrhagia resulted in 34–54% reduction in menstrual blood loss. Following tranexamic acid treatment, patient's quality-of-life parameters improved by 46–83%, compared with 15–45% for norethisterone treatment. When compared with placebo, tranexamic acid use significantly decreased the blood loss by 70% in women with menorrhagia secondary to an intrauterine device ($p<0.001$). Limited evidence indicated potential benefit in fibroid patients with menorrhagia. No thromboembolic event was reported in all studies analyzed. *Conclusions.* Available evidence indicates that tranexamic acid treatment is effective and safe, and could potentially improve quality of life of patients presenting with idiopathic and non-functional heavy menstrual bleeding. Data on the therapeutic efficacy of tranexamic acid in patients with symptomatic fibroids are limited, and further studies are therefore needed.

**Abbreviations:** DS, diclofenac sodium; DUB, dysfunctional uterine bleeding; ETM, ethamsylate; HMB, heavy menstrual bleeding; IUD, intrauterine conctraceptive device; Kabi 2161, pro-drug of tranexamic acid; MA, mefenamic acid; MBL, menstrual blood loss; MPA, medroxyprogesterone acetate; n/a, not applicable; NorE, norethisterone; NS, not significant; PBAC, pictorial blood loss assessment chart; TA, tranexamic acid.

## Introduction

Heavy menstrual bleeding (HMB) is an important gynecological problem that affects more than 30% of women at some point in their lives. It can interfere with a woman's physical, social, emotional and/or material quality of life (1). Menorrhagia is clinically defined as menstrual blood loss (MBL) of 80mL or more per menstrual cycle (2), but the diagnosis is usually based on a woman's perception of her menstrual blood loss and the effect that it has on her daily life. Apart from its social inconvenience, HMB can also cause anemia, which may be difficult to treat even with continuous iron therapy. The most common gynecological causes of HMB are leiomyoma and dysfunctional uterine bleeding (DUB) (3). In other women, bleeding disorders such as von Willebrand's disease and platelet disorders may be the underlying

cause of menorrhagia. However, 80% of women treated for menorrhagia have no anatomical pathology, and over one-third of the women undergoing hysterectomy for HMB have anatomically normal uteri removed (4). These women are said to have idiopathic menorrhagia, i.e., heavy menstrual bleeding for which no underlying cause has been found. Besides uterine fibroids, menorrhagia can also be secondary to intrauterine devices (IUDs) and endometrial polyps.

As excessive uterine bleeding can be the manifestation of a vast array of differential diagnoses, treatment of HMB can be challenging and often requires extensive work-up to determine the underlying cause of bleeding. Treatment can be either surgical or medical (5). Surgical treatment of menorrhagia includes myomectomy, endometrial ablation, hysteroscopy, hysterectomy, or less invasive radiological techniques, such as uterine artery embolization. Medical treatment includes a variety of hormonal and non-hormonal agents. In contrast to the surgical options, medical treatment of menorrhagia has questionable efficacy and meager effects on patients' quality of life (6). For that reason, there is a need for more effective agents for the medical treatment of menorrhagia. Ideal medical treatment should be effective regardless of the etiology of bleeding.

The US Food and Drug Administration has recently approved an oral formula of tranexamic acid (TA) for clinical use in the USA. Its pharmacological mechanism involves reversibly blocking lysine binding sites on plasminogen, preventing plasmin and fibrin polymer interaction and resulting in fibrin degradation, stabilization of clots and reduced bleeding. Tranexamic acid has been used routinely for many years to reduce blood loss and the need for blood transfusion during and after surgical procedures (7), such as coronary artery bypass, scoliosis surgery and knee arthroplasty. TA has been used for the treatment of HMB outside of the USA for several decades (8). Several randomized clinical trials have examined the role of TA in the treatment of gynecological bleeding. Although leiomyoma represent an important cause of abnormal uterine bleeding in women of reproductive age (9), the effectiveness of TA treatment in these patients remains unknown. Thus far, most of the systemic reviews published on TA involve idiopathic HMB. The purpose of this systematic review is to investigate the effectiveness of the antifibrinolytic agent TA in the treatment of idiopathic and non-functional heavy menstrual bleeding.

## Material and methods

### *Criteria for study inclusion*

We included all trials in the English language that compared the efficacy of TA vs. placebo, no treatment, or any other medical therapy for the treatment of heavy uterine bleeding in non-pregnant women. Inclusion criteria for this study were as follows: (a) women of reproductive age; (b) presenting with heavy menstrual bleeding measured either objectively or subjectively; (c) uterine fibroids; (d) DUB; and (e) menorrhagia secondary to IUD. Exclusion criteria were as follows: pregnancy; postmenopausal bleeding (>1 year from the last menstrual period); and gynecological malignancies.

### *Search strategy and databases*

The study inclusion was determined and reviewed by two authors. Electronic databases were searched from January 1970 to February 2011 (PubMed and Medline) and from 1980 to February 2011 (EMBASE) for studies published in English (Figure 1). Searching for 'tranexamic acid and menorrhagia' in PubMed produced 118 results; 22 of these abstracts were potentially eligible for the review. These were screened by the authors to exclude those studies which were ineligible. At the end, 10 of those studies were included in this systematic review. From Medline (Ovid), of 115 results obtained with the aforementioned search method, 26 abstracts were deemed potentially available, but none of the articles, other than some which were already obtained by searching PubMed, were included in this review. Upon searching for 'tranexamic acid and uterine bleeding' in Embase, 98 articles were retrieved, some of which were previously obtained from the searches in PubMed and Medline. Of those 98 articles, none of the articles, other than those obtained from other searches, were included in this review. An extensive review of the database results was undertaken in order to determine which studies met the inclusion criteria and at the end, 10 studies were deemed to be appropriate for inclusion in this systematic review. The algorithm for published data collection is depicted in Figure 1.

### *Outcome measures*

For TA vs. placebo, no treatment, or any other medical therapy, the primary outcome of interest was the objective reduction in idiopathic and non-functional heavy menstrual bleeding. Secondary outcomes to be studied were the effect of the intervention on the patient's quality of life.

### *Quality assessment of included studies*

The quality of each individual piece of evidence was assessed by two independent investigators (B.N. and M.C.T.) using the US Preventive Service Task Force grading system (10). We did not compute summary measures of association or conduct meta-analysis owing to heterogeneity across studies with respect to study design, study population recruitment, lengths of follow up, etiology of HMB and outcome measured.

## Results

A total of 10 studies qualified for inclusion in this review; five double-blind, randomized controlled trials (11–15), two randomized controlled trials (16,17), one prospective cohort

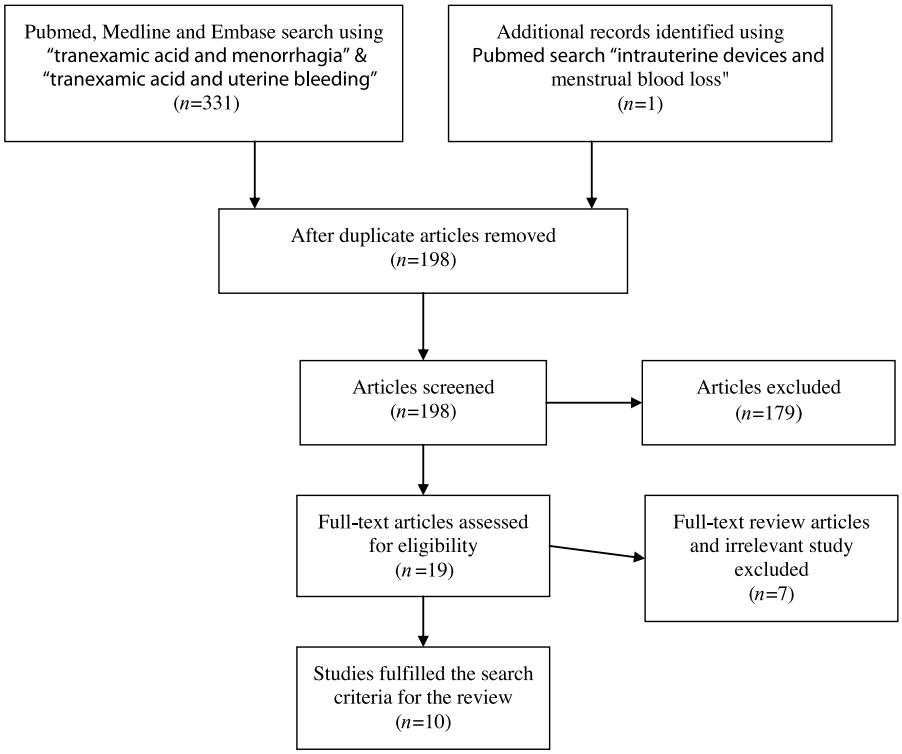


**Figure 1.** An algorithm of the data search for publication.

(18), one comparative (19) and one observational study (20). The characteristics of the included studies are summarized in Table 1; the quality grading and risk of bias are depicted in Table 2.

### *Primary outcomes*

#### ***Tranexamic acid for the treatment of idiopathic HMB***

Three of the included studies compared TA vs. placebo in women with idiopathic HMB (11–13). Two of the studies evaluated the effect of tranexamic acid compared with placebo on the duration of menses, and no statistically significant difference was found: 5.8 vs. 6.1 days in the study by Edlund et al. (12) and 17.8 vs. 15.5 days in the study by Callender et al. (11), respectively. However, treatment with TA caused a statistically significant reduction in MBL compared with placebo in all three studies. MBL decreased by 34–54% from baseline in women treated with TA (Table 3). There was no difference in adverse effects between the treatment and placebo groups. In the study by Callender et al. (11), patients who had menorrhagia for which no organic cause was found were followed for nine menstrual cycles. They received no treatment for the first three menstrual periods. Then, during the second and third three menstrual periods the patients received either TA (1g) or placebo four times a day for the first four days of menstruation. The order of treatments was randomized. Results showed that TA treatment for the first four days of menstruation caused a significant reduction in MBL compared with placebo or with no treatment. In the trial by Edlund et al. (12), Kabi 2161, an ester pro-drug of tranexamic acid, was compared at two different dose regimens with placebo in patients with menorrhagia. In this double-blind randomized study, 26 patients were given treatment with 1200mg Kabi 2161 twice a day, 28 patients received 600mg Kabi 2161 four times a day, and 14 patients received placebo four times a day, during the first five days of the menstrual cycle. The main efficacy variable in the study was the reduction of blood loss objectively measured using the alkaline hematin method. Results showed that Kabi 2161 at 600mg four times a day compared with placebo caused a statistically significant reduction in MBL of 41% ($p<0.001$) and a dose of 1200mg twice daily caused a 33% reduction in MBL ($p<0.001$). The difference between the treated groups who received different dose regimens, however, was not statistically significant, although the exact $p$-value or power of the study is not mentioned in the study. In contrast, MBL was unchanged in those patients who received placebo. This study showed that a treatment regimen consisting of Kabi 2161 1200mg twice a day was

**Table 1.** Characteristics of included studies.

| First author | Year | Study type | Sample Size | Inclusions | Intervention (number of patients) | Number of cycles |
|---|---|---|---|---|---|---|
| Callender (11) | 1970 | Randomized, double-blind | 16 | Idiopathic menorrhagia | No treatment days 1–4 (16) | 3 |
| | | | | | Placebo days 1–4 (16) | 3 |
| | | | | | TA 1 g four times daily days 1–4 (16) | 3 |
| Ylikorkala (18) | 1983 | Prospective cohort | 19 | IUD-induced menorrhagia | placebo days 1–5 (19) | 1 |
| | | | | | DS 50 mg three times daily day 1, 25 mg three times daily days 2–5 (19) | 2 |
| | | | | | TA 1.5 g three times daily days 1–5 (19) | 2 |
| Edlund (12) | 1995 | Randomized, double-blind | 68 | Idiopathic menorrhagia | Placebo days 1–5 (14) | 3 |
| | | | | | Kabi 2161 600 mg four times daily days 1–5 (28) | 3 |
| | | | | | Kabi 2161 1200 mg twice daily days 1–5 (26) | 3 |
| Preston (14) | 1995 | Randomized, double-blind | 46 | Idiopathic menorrhagia | TA 1 g four times daily days 1–4 (25) | 2 |
| | | | | | NorE 5 mg twice daily days 19–26 (21) | 2 |
| Bonnar (16) | 1996 | Randomized | 76 | Idiopathic menorrhagia | TA 1 g four times daily days 1–5 (26) | 3 (+3 control) |
| | | | | | MA 500 mg three times daily days 1–5 (23) | 3 (+3 control) |
| | | | | | ETM 500 mg four times daily days 1–5 (27) | 3 (+3 control) |
| Lakhani (19) | 1998 | Prospective comparative | 36 | Patients with DUB | TA 1 g three times daily (24) | 2 |
| | | | | Patients with uterine fibroids | TA 1 g three times daily (12) | 2 |
| Winkler (20) | 2001 | Prospective observational | 849 | Menorrhagia regardless of cause | TA 3–6 g/day 3–4 days/cycle | 3 |
| Kriplani (17) | 2006 | Randomized | 103 | DUB | TA 500mg four times daily days 1–5 | 3 |
| | | | | | MPA 10 mg twice daily days 5–25 | 3 |
| Lukes (13) | 2010 | Randomized, double-blind, multicenter | 187 | Menorrhagia, normal pelvic examination | TA 3.9 g/day days 1–5 (115) | 4 (+2 control) |
| | | | | Included patients with fibroids unless surgical treatment was warranted | Placebo days 1–5 (72) | 4 (+2 control) |
| Weström (15) | 1970 | Double-blind, randomized | 65 | IUD-induced menorrhagia | TA 1.5 g four times daily for 5 days (34) | 3 |
| | | | | | Placebo for 5 days (31) | 3 |

Abbreviations: DS, diclofenac sodium; DUB, dysfunctional uterine bleeding; ETM, ethamsylate; IUD, intrauterine contraceptive device; Kabi 2161, pro-drug of tranexamic acid; MA, mefenamic acid; MPA, medroxyprogesterone acetate; NorE, norethisterone; TA, tranexamic acid.

equally effective as the same drug given at 600mg four times a day for the reduction in menstrual blood flow. The authors concluded that taking a pill twice a day compared with four times a day is more likely to favor patient compliance. In the trial by Lukes et al. (13), leiomyoma patients were included in the study unless surgical treatment was required. In this study, after two pretreatment menstrual cycles, women were randomized to receive either TA (3.9g/day) or placebo for up to five days per menstrual cycle for six cycles. Women who received TA had a significantly greater reduction in MBL compared with placebo, 40.4 vs. 8.2%, respectively. More than two-thirds of the women treated with TA experienced a clinically meaningful reduction in MBL and a significantly greater proportion of TA-treated menstrual cycles reached MBL volumes considered as normal range (less than 80mL per cycle) compared with the placebo group.

When compared with other therapeutic agents for objective reduction of blood loss, the therapeutic efficacy of TA

**Table 2.** Quality assessment of included studies.

| First author | Strengths and weaknesses | Quality grade |
|---|---|---|
| Callender (11) | Patient selection problem<br>Unknown power of study<br>Medication compliance issue | I, fair |
| Ylikorkala (18) | Blood loss objectively measured<br>Small sample size | II-2, fair |
| Edlund (12) | Multicenter study<br>Precise patient selection criteria<br>Blood loss objectively measured<br>Unknown patient compliance with medication | I, good |
| Preston (14) | Well-designed trial<br>Bodyweight was significantly different between two study groups<br>Precise patient allocation and selection | I, good |
| Bonnar (16) | Well-designed trial<br>Single center<br>Significantly high discontinuation rate in ethamsylate group | I, good |
| Lakhani (19) | Small sample size<br>Patient selection confounders<br>No detail on the size and location of fibroid | II-3, poor |
| Winkler (20) | Outcome measurement based on subjective impression<br>Subjective diagnosis of menorrhagia<br>No etiological diagnosis of bleeding<br>Women receiving hormone replacement therapy were also included | II-3, fair |
| Kriplani (17) | Adequate patient selection<br>Unknown power of study<br>Subjective measurement of blood loss<br>Analysis did not include intent-to-treat population | I, poor |
| Lukes (13) | Multicenter, well-designed trial<br>Objective measurement of blood loss<br>Inclusion of fibroid patient could be confounding factor | I, good |
| Weström (15) | No detail on uterine pathology screening<br>Two types of intrauterine contraceptive device in this study<br>Allocation seems to be adequate | I, fair |

was found to be superior to ethamsylate, mefenamic acid (16) and norenthisterone (14), but comparable to medroxyprogesterone acetate (MPA; 17). As in prior studies, TA treatment had no effect on the duration of bleeding when compared with the control group (average of 4.6 days for TA vs. 5.5 days for MPA after 3 months of treatment). Compared with control cycles, ethamsylate had no effect on reducing blood loss, while mefenamic acid and TA reduced the bleeding by 20 and 54%, respectively (16). Fifty-six percent of TA-treated cycles achieved blood loss <80mL compared with only 9.5% of menstrual cycles treated with norenthisterone (14). When TA 2g/day used for the first five days of the menstrual period was compared with 20mg daily of MPA from day 5 to day 25 of the cycle for three months, the mean reduction of MBL with TA was 58, 61 and 60% at the first, second and third months of treatment, respectively ($p<0.005$). The reduction with MPA was 55, 52 and 58% at the three follow ups during treatment; this was also significant when compared with baseline ($p<0.005$). However, the effect of TA and MPA in reducing MBL was found to be comparable ($p=0.78$). The incidence of adverse effects was lower in the TA group (16.3%) compared with MPA (33.3%), but this was statistically insignificant ($p=0.09$). A significantly higher discontinuation rate was observed in the MPA-treated group, mostly due to treatment failure, when compared with the TA treatment group (26.7 vs. 4.1%, $p=0.002$; 17). The recurrence of HMB after stopping therapy was not statistically significant between the two groups: 66.7% for TA vs. 50% for MPA. The risk of a type II error in this study cannot be excluded owing to a higher drop-out rate in the group who received MPA. As it is unclear whether the authors used intention-to-treat analysis and more patients in the MPA group stopped treatment, the effect of MPA on HMB may have been overestimated.

### *Tranexamic acid for the treatment of non-functional HMB*

Two studies evaluated the effect of TA on the increase in MBL that generally follows insertion of an IUD (15,18). In a double-blind study by Weström et al. (15), 65 women (predominantly with Lippes' Loop C IUD) were randomized to receive either TA (34 patients) or placebo tablets (31 patients). In the women who received placebo, insertion of the IUD was followed by an increase in the MBL, with an average of 29.6mL per menstruation, or an 82.7% increase over the control (no IUD) menstruation. In the women who were treated with TA, MBL increased by 4.1mL or 11.5% after IUD insertion. The effect of TA treatment appeared not to be affected by the type of IUD. In one prospective control trial using the copper IUD (18), TA, diclofenac sodium and placebo were given to patients who had IUD-induced menorrhagia. Treatment with TA resulted in a 56% ($p<0.001$) reduction in MBL when compared with placebo, while treatment with diclofenac sodium resulted in a 24% ($p<0.001$) reduction in MBL when compared with placebo. The placebo treatment did not significantly change MBL compared with baseline.

The therapeutic effect of TA on HMB induced by leiomyoma is even less clear, because there is no specific and well-designed study on this subject. In one study by Lakhani et al. (19), the main objective was to investigate the effects of TA on uterine vascular resistance in women with DUB and in women with menorrhagia associated with fibroids. That study included 24 women with DUB and 12 women with at

**Table 3.** Results of included studies.

| First author | Inclusions | Intervention (no. of patients) | Mean menstrual blood loss | | | |
|---|---|---|---|---|---|---|
| | | | Baseline (mL) | During treatment (mL) | Change from baseline (%) | *p*-Value |
| Callender (11) | Idiopathic menorrhagia | No treatment days 1–4 (16) | 197 | n/a | No change | – |
| | | Placebo days 1–4 (16) | 197 | 185 | Decreased 6% | NS |
| | | TA 1g four times daily days 1–4 (16) | 197 | 122 | Decreased 38% | <0.02 |
| Ylikorkala (18) | IUD-induced menorrhagia | Placebo days 1–5 (19) | 135 | 128 | Decreased 5% | NS |
| | | DS 50mg three times daily day 1, 25mg three times daily days 2–5 (19) | 135 | 102 | Decreased 24% | <0.01 |
| | | TA 1.5g three times daily days 1–5 (19) | 135 | 59 | Decreased 56% | <0.01 |
| Edlund (12) | Idiopathic menorrhagia | Placebo days 1–5 (14) | 243 | 252 | Increased 4% | NS |
| | | Kabi 2161 600mg four times daily days 1–5 (28) | 235 | 163 | Decreased 33% | <0.01 |
| | | Kabi 2161 1200mg twice daily days 1–5 (26) | 268 | 164 | Decreased 41% | <0.01 |
| Preston (14) | Idiopathic menorrhagia | TA 1g four times daily days 1–4 (25) | 175 | 97 | Decreased 45% | <0.0001 |
| | | NorE 5mg twice daily days 19–26 (21) | 173 | 208 | Increased 20% | 0.26 (NS) |
| Bonnar (16) | Idiopathic menorrhagia | TA 1g four times daily days 1–5 (26) | 164 | 75 | Decreased 54% | <0.001 |
| | | MA 500mg three times daily days 1–5 (23) | 186 | 148 | Decreased 20% | <0.001 |
| | | ETM 500mg four times daily days 1–5 (27) | 170 | 175 | Increased 3% | NS |
| Lakhani (19) | Patients with DUB | TA 1g three times daily (24) | 210 | 138 | Decreased 34% | 0.0001 |
| | Patients with uterine fibroids | TA 1g three times daily (12) | 204 | 186 | Decreased 9% | 0.05 (NS) |
| Winkler (20) | Menorrhagia regardless of cause | TA 3–6g/day 3–4days/cycle | n/a | n/a | After first treatment 87% of patients reported subjective decrease | <0.0001 |
| | | | | | After third treatment 94% of patients reported subjective decrease | <0.0001 |
| Kriplani (17) | DUB | TA 500mg four times daily days 1–5 | 357 (PBAC) | 142 (PBAC at 3months) | Decreased 60.3% at 3months | <0.005 |
| | | MPA 10mg twice daily days 5–25 | 370 (PBAC) | 157 (PBAC at 3months) | Decreased 57.7% at 3months | <0.005 |
| Lukes (13) | Menorrhagia, normal pelvic examination | TA 3.9g/day days 1–5 (115) | 172 | 102 | Decreased 40% | <0.001 |
| | Included patients with fibroids unless surgical treatment was warranted | Placebo days 1–5 (72) | 153 | 140 | Decreased 8% | NS |
| Weström (15) | IUD-induced menorrhagia | TA 1.5g four times daily for 5 days (34) | 35.7 | 39.8 | Increased 11.5% | <0.001 TA vs. placebo |
| | | Placebo for 5 days (31) | 35.8 | 65.4 | Increased 82.7% | |

Abbreviations: DS, diclofenac sodium; DUB, dysfunctional uterine bleeding; ETM, ethamsylate; IUD, intrauterine contraceptive device; Kabi 2161, pro-drug of tranexamic acid (TA); MA, mefenamic acid; n/a, not applicable; NorE, norethisterone; NS, not significant; PBAC, pictorial blood loss assessment chart.

least one fibroid greater than 2.0cm on ultrasound examination. MBL was assessed using a validated pictorial blood chart. In women with DUB, the mean estimated MBL decreased significantly with treatment by 72.4mL, a change of 30%, from 210.0 to 137.6mL. In women with fibroids, there were no significant changes in the mean estimated MBL after treatment with TA. Information on fibroid location was absent in this study. In the study by Lukes et al. (13), patients with a diagnosis of leiomyoma were included in this multicenter randomized controlled trial. Forty-two of 117 patients (36.5%) and 26 of 72 patients (36.1%) with leiomyoma were noted in the TA group and placebo group, respectively. Treatment with TA resulted in consistent improvement of menorrhagia irrespective of baseline blood loss or presence of fibroid. In addition, more than two-thirds of the women treated with TA experienced a clinically meaningful reduction in menstrual blood loss. The limitation of this study was the inability to determine the magnitude of improvement in those patients who had HMB associated with leiomyoma. The dimension and type of fibroid included in this study were not available.

### *Secondary outcomes*

A few studies have examined the effect of TA on the quality of life in women with heavy menstrual bleeding. Winkler (20) evaluated 849 women with HMB in Germany using a questionnaire on life quality. Patients were given TA 3–6g/day for 3–4 days per menstrual cycle, with the prescribed dose being determined by the patient's gynecologist. Patients' Quality-of-life was assessed at baseline and after the first and the third treated menstruations. The proportion of women who felt a considerable degree of impairment during menstruation was reduced from the baseline 60–80% to less than 10% during the third treated menstruation ($p<0.0001$). These reductions were statistically significant. The quality-of-life improvement and patient satisfaction were strongly associated with improvement of HMB. After the first and third cycles of TA treatment, 87 and 94% of patients perceived a decrease or strongly decreased volume of bleeding, respectively. In the trial by Preston et al. (14), when asked about the impact of TA treatment on their quality-of-life, 83, 67 and 46% of the TA group indicated improvement of their flooding/leakage, limitation of social life and sex life, respectively, compared with only 45, 45 and 15% in the norenthisterone group ($p<0.029$). In the trial by Lukes et al. (13), the mean improvement in score for limitation on physical activity ($-0.51$, $p<0.01$) and social or leisure activities ($-0.55$, $p<0.01$) was significantly greater in the TA group compared with the placebo group. In all studies analysed, only mild to moderate adverse effects were reported, mostly gastrointestinal, and there were no reports of thromboembolic events with the use of TA.

## Discussion

Based on the studies included in this review, TA is far superior to placebo, diclofenac, mefenamic acid, ethamsylate and luteal phase norethisterone for quantitative reduction in idiopathic HMB. When compared with luteal phase norethisterone, TA treatment has shown improved quality-of-life measures, leading to reduced flooding/leakage and improved sex life. Interestingly, in these studies TA was not shown to have an effect on the duration of menstruation. Adverse effects associated with tranexamic acid treatment were not serious, consisting mainly of gastrointestinal symptoms, such as nausea and diarrhea. Although TA acid treatment poses a potential risk for thromboembolic events owing to its antifibrinolytic effect, there were no reports of thromboembolic events resulting from TA treatment. Furthermore, TA has been widely used in Scandinavia as a first-line treatment for menorrhagia since the early 1970s; over a 19-year time frame and 238,000 patient-years of treatment, there has been no reported increase in the incidence of thromboembolic events (21–23). The optimal dose of TA and the duration of treatment remain unknown. Thus, to some extent, the discrepancy of the dose used is likely to explain some of the variable efficacy demonstrated in the different studies. The US Food and Drug Administration has approved tranexamic acid at a dosage of 1300mg (two 650mg tablets) three times daily for five days each menstrual cycle (24). Most of the studies of TA for menorrhagia used a dosage of 3–6g/day, divided into four to six doses (25). The oral bioavailability of tranexamic acid is only about 35%, which makes frequent administration necessary (26). The disadvantages of frequent administration include decreased patient compliance and increased risk of gastrointestinal adverse effects. Using Kabi 2161, a pro-drug of tranexamic acid that exhibits increased gastrointestinal absorption and oral bioavailability approaching 90% (27), Edlund et al. have demonstrated that two doses (1200mg twice daily) have comparable efficacy to four doses (600mg four times daily) in the treatment of idiopathic menorrhagia. A two-dose regimen is more likely to favor patient compliance and will have fewer gastrointestinal adverse effects (12).

Excessive and prolonged menstrual bleeding is the major adverse effect associated with the IUD and the main reason for having it removed. The copper IUD seems to increase endometrial prostaglandin levels, partly due to prostaglandin production by macrophages accumulating on the surface of the device, and this in turn may be another reason for the heavy menstrual bleeding associated with IUD use (28). Tranexamic acid has been shown to be far superior in the treatment of menorrhagia secondary to copper IUD when compared with diclofenac sodium and placebo (18). This may suggest that an antifibrinolytic pathway may be superior to the anti-inflammatory effect in the treatment of IUD-related menorrhagia. Furthermore, the effectiveness of the

antifibrinolytic agent was clearly demonstrated when aminocaproic acid, an antifibrinolytic agent similar to TA, was used successfully to reduce IUD-induced menorrhagia when compared with ethamsylate (29).

The effect of TA on the heavy bleeding caused by leiomyoma remains unknown owing to limited data. Our search of the literature did not yield any randomized controlled trials studying the efficacy of TA in the treatment of menorrhagia secondary to uterine fibroids. There were only two studies that included patients with fibroids when investigating the efficacy of TA for the treatment of menorrhagia. The study by Lukes et al. (13) was a randomized controlled trial investigating the efficacy of TA compared with placebo for the treatment of HMB in women without any abnormal pelvic pathology. The potential bias of this study was that patients with a diagnosis of fibroid were included in this study unless the fibroids were of sufficient number and size to warrant surgical management. Although the intent of this study was not to evaluate the effectiveness of TA on menorrhagia secondary to uterine fibroids, results indicated that TA was effective in the treatment of HMB regardless of the presence or absence of uterine fibroids. However, based on the design of the study, it is hard to draw a definite conclusion on whether the size and type of the fibroids had any influence on the effectiveness of the treatment. Lakhani et al. (19) investigated the effects of TA on uterine vascular resistance in women with dysfunctional uterine bleeding and in women with fibroids. The authors found that the resistance index, pulsatility index and MBL decreased significantly in women with dysfunctional uterine bleeding after treatment with TA. In this study, women with fibroids were found to have no significant change in the resistance index, pulsatility index or MBL with TA treatment. However, this finding may be the consequence of an inadequate power of the study to detect such changes in women who have a low baseline pulsatility index, who were also those women who had the largest uterine volumes (i.e. had uterine fibroids). The potential bias of this study was the lack of stratification by size and type of fibroid. By preventing fibrin degradation and thereby stabilizing clots, TA can potentially reduce bleeding from fibroids. Nonetheless, based on the scarce evidence, it is unclear at this point which fibroid characteristics determine the success of TA treatment in the control of bleeding. In order to better understand the effect, if any, of TA on menorrhagia secondary to fibroids, randomized controlled trials comparing tranexamic acid with placebo or other treatments (such as oral contraceptives) are needed. Given the prevalence of menorrhagia and uterine fibroids and the significant impact on women's lives, such a study may revolutionize the medical treatment of menorrhagia by providing an alternative to surgical therapy and preserving future fertility.

Evidence showed that patients' improvement in social or leisure and physical activity is strongly associated with the objective reduction of the volume of bleeding; this quality-of-life enhancement seems to occur even before a significant decrease in menstrual bleeding is achieved (13). Women receiving TA reported significant improvements in health-related quality-of-life parameters compared with those receiving placebo. Improvements in both MBL and health-related quality-of-life parameters were observed during the first treatment cycle and were maintained throughout the duration of treatment (13). In addition, treatment with TA resulted in a dramatic improvement in patient quality of life with regard to alertness, productivity, cleanliness, action radius and overall wellness (20).

A review such as this one is hampered by a wide variation in published reports, with different methods, dosages of tranexamic acid, objective vs. subjective measurement of menstrual bleeding, definitions and screening for heavy menstrual bleeding. The limited data published on the effect of TA on induced HMB were the weakness of this review, especially with regard to leiomyomas. Previous systematic reviews have focused mainly on the effect of TA on idiopathic HMB, and our systematic review is the first one to evaluate the clinical utility of the TA for the treatment of HMB irrespective of the etiology. Despite our limitation, there is overwhelming evidence to support the effectiveness of TA in significantly reducing the bleeding and improving the life impairment that results from idiopathic and non-functional HMB. The finding of this present systemic review on leiomyoma is inconclusive and should be interpreted with caution owing to limited evidence.

## Conclusion

Available evidence indicates that treatment with TA is effective and could potentially improve the quality of life of patients presenting with idiopathic and secondary heavy menstrual bleeding. TA appears to be superior to placebo, the non-steroidal anti-inflammatory drug mefenamic acid, the hemostatic agent ethamsylate and luteal phase norethisterone for the treatment of idiopathic heavy menstrual bleeding. TA is also effective as treatment for unscheduled bleeding and menorrhagia caused by the IUD. Further research synthesis with individual patient data meta-analysis can be useful. Based on the current evidence, it is premature to support the complete effectiveness of TA for the treatment of heavy uterine bleeding resulting from uterine fibroids. The impact of fibroid type, size and location on the therapeutic effectiveness of TA has yet to be studied.

## Funding

No specific funding.

## References


1. National Institute for Health and Clinical Excellence. NICE clinical guideline 44: heavy menstrual bleeding. London, UK: National Health Service; January 2007.
2. Hallberg I, Högdahl AM, Nilsson L, Rybo G. Menstrual blood loss – a population study. Variation at different ages and attempts to define normality. Acta Obstet Gynecol Scand. 1966;45:320–51.
3. Oehler MK, Rees MC. Menorrhagia: an update. Acta Obstet Gynecol Scand. 2003;82:405–22.
4. Clarke A, Black N, Rowe P, Mott S, Howle K. Indications for and outcome of total abdominal hysterectomy for benign disease: a prospective cohort study. Br J Obstet Gynaecol. 1995;102:611–20.
5. American College of Obstetricians and Gynecologists. Alternatives to hysterectomy in the management of leiomyomas. ACOG practice bulletin no. 96. Obstet Gynecol. 2008;112:387–400.
6. Coulter A, Peto V, Jenkinson C. Quality of life and patient satisfaction following treatment for menorrhagia. Fam Pract. 1994;11:394–401.
7. Ido K, Neo M, Asada Y. Reduction of blood loss using tranexamic acid in total knee and hip arthroplasties. Arch Orthop Trauma Surg. 2000;120:518–20.
8. Wellington K, Wagstaff AJ. Tranexamic acid: a review of its use in the management of menorrhagia. Drugs. 2003;63:1417–33.
9. Stein K, Ascher-Walsh C. A comprehensive approach to the treatment of uterine leiomyomata. Mt Sinai J Med. 2009;76:546–56.
10. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001;20:21–35.
11. Callender ST, Warner GT, Cope E. Treatment of menorrhagia with tranexamic acid. A double blind trial. Br Med J. 1970;4:214–6.
12. Edlund M, Andersson K, Rybo G, Lindoff C, Astedt B, von Schoultz B. Reduction of menstrual blood loss in women suffering from idiopathic menorrhagia with a novel antifibrinolytic drug (Kabi 2161). Br J Obstet Gynaecol. 1995;102:913–7.
13. Lukes AS, Moore KA, Muse KN, Gersten JK, Hecht BR, Edlund M, et al. Tranexamic acid treatment for heavy menstrual bleeding: a randomized controlled trial. Obstet Gynecol. 2010;116:865–75.
14. Preston JT, Cameron IT, Adams EJ, Smith SK. Comparative study of tranexamic acid and norethisterone in the treatment of ovulatory menorrhagia. Br J Obstet Gynaecol. 1995;100:401–5.
15. Weström L, Bengtsson LP. Effect of tranexamic acid (AMCA) in menorrhagia with intrauterine contraceptive devices. J Reprod Med. 1970;5:154–61.
16. Bonnar J, Sheppard B. Treatment of menorrhagia during menstruation: randomised controlled trial of ethamsylate, mefenamic acid, and tranexamic acid. BMJ. 1996;313:579–82.
17. Kriplani A, Kulshrestha V, Agarwal N, Diwakar S. Role of tranexamic acid in management of dysfunctional uterine bleeding in comparison with medroxyprogesterone acetate. J Obstet Gynaecol. 2006;26:673–8.
18. Ylikorkala O, Viinikka L. Comparison between antifibrinolytic and antiprostaglandin treatment in the reduction of increased menstrual blood loss in women with intrauterine contraceptive devices. Br J Obstet Gynaecol. 1983;90:78–83.
19. Lakhani KP, Marsh MS, Purcell W, Hardiman P. Uterine artery blood flow parameters in women with dysfunctional uterine bleeding and uterine fibroids: the effects of tranexamic acid. Ultrasound Obstet Gynecol. 1998;11:283–5.
20. Winkler UH. The effect of tranexamic acid on the quality of life of women with heavy menstrual bleeding. Eur J Obstet Gynecol Reprod Biol. 2001;99:238–43.
21. Rybo G. Tranexamic acid therapy: effective treatment in heavy menstrual bleeding: clinical update on safety. Therapeutic Advances. 1991;4:1–8.
22. Berntorp E, Follrud C, Lethagen S. No increased risk of venous thrombosis in women taking tranexamic acid. Thromb Haemost. 2001;86:714–5.
23. Lethaby A, Farquhar C, Cooke I. Antifibrinolytics for heavy menstrual bleeding. Cochrane Database Syst Rev. 2000;(4):CD000249.
24. Barbieri RL. A new (to the US) first-line agent for heavy menstrual bleeding (Editorial). OBG Management. 2010;22:9–12.
25. Nilsson L, Rybo G. Treatment of menorrhagia with an antifibrinolytic agent, tranexamic acid (AMCA). A double blind investigation. Acta Obstet Gynecol Scand. 1967;46:572–80.
26. Pihlbrant A, Schannong M, Vessman J. Pharmacokinetics and bioavailability of tranexamic acid. Eur J Clin Pharmacol. 1981;20:65–72.
27. Svahn CM, Schannong M, Stenberg U, Widlund L. Absorption of tranexamic acid as a prodrug in healthy volunteers. Arzneim-Forsch Drug Res. 1988;38: 735–8.
28. Hillier K, Kasonde JM. Prostaglandin E and F concentrations in human endometrium after insertion of intrauterine contraceptive device. Lancet. 1976;i:15–6.
29. Kasonde JM, Bonnar J. Effect of ethamsylate and aminocaproic acid on menstrual blood loss in women using intrauterine devices. British Medical Journal. 1975;4:21–2.

Acta Obstet Gynec Scand 51: 347–350, 1972

# THE EFFECT OF TRANEXAMIC ACID (AMCA) ON POSTOPERATIVE BLEEDING AFTER CONIZATION

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*Abstract.* A double blind randomized trial was made to ascertain the effect of tranexamic acid (AMCA) (Cyklokapron®) on the postoperative blood loss after conization. The case material consisted of 50 women referred to the clinic because of dysplasia or non-invasive cancer of the cervix. Five patients were excluded for various reasons. The treatment started in the evening of the day of operation and was continued for another 12 days, the dose being three tablets every 8 hours, corresponding to 4.5 g of tranexamic acid daily when the active drug was given. During the first 7 postoperative days, when the patients were in hospital, the blood losses were determined quantitatively. Prophylactic treatment with tranexamic acid reduced the postoperative blood loss as compared with the placebo group, the blood losses being $23 \pm 3.2$ ml and $79 \pm 20.4$ ml respectively. Sudden profuse bleeding postoperatively, requiring remedial measures, occurred in 7 patients, all in the placebo group. With the exception of 1 patient in the placebo group, who complained of nausea, no side effects were recorded.

The conization technique for non-invasive cancer of the cervix may be complicated by postoperative bleeding. There are two types of such bleeding. One consists of a continuous, successively decreasing loss of blood during the postoperative period, whereas the other is a sudden, heavy blood loss, usually occurring within the first 2 weeks following the operation. The latter complication often requires such measures as transfusions or further surgery. Some authors have reported good results in reducing bleeding complications after conization when epsilon-aminocaproic acid (EACA) is used as a prophylactic agent (2, 3). However, in these investigations, the blood loss was not determined quantitatively, but estimated by the fall in the haemoglobin concentration in venous blood.

The mode of action of EACA involves the suppression of the activation of plasminogen to plasmin. Endometrial tissue is known to contain a relatively high concentration of plasminogen activators (6), and the menstrual blood loss can be reduced by administering drugs with an inhibitory effect on plasminogen activation (4, 5). Furthermore, plasminogen activators are present in the cervical tissue (3). The bleeding following operation on the cervix may be due to the action of these activators on the haemostatic mechanism.

The introduction of a new antifibrinolytic agent, tranexamic acid (AMCA; Cyklokapron®, AB KABI, Stockholm, Sweden), involves lower dosages and produces fewer side effects than treatment with EACA, although the effect on fibrinolytic bleeding is reported to be the same with both preparations (4, 5). In view of this, a study of the effect of tranexamic acid on blood loss after conization of the cervix seemed to be of value. Consequently, a clinical trial was performed to compare the effect of tranexamic acid with that of a placebo, employing a double-blind technique with randomization.

## MATERIAL AND METHODS

The series consisted of 50 non-selected women (aged 23–62) referred to the Department of Obstetrics and Gynaecology because of dysplasia or non-invasive cancer of the cervix. The diagnosis had previously been established by means of cytology, curettage and/or biopsies from the portio. The patients were operated on by different surgeons according to a standard scheme used in the clinic. The portio was stained by means of the Schiller technique, and the descending branches of the uterine artery were ligated. Thereafter a cone, with its base on the portio and its apex pointing towards the internal cervical os, was excised. The base included all the

Table I. *Blood loss in connection with conization in 22 women treated with tranexamic acid*

| Patient no. | Blood loss (ml) | Day after operation when sudden, profuse bleeding occurred | Remarks |
|---|---|---|---|
| 1 | 20 | | Used oral contraceptives |
| 2 | 17 | | |
| 3 | 44 | | |
| 4 | 4 | | |
| 6 | 10 | | |
| 8 | 3 | | |
| 12 | 24 | | |
| 15 | 41 | | |
| 17 | 39 | | |
| 19 | 11 | | |
| 22 | 14 | | |
| 28 | 21 | | |
| 29 | 26 | | |
| 30 | 19 | | |
| 33 | 24 | | |
| 36 | 24 | | |
| 37 | 63 | | |
| 38 | 9 | | Used oral contraceptives |
| 42 | 27 | | |
| 45 | 10 | | |
| 48 | 13 | | |
| 49 | 46 | | |
| Mean value | 23 ± 3.2 | | |

Schiller-negative parts. Stitches were applied to bleeding vessels until the bleeding stopped. The wound cavity was not covered by so-called Sturmdorf sutures, in order to avoid the risk of enclosing dysplastic tissue in cervical crypts, which might reduce the reliability of the post-operative cytological follow-up examination. After operation a perforated glass tube was usually inserted in the cervical canal and a pack in the vagina. The pack was removed on the following day, but the glass tube was generally left for 4 to 5 days.

Tranexamic acid therapy was started on the evening following operation, three tablets being administered. Alternatively three tablets of a placebo were given. The tablets were similar in shape and taste. Each tablet of the active substance contained 0.5 g tranexamic acid. Therapy was continued for 12 more days in a dosage of 3 tablets every 8 hours. Thus, each patient treated with the active substance received a total of 4.5 g of tranexamic acid per day, which amounts to 55.5 g for the whole period of treatment. The period in hospital ranged from 7 to 10 days. Administration of drug or placebo was by random selection.

No other drug was given during the investigation. However, 2 patients in the tranexamic acid group (nos. 1 and 38) and 3 in the placebo group (nos. 5, 21 and 27) were on oral contraceptives before the operation, and this medication was not discontinued.

For 7 days after operation, during which time the patients were in hospital, all sanitary towels, tampons etc., were collected, and the blood loss was determined quantitatively by the method described by Hallberg & Nilsson (1). These determinations were performed in order to evaluate the postoperative blood loss. Furthermore, a record was made of any sudden more profuse bleeding which required such measures as transfusion, infusion of plasma expanders (Macrodex®), injection of antifibrinolytic agents or resuturing for control of blood loss. For practical reasons, it was not possible to measure such blood loss.

The blood loss during operation was not determined, since differences in surgical technique might cause considerable variations in the blood loss. Any side effects which occurred during treatment were recorded.

Five patients were excluded before the code was broken. Three patients (nos. 23 and 25 in the tranexamic acid group, and no. 24 in the placebo group) were excluded because during the course of the operation they had been given by mistake a vasopressor analogue (Octapressin®) by infiltration into the cervix, 1 patient (no. 9 in the placebo group) was excluded because she had been given EACA intravenously immediately after the operation in order to stop bleeding induced by surgery, and with the fifth patient (no. 20 in the tranexamic acid group), there was some uncertainty as to whether she had been treated as scheduled and, consequently, she was also excluded. Thus the tranexamic acid group consisted of 22, and the placebo group of 23 patients.

## RESULTS

Tables I and II show the continuous blood losses during the postoperative week in women treated with tranexamic acid and the placebo respectively. The mean values were $23 \pm 3.2$ ml and $79 \pm 20.4$ ml. The difference between the mean values is statistically significant when tested by Student's *t*-test ($p < 0.05$).

The results were also calculated for both groups after excluding the women taking contraceptives. The mean value of the blood loss in subjects who were given tranexamic acid was then $24 \pm 3.5$ ml and in those given the placebo $87 \pm 2.9$ ml. Apparently, these exclusions did not influence the results. The difference between the mean values is statistically significant ($p < 0.05$).

Sudden, profuse bleeding occurred postoperatively in 7 patients, all of whom were in the placebo group. It is of interest to note that none of the patients who received tranexamic acid had this bleeding complication. Such bleeding occurred from 5 to 10 days after operation (Table II). In 3 of the patients (nos. 11, 13 and 31) resuturing was necessary and they were also treated

Table II. *Blood loss in connection with conization in 23 women treated with placebo*

| Patient no. | Blood loss (ml) during 7 postoperative days | Day after operation when sudden, profuse bleeding occurred | Remarks |
|---|---|---|---|
| 5 | 30 | | Used oral contraceptives |
| 7 | 285 | | |
| 10 | 13 | | |
| 11 | 372 | 6 | Sutured. Treatment with blood and EACA. |
| 13 | 63 | 7 | Sutured. Treatment with blood and EACA. |
| 14 | 13 | | |
| 16 | 18 | | |
| 18 | 263 | | |
| 21 | 7 | | Used oral contraceptives. |
| 26 | 40 | 7 | Treatment with EACA in Macrodex® infusion. |
| 27 | 37 | | Used oral contraceptives. |
| 31 | 124 | 5 | Sutured. Treatment with blood and EACA. |
| 32 | 127 | 6 | Treatment with EACA and Macrodex®. |
| 34 | 38 | | |
| 35 | 30 | | |
| 39 | 62 | | |
| 40 | 63 | 10 | Treatment with tamponade and EACA. |
| 41 | 50 | | |
| 43 | 96 | | |
| 44 | 31 | | |
| 46 | 22 | | |
| 47 | 3 | | |
| 50 | 25 | 8 | Readmission to hospital. Treatment with EACA and Macrodex®. |
| Mean value | 79 ± 20.4 | | |

with blood transfusion and EACA. In 3 cases (nos. 26, 32 and 50) bleeding was controlled by means of EACA and Macrodex®, and in 1 case (no. 40) treatment consisted in tamponade and EACA.

With the exception of 1 patient in the placebo group, who complained of nausea, no side effects were recorded.

## DISCUSSION

Conization of the portio-cervix has become increasingly common as a result of cytological screening of the population for carcinoma of the cervix. Though cone-biopsy is a relatively simple procedure, there is always a risk of postoperative bleeding. In some cases bleeding necessitates blood transfusions or infusion of plasma expanders or even surgery. Consequently, in many clinics a relatively long period in hospital following conization is customary.

The results of the present investigation show that prophylactic administration of an antifibrinolytic drug, such as tranexamic acid, reduces the "small" continuous postoperative blood loss. It is important, however, to recognize that also the frequency of sudden, profuse bleeding, which sometimes occurs postoperatively, may be effectively reduced. This type of complication often requires repeated surgery or transfusion. Administration of an antifibrinolytic agent not only seems to be very effective in preventing such complications, but may also contribute towards reducing the duration or stay in hospital, to the advantage of both the patient and the economy of the hospital.

The present study also shows that the postoperative bleeding complications after conization are minimized when tranexamic acid is administered prophylactically. Virtually the same results were obtained by Jensen (2) and Kullander (3) using another antifibrinolytic preparation—EACA. However, in their investigations the postoperative blood losses were not determined objectively. The effect of the blood loss on the haemoglobin concentration was used as a para-

meter, and postoperative bleeding which necessitated the application of special measures was recorded. It is reasonable to assume that the effect of antifibrinolytic drugs is due to an inhibition of the action of the plasminogen activators present in the cervical tissue.

Oral contraceptives influence many processes in the human body. The effect of contraceptive pills on the haemostatic mechanism is still obscure, but the possibility of such influence cannot be rejected. Some of the patients in this study were using oral contraceptives before they were admitted for conization. This medication was not discontinued during or after operation. The inclusion of these patients did not, however, affect the results.

Differences in surgical technique may cause variation in the postoperative blood loss. Even if a standardized operative technique was used, such a source of error could not be excluded since different surgeons performed the operations. However, the fact that the double-blind method was applied in this trial and that differences in the surgical procedure must have occurred in both the placebo group and the tranexamic acid group minimizes the risk that such an error could affect the results.

In view of the results of this study, it may reasonably be concluded that tranexamic acid administered prophylactically after conization, reduces postoperative bleeding complications.

## REFERENCES

1. Hallberg, L. & Nilsson, L.: Determination of menstrual blood loss. Scand J Clin Lab Invest *16:* 244, 1964.
2. Jensen, H.: Epsilon-amino-kapronsyre ved portioplastikk. Blödningsprofylaktisk effekt. Nord Med *74:* 562, 1966.
3. Kullander, M. S.: L'utilisation de l'acide epsilon amino caproique comme hémostatique dans les conisations du col uterin. Grenoble Médico-Chirurgical *6:* 505, 1968.
4. Nilsson, L. & Rybo, G.: Treatment of menorrhagia with an antifibrinolytic agent, tranexamic acid (AMCA). Acta Obstet Gynec Scand *46:* 572, 1967.
5. Nilsson, L. & Rybo, G.: Treatment of menorrhagia. Amer J Obstet Gynec *110:* 713, 1971.
6. Rybo, G.: Clinical and experimental studies on menstrual blood loss. Acta Obstet Gynec Scand *45:* suppl. 7, 1966.

*Submitted for publication March 20, 1972*

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International Journal of Women's Health

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REVIEW

# Tranexamic acid for the treatment of heavy menstrual bleeding: efficacy and safety

This article was published in the following Dove Press journal:
International Journal of Women's Health
16 August 2012
Number of times this article has been viewed

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**Abstract:** Tranexamic acid has proven to be an effective treatment for heavy menstrual bleeding (HMB). It reduces menstrual blood loss (MBL) by 26%–60% and is significantly more effective than placebo, nonsteroidal anti-inflammatory drugs, oral cyclical luteal phase progestins, or oral etamsylate, while the levonorgestrel-releasing intrauterine system reduces MBL more than tranexamic acid. Other treatments used for HMB are oral contraceptives, danazol, and surgical interventions (endometrial ablation and hysterectomy). Medical therapy is usually considered a first-line treatment for idiopathic HMB. Tranexamic acid significantly improves the quality of life of women treated for HMB. The recommended oral dosage is 3.9–4 g/day for 4–5 days starting from the first day of the menstrual cycle. Adverse effects are few and mainly mild. No evidence exists of an increase in the incidence of thrombotic events associated with its use. An active thromboembolic disease is a contraindication. In the US, a history of thrombosis or thromboembolism, or an intrinsic risk for thrombosis or thromboembolism are considered contraindications as well. This review focuses on the efficacy and safety of tranexamic acid in the treatment of idiopathic HMB. We searched for medical literature published in English on tranexamic acid from Ovid Medline, PubMed, and Cinahl. Additional references were identified from the reference lists of articles. Ovid Medline, PubMed, and Cinahl search terms were "tranexamic acid" and "menorrhagia" or "heavy menstrual bleeding." Searches were last updated on March 25, 2012. Studies with women receiving tranexamic acid for HMB were included; randomized controlled studies with a description of appropriate statistical methodology were preferred. Relevant data on the physiology of menstruation and the pharmacodynamics and pharmacokinetics of tranexamic acid are also included.

**Keywords:** tranexamic acid, heavy menstrual bleeding, menorrhagia

## Introduction

Heavy menstrual bleeding (HMB) has a significant impact on many women's lives.[1] The etiology is variable and can be either local, systemic, or iatrogenic. In half of all cases, no specific etiology is identified and HMB is called idiopathic.[2] Heavy regular menstrual bleeding, or menorrhagia, is quantitatively defined as menstrual blood loss (MBL) of 80 mL or more per cycle.[3,4] The definition has been widely adopted in clinical studies, while in practice, diagnosis is typically based on the subjective perception of MBL and its impact on quality of life (QOL).

There are a number of medical and surgical alternatives available for the treatment of HMB. These include the levonorgestrel-releasing intrauterine system (LNG-IUS), oral progestins, oral contraceptives, danazol, non-steroidal anti-inflammatory drugs (NSAIDs), and antifibrinolytic drugs, as well as endometrial ablation and hysterectomy.

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http://dx.doi.org/10.2147/IJWH.S13840

Many national guidelines (eg, in the UK and Finland) consider the medical alternatives a first-line treatment, especially for idiopathic HMB. Potential complications caused by surgical interventions can thus be avoided in many cases.

Tranexamic acid is an antifibrinolytic drug that has proven effective for HMB in clinical use. It has been used to treat HMB for over four decades in many European countries. In the US, however, tranexamic acid was not approved for the treatment of menorrhagia until 2009.[5] The novel modified-release formulation of oral tranexamic acid approved in the US was designed to increase patient tolerability by reducing the gastrointestinal adverse effects, which have previously been connected with the use of oral tranexamic acid.[6]

Long-term usage of tranexamic acid for HMB is likely, and thus, adverse events affecting safety are of particular importance. There has been concern about the possible increase of thromboembolic events with the use of tranexamic acid due to its mechanism of action.[7,8] This review evaluates the use of tranexamic acid in the management of regular HMB in terms of efficacy, tolerability, dosage, and cost.

## Physiology of idiopathic heavy menstrual bleeding

Menstruation is a highly synchronized physiological event that occurs in four steps.[9] First is the premenstrual dissolution of the stromal extracellular matrix. It is dependent on the extracellular matrix-degrading effects of matrix metalloproteinases and changes in plasminogen activator inhibitors. In step two, endometrial vasoconstriction occurs. Prostaglandins and other prostanoids as well as endothelins are the key players during this phase. Step three involves secondary vasodilatation, vascular disruption, and tissue sloughing, which begins on the first day of menstruation. MBL is mainly (75%) arterial, emerging from the spiral arterioles.[10] During this phase, prostanoids, endothelins, matrix metalloproteinases, and plasminogen activators and inhibitors interact and participate. In step four, postmenstrual endometrial repair and regeneration begin. This involves thrombin effects on extracellular matrix degradation and postmenstrual angiogenesis. Angiogenesis is the key process in re-establishing endometrial vascular function.[11] The two principal mediators of endometrial functioning are estrogen and progesterone, which exert their effects through cellular receptors.[12]

The pathogenesis of idiopathic heavy bleeding is poorly understood. Changes in the relationship between serum and local concentrations of vasoactive compounds, such as prostaglandins, endothelins, prostacyclins, and phospholipases, are associated with this bleeding problem.[13,14] Also, endometrial fibrinolytic enzymes appear to have an important role in menstrual hemostasis, tissue shedding, and repair. Plasmin and plasminogen activator activity are increased in the menstrual fluid or in endometrial extracts in women with dysfunctional bleeding, suggesting increased fibrinolysis.[15–17]

## Pharmacodynamics and pharmacokinetics of tranexamic acid

Tranexamic acid exerts its antifibrinolytic effect by reversibly blocking lysine binding sites on plasminogen, thus preventing plasmin from interacting with lysine residues on the fibrin polymer, causing subsequent fibrin degradation.[6] In women with menorrhagia, fibrinolytic activity is high, likely due to high levels of plasmin and plasminogen activators from the endometrium.[18] The majority of pharmacokinetic studies of tranexamic acid involve intravenous administration,[19,20] and studies with oral formulations are with healthy males, but not females.[21] These studies show that the mean maximum plasma concentration after 2 g of oral tranexamic acid was achieved 2–3 hours post-dose and was not affected by food.[21] Tranexamic acid is minimally bound to plasma proteins (3%) at therapeutic concentrations, which makes it highly binding to plasminogen.[22] The main elimination route of tranexamic acid is via the kidneys, with an elimination half-life of about 2 hours.[21] Caution is advised when administering tranexamic acid to patients with renal insufficiency.

## Therapeutic efficacy of tranexamic acid in heavy menstrual bleeding

We identified 11 randomized controlled studies (n = 15–294) of variable design on oral tranexamic acid in the treatment of HMB (Table 1).[23–33] Studies included women of reproductive age with regular HMB. Duration of the intervention varied from one to six cycles. MBL was assessed directly using a validated alkaline hematin method[34] in seven studies, indirectly by pictorial blood loss assessment chart (PBAC)[35,36] score in two studies, and by other indirect measurements in the remaining two studies. The primary outcome in all studies was the effect of treatment on MBL. Other outcome measures included duration of bleeding, number of sanitary napkins/tampons used, number of large stains, hemoglobin concentration, and QOL. Side effects/adverse effects were recorded to some extent in all studies. Tranexamic acid was compared with placebo, NSAIDs, oral progestins, LNG-IUS, oral hemostatic agent etamsylate, and intranasal desmopressin. The main results, discussed in detail below, are summarized in Table 1.

**Table 1** Tranexamic acid in the treatment of heavy menstrual bleeding

| Trial | Intervention method | n | Selection criteria | Outcome measures | Main results |
|---|---|---|---|---|---|
| Andersch et al[23] | 1. TA 1.5 g × 3 pd 1–3 and 1 g × 2 pd 4–7 | 15 | Women aged 34–49 years | MBL (AHM) | Mean MBL change from baseline: |
| | | | MBL > 80 mL per cycle | Duration of bleeding | TA −53%[c] and FLU −24%,[c] $P < 0.01$ |
| | 2. FLU 100 mg × 2 pd 1–5 | 15 | Regular cycle | | No effect on duration of bleeding |
| | Total | 15 | | | Discontinuation: 0% |
| | Duration: 2 screening and 2 + 2 treatment cycles | | | | |
| | Randomized open cross-over study | | | | |
| | Method of randomization unclear | | | | |
| Bonnar and Sheppard[24] | 1. ETM 500 mg × 4 pd 1–5 | 27 | Women aged 35–46 years | MBL (AHM) | Mean MBL change from baseline: |
| | 2. TA 1 g × 4 pd 1–5 | 26 | MBL > 80 mL per cycle | Duration of bleeding | ETM +3%, TA −54%,[e] and MEF −20%,[e] |
| | 3. MEF 500 mg × 3 pd 1–5 | 23 | Normal hysteroscopy, endometrial | Number of sanitary napkins used | $P < 0.05$ TA compared with MEF, |
| | Total | 76 | biopsy, and cervical cytology | | $P < 0.001$ TA compared with ETM |
| | Duration: 3 placebo and 3 treatment cycles | | | | No effect on duration of bleeding |
| | | | | | Reduction in the number of napkins used: |
| | Randomization by computer-generated list to one of three groups | | | | $P < 0.01$ TA compared with baseline |
| | Blinding unclear | | | | Discontinuation: ETM 41%, TA 15%, and MEF 13% |
| Callender et al[25] | 1. TA 1 g × 4 pd 1–4 | 20 | Women aged 33–48 years | MBL (Total body counter) | Mean MBL change from baseline: |
| | 2. Placebo pd 1–4 | 20 | Subjectively perceived menorrhagia | | TA −36%[b] and placebo −6%, $P < 0.05$ |
| | Total | 20 | or iron deficiency anemia | Duration of bleeding | No effect on duration of bleeding |
| | Duration: 3 + 3 treatment cycles | | | Number of napkins used | Reduction in the number of napkins used: |
| | Randomized double-blind cross-over study | | | | $P < 0.01$ TA compared with placebo |
| | | | | | Discontinuation: 20% |
| Freeman et al[26] | 1. TA 650 mg × 3 pd 1–5 | 115 | Women aged 18–49 years | MBL (AHM) | Mean MBL change from baseline: |
| | 2. TA 1.3 g × 3 pd 1–5 | 112 | Average MBL ≥ 80 mL over | QOL (MIQ) | TA low dose −26%, TA high dose −39%, and |
| | 3. Placebo pd 1–5 | 67 | two cycles | Number of large stains | placebo −2%, $P < 0.0001$ both TA groups |
| | Total | 294 | Regular cycle | | compared with placebo |
| | Duration: 2 screening and 3 treatment cycles | | Uterine fibroids not excluded unless surgical management warranted | | QOL: improvements in limitations in social/leisure activities, and physical activities in both TA groups compared with placebo ($P \leq 0.0055$) |
| | Randomized double-blind placebo-controlled study | | | | Discontinuation: TA lower dose 9%, TA higher dose 13%, and placebo 9% |
| Kouides et al[27] | 1. TA 1 g × 4 pd 1–5 | 67 | Women aged 18–50 years | MBL (PBAC) | Mean MBL (PBAC) change from baseline: |
| | 2. IN-DDAVP 300 μg × 1 pd 2–3 | 49 | Abnormal laboratory hemostasis | QOL (HRQOL, SF-36, CES-D, and RUTA) | TA −38% and IN-DDAVP −23%, $P = 0.0002$ |
| | Total | 116 | | | QOL: improved in both groups (significantly on RUTA scale) |
| | Duration: 2 + 2 treatment cycles | | PBAC score ≥ 100 | | Discontinuation: 43% IN-DDAVP→TA and 33% TA→ IN-DDAVP |
| | Randomized open cross-over study | | Regular cycle | | |
| | Method of randomization unclear | | Uterine fibroids not excluded if uterus <12 weeks gestational size | | |

(*Continued*)

**Table 1** (*Continued*)

| Trial | Intervention method | n | Selection criteria | Outcome measures | Main results |
|---|---|---|---|---|---|
| Kriplani et al[28] | 1. TA 500 mg × 4 pd 1–5<br>2. MPA 10 mg × 2 pd 5–25<br>Total<br>Duration: 3 months of treatment and 3 months of follow-up<br>Randomized open study | 49<br>45<br>94 | Women presenting with heavy menstrual bleeding<br>PBAC score > 100 | MBL (PBAC)<br>Duration of bleeding<br>Hemoglobin<br>QOL (VAS) | Mean MBL (PBAC) change from baseline:<br>TA –60%[d] and MPA –58%[d]<br>Duration of bleeding decreased in both groups ($P < 0.005$)<br>Hemoglobin increased in both groups (TA, $P = 0.003$; MPA, $P = 0.019$)<br>Discontinuation: TA 4% and MPA 27% |
| Lukes et al[29] | 1. 1.3 g × 3 pd 1–5<br>2. Placebo pd 1–5<br>Total<br>Duration: 2 screening and 6 treatment cycles<br>Randomized double-blind placebo-controlled study | 115<br>72<br>187 | Women aged 18–49 years<br>Average MBL ≥ 80 mL over two cycles<br>Regular cycle<br>Uterine fibroids not excluded unless surgical management warranted | MBL (AHM)<br>QOL (MIQ)<br>Number of large stains<br>Hemoglobin and ferritin | Mean MBL change from baseline:<br>TA –40% and placebo –8%, $P < 0.001$<br>QOL: improvements in limitations in social/leisure activities and physical activities, work inside and outside the home, and self-perceived MBL compared with placebo ($P < 0.001$)<br>No significant increase in hemoglobin<br>Discontinuation: TA 24% and placebo 26% |
| Milsom et al[30] | 1. LNG-IUS (release of 20 μg/day)<br>2. FLU 100 mg × 2 pd 1–5<br>3. TA 1.5 g × 3 pd 1–3 and 1 g × 2 pd 4–5<br>Total<br>LNG-IUS 12 months open-label, then randomization to non-blind treatment (FLU and TA) for 2 + 2 cycles in cross-over fashion<br>Method of randomization unclear | 16<br>15<br>15<br>15 | Women aged 31–49 years<br>MBL > 80 mL per cycle<br>Regular cycle | MBL (AHM)<br>Hemoglobin | Mean MBL change from baseline:<br>LNG-IUS –83%[e] at 3 months, –88%[e] at 6 months, and –96%[e] at 12 months, FLU –24%,[a] and TA –47%,[c]<br>P < 0.001 LNG-IUS compared with FLU,<br>$P < 0.01$ LNG-IUS compared with TA,<br>$P < 0.05$ TA compared with FLU<br>Hemoglobin increase: LNG-IUS 10%, FLU 0%, and TA 0% |
| Nilsson and Rybo[31] | 1. TA 250 mg × 6 pd 1–4 and 500 mg × 6 pd 1–4<br>2. TA 500 mg × 6 pd 1–4 and 1 g × 6 hourly pd 1–4<br>3. Placebo × 6 pd 1–4<br>Total<br>Duration: 2 screening and 1 + 1 + 1 treatment cycles<br>Randomized double-blind cross-over study<br>Method of randomization unclear<br>Only one cycle of treatment on each dosage | 36 | Women aged 15–49 years<br>Subjectively perceived menorrhagia | MBL (AHM) | Mean MBL change from baseline:<br>TA –38% (total dose of 12 g per cycle) and –51% (total dose of 24 g per cycle)<br>Discontinuation: 0% |
| Preston et al[32] | 1. TA 1 g × 4 pd 1–4<br>2. NOR 5 mg × 2 pd 19–26 | 25<br>21 | Age 18 years or more<br>Average MBL > 80 mL over | MBL (AHM)<br>QOL | Mean MBL change from baseline:<br>TA –45%[f] and NOR +20% |

| | | | | | |
|---|---|---|---|---|---|
| | Total<br>Duration: 2 placebo and 2 treatment cycles<br>Randomized double-blind placebo-controlled study | 46 | two cycles<br>Regular cycle<br>Confirmed to be ovulating | (using 5-point scale) | Reduced flooding/leakage and improved sex life in TA-group<br>Discontinuation: 0% |
| Vermylen et al[33] | 1. TA 500 mg × 6 starting from pd 1 until bleeding stops<br>2. Placebo × 6 starting from pd 1 until bleeding stops<br>Total<br>Randomized double-blind cross-over study | 22<br><br>22<br><br>22 | Subjectively perceived menorrhagia | MBL (mean hemoglobin loss from sanitary napkins)<br><br>Duration of bleeding<br>Number of sanitary napkins used | Mean MBL reduction 35% in TA-group<br>No effect on duration of bleeding<br>No reduction in the number of napkins used<br>Discontinuation: 27% |

**Notes:** [a]$P < 0.05$; [b]$P < 0.02$; [c]$P < 0.01$; [d]$P < 0.005$; [e]$P < 0.001$; [f]$P < 0.0001$.

**Abbreviations:** AHM, alkaline hematin method; CES-D, Center for Epidemiologic Studies Depression Scale; ETM, etamsylate; FLU, flurbiprofen; HRQOL, Health-Related Quality of Life; IN-DDAVP, intranasal desmopressin; IUCD, intrauterine copper device; IUD, intrauterine device; LNG-IUS, levonorgestrel-releasing intrauterine system; MBL, menstrual blood loss; MEF, mefenamic acid; MIQ, Menorrhagia Impact Questionnaire; MPA, medroxyprogesterone acetate; NOR, norethisterone; OC, oral contraceptive; PBAC, Pictorial Blood loss Assessment Chart; pd, period day; QOL, quality of life; RUTA, Modified Ruta Menorrhagia Severity Scale; SF-36, Short Form-36; TA, tranexamic acid; VAS, visual analog scale.

## Effect on menstrual blood loss

Compared with the baseline, tranexamic acid 1.5–4.5 g/day taken for 4–7 days per cycle reduced mean MBL by 26%–60% ($P < 0.05$) (five studies did not provide the *P*-value).[23–33]

In comparison with placebo, tranexamic acid reduced mean MBL from the baseline by 26%–50%, while a 2%–8% reduction was seen in the placebo groups ($P < 0.05$) (two studies did not provide the *P*-value).[25,26,29,31,33] In a randomized, placebo-controlled, double-blind study (n = 187) by Lukes et al,[29] MBL declined to less than 80 mL (standard definition of heavy menstrual bleeding) in 43% of menstrual cycles in women receiving 3.9 g of tranexamic acid per day compared with 17% of cycles in women receiving placebo ($P < 0.001$). Furthermore, MBL was reduced at least 50 mL per cycle in 56% of cycles in the tranexamic acid group compared with 19% of cycles in the placebo group ($P < 0.001$). The percentage of cycles in which a patient-perceived meaningful reduction in MBL of 36 mL/22%[37] was achieved was greater in the tranexamic acid group (69%) than in the placebo group (17%) ($P < 0.001$). The presence of uterine fibroids was not an exclusion criterion in this study unless the fibroids were of a sufficient number and size to warrant surgical treatment. Treatment with tranexamic acid was similarly effective in reducing mean MBL regardless of the presence of fibroids.[29]

Compared with NSAIDs, mean MBL was significantly more decreased with tranexamic acid than with flurbiprofen 200 mg/day for 5 days ($P < 0.05$)[23,30] or mefenamic acid 1.5 g/day for 5 days ($P < 0.05$).[24] In the study by Bonnar and Sheppard,[24] mean MBL declined to normal levels (less than 80 mL per cycle) in 100% of patients receiving tranexamic acid. The same study also compared tranexamic acid with an oral hemostatic agent, etamsylate 2 g/day for 5 days: etamsylate increased mean MBL by 3% relative to the reduction of 54% seen with tranexamic acid ($P < 0.001$).[24]

A study of an oral progestin and tranexamic acid showed that tranexamic acid 4 g/day for 4 days reduced mean MBL by 45%, whereas norethisterone 10 mg/day for 7 days during the luteal phase of the menstrual cycle increased MBL by 20%. Mean MBL declined to normal in 56% of women receiving tranexamic acid compared with 10% of those taking norethisterone.[32] A randomized open-label study by Kriplani et al[28] compared tranexamic acid 2 g/day for 5 days with medroxyprogesterone acetate (MPA) 20 mg/day for 21 days starting from the fifth day of the menstrual cycle. Mean reduction in MBL, assessed using the PBAC score, was 60% in the tranexamic acid group and 58% in the MPA group. However, a lack of response was seen in 29% of women receiving MPA compared with only

6% of women receiving tranexamic acid ($P < 0.003$), and 27% of women in the MPA group discontinued because of bleeding problems and side effects compared with 4% in the tranexamic acid group ($P < 0.002$). Furthermore, during the six-month total study period, 18% of the MPA group underwent hysterectomy compared with 4% of the tranexamic acid group ($P < 0.002$).[28]

Compared with LNG-IUS, tranexamic acid was significantly less effective; the mean reduction of MBL after four cycles was 47% compared with 83% after three months of treatment with LNG-IUS ($P < 0.01$).[30]

The effect of intranasal desmopressin and tranexamic acid was studied in women with HMB and abnormal laboratory hemostasis in a randomized, open-label, cross-over trial (n = 116). Women with confirmed menorrhagia (PBAC score ≥ 100) had abnormal hemostasis in 73% of cases. Platelet aggregation and/or release abnormality was the most common abnormality (75%), 11% had subnormal coagulation factor level, 7% Von Willebrand disease, and 7% prolonged closure time. The mean decrease in PBAC score from the baseline was −105.7 for tranexamic acid 4 g/day for 5 days and −64.1 for intranasal desmopressin 300 μg once per day for 2 days ($P = 0.002$).[27]

Treatment of heavy menstrual bleeding with tranexamic acid had no effect on duration of bleeding in most studies.[23–25,33] The study comparing tranexamic acid with MPA, however, reported that the duration of bleeding decreased significantly compared with the baseline in both groups ($P < 0.005$).[28] Number of sanitary napkins/tampons used was reported in three studies and decreased significantly with tranexamic acid treatment compared with the baseline or placebo ($P < 0.01$) in two of them.[24,25] The study comparing tranexamic acid with MPA found a significant increase in mean hemoglobin concentration in both groups over the three-month intervention ($P = 0.003$ and 0.019),[28] while the other two studies reporting such data found no increase in hemoglobin during 4–6 cycles of treatment with tranexamic acid compared with the baseline.[29,30]

### Effect on quality of life

Two randomized, placebo-controlled, double-blind studies used a validated disease-specific Menorrhagia Impact Questionnaire (MIQ) for assessing the change in QOL related to treatment of heavy menstrual bleeding with tranexamic acid.[26,29] Freeman et al[26] (n = 294) administered tranexamic acid for three cycles in doses of 1.95 g/day for 5 days compared with 3.9 g/day for 5 days and showed that mean MIQ scores for limitations in social or leisure activities and physical activities decreased significantly in both tranexamic acid groups compared with placebo ($P \leq 0.0055$). Lukes et al[29] used a dosage of 3.9 g/day for 5 days over six cycles (n = 187). Similar results were obtained in their study; mean MIQ scores for limitations in social or leisure activities and physical activities, work outside or inside the home, and self-perceived MBL decreased significantly in the tranexamic acid group compared with placebo ($P < 0.001$), and the improvements were maintained throughout six cycles of treatment.[29] In the study comparing tranexamic acid 4 g/day for 5 days with intranasal desmopressin, changes in QOL were assessed by four validated instruments (Health-Related Quality of Life, Short Form-36, Center for Epidemiologic Studies Depression Scale, and disease-specific modified Ruta Menorrhagia Severity Scale). While all instruments showed improvements in both treatment groups after two treatment cycles compared with the baseline, only Ruta Menorrhagia Severity scores decreased significantly, without differences between the groups ($P \leq 0.008$).[27] A non-validated questionnaire using a five-point scale was utilized in a randomized, double-blind, placebo-controlled study (n = 46) comparing tranexamic acid 4 g/day for 4 days with norethisterone 10 mg/day for 7 days during the luteal phase of the menstrual cycle over two cycles. A larger proportion of women in the tranexamic acid group than in the norethisterone group experienced improved sex life (46% versus 15%; $P = 0.029$) and reduced flooding/leakage (83% versus 45%; $P = 0.008$) compared with the baseline or placebo.[32] Improvements are also reported in a large open-label uncontrolled study (n = 849) investigating the effect of tranexamic acid 3–6 g/day for 3–4 days over three months on QOL. QOL was assessed using a self-developed questionnaire with a five-point scale. Concomitant medication was permitted, yet most women (84%) used only tranexamic acid. After the third cycle, 81% were satisfied or very satisfied with the treatment, and 94% judged their MBL to be decreased or strongly decreased. Compared with the baseline, treatment with tranexamic acid during the third cycle reduced the proportion of women feeling a considerable degree of impairment during menstruation by more than 60% ($P < 0.0001$), and increased the proportion of women feeling fit and active by 63% and those feeling no or little impairment in social activities during menstruation by 58% ($P < 0.0001$).[38]

## Tolerability of tranexamic acid

Freeman et al[26] assessed the efficacy of a new oral formulation of tranexamic acid 1.95 g/day or 3.9 g/day for 5 days in a randomized, placebo-controlled, double-blind study (n = 294) over three cycles. The majority of participants (87%) reported

adverse effects, with no significant differences between the three groups. Four women using tranexamic acid withdrew from the study because of adverse effects, which were considered definitely not or probably not related to study treatment. The most frequently reported adverse effects, occurring in ≥5% of tranexamic acid-treated women and at twice the rate of placebo-treated women, were viral upper respiratory infection (7%–10%), fatigue (4%–11%), musculoskeletal pain (5%–9%), arthralgia (4%–6%), myalgia (5%–4%), and nasal congestion (3%–7%). All but one of the higher percentages of these adverse effects were seen in the 1.95 g/day tranexamic acid group.[26] The efficacy of a new oral formulation of tranexamic acid 3.9 g/day for 5 days over six cycles was studied in a randomized, placebo-controlled, double-blind trial (n = 187).[29] The majority of adverse events were mild to moderate. No serious adverse events considered related to the treatment occurred. The most common adverse effects in both groups were menstrual discomfort/cramps (50%–62%), headache (50%–56%), back pain (19%–24%), and nausea (15%); no significant differences were present between the groups.[29] In the study by Kouides et al,[27] 7% of the women reported side effects in the tranexamic acid group and 8% in the intranasal desmopressin group. Headache was the most commonly reported side effect in both groups. Kriplani et al[28] (n = 94) compared tranexamic acid 2 g/day for 5 days with MPA 20 mg/day taken for 21 days. The duration of the intervention was three months. Side effects were reported in 16% of women in the tranexamic acid group compared with 33% of women in the MPA group.[28]

A long-term follow-up is available from an open-label single-arm study of 27 cycles (n = 723) of treatment with a new oral formulation of tranexamic acid 3.9 g/day for 5 days. The most commonly reported adverse effects were headache, menstrual discomfort, and back pain, and most of the adverse effects were mild to moderate in severity. Furthermore, adverse effects were largely considered unrelated to treatment with tranexamic acid.[39]

In the older studies, there was no significant increase in reported adverse effects with tranexamic acid when compared with placebo.[25,31,33] Furthermore, Lethaby et al[40] have evaluated studies older than those discussed above in a Cochrane Review from the year 2000. They concluded that there was no significant increase in reported adverse events with tranexamic acid therapy compared with placebo or the other treatments studied.[40]

None of the studies, together including well over 2500 women, cited in this review have reported thromboembolic events with tranexamic acid treatment. Furthermore, in an observational population-based study over a 19-year period and with 238,000 women-years of treatment with tranexamic acid, no reported increase occurred in the incidence of thromboembolic events.[41,42] A more recent Swedish nested case-control study reported that the use of tranexamic acid for menorrhagia was associated with an increased risk for venous thromboembolism (adjusted odds ratio 3.20 [95% CI 0.65–15.78]).[43] However, the risk estimate did not reach statistical significance, and there were only three exposed cases using tranexamic acid compared with four exposed controls.

## Dosage of tranexamic acid in the treatment of heavy menstrual bleeding

Orally administered tranexamic acid is available as 250 mg, 500 mg, or 650 mg tablets and/or capsules and as a syrup containing 500 mg in 5 mL. In Europe, the recommended oral dosage of tranexamic acid for the treatment of menorrhagia is 1 g three times a day for up to 4 days. The dosage may be increased, but a total dose of 4 g per day should not be exceeded. Active thromboembolic disease, severe renal failure, and hypersensitivity to tranexamic acid are listed as contraindications. Caution is warranted when administering tranexamic acid to patients with a history of thromboembolic disease.[22] In the US, the recommended oral dosage is 1.3 g three times a day for up to 5 days. Active thromboembolic disease, a history of thrombosis or thromboembolism, an intrinsic risk for thrombosis or thromboembolism, and hypersensitivity to tranexamic acid are contraindications. Caution is required in the concomitant use of hormonal oral contraceptives with tranexamic acid because the risk of thrombotic events may further increase.[5]

Dosage reductions are recommended for patients with renal impairment, according to serum creatinine concentration.[5,22]

Two randomized, double-blind, placebo-controlled studies compared different dosages of tranexamic acid in the treatment of menorrhagia. Freeman et al[26] (n = 294) compared the efficacy of a new oral formulation of tranexamic acid 1.95 g/day for 5 days with 3.9 g/day for 5 days. Mean MBL reduction from the baseline was 26% in the 1.95 g/day group compared with 39% in the 3.9 g/day group. The mean reduction in MBL of more than 50 mL per cycle was achieved with the dosage of 3.9 g/day (65 mL), while the reduction was less in the 1.95 g/day group (47 mL). No significant differences emerged in the adverse effects recorded between the two groups.[26] Nilsson and Rybo[31] (n = 36) compared tranexamic acid 1.5 g/day, 3 g/day, and 6 g/day, each for 4 days. Mean MBL reduction was 38% with a total dose of 12 g per cycle

and 51% with a total dose of 24 g per cycle.[31] Both of these studies demonstrate a dose-response relationship in efficacy. The majority of treatment studies comparing tranexamic acid with either placebo or other medical therapies have used a tranexamic acid dosage of 4–4.5 g/day (Table 1).

## Cost of the treatment of heavy menstrual bleeding with tranexamic acid

Health economic analyses of tranexamic acid in the treatment of HMB are few and do not adhere to recommended methodological guidelines. A retrospective, literature-based Norwegian study[44] evaluated six medical treatments (NSAIDs, antifibrinolytic drugs, combined oral contraceptives, progestogens including LNG-IUS, transcervical resection, and hysterectomy). The only outcome measure was MBL, and the costs did not include complications, re-treatments, or follow-up time. The cost-effectiveness ratio favored medical treatments. Unfortunately, this study was based on a weak methodology and the results are unreliable. Moreover, the sole outcome measure gave limited information on the effectiveness of the treatments.

Recognizing the lack of health economic evidence on pharmaceutical treatments for HMB, the National Institute for Health and Clinical Excellence (NICE) guidelines for heavy menstrual bleeding developed a state-transition (Markov) model to assess the cost-effectiveness of four treatments (combined oral contraceptives, tranexamic acid, LNG-IUS, and NSAIDs). The analysis showed that compared with no treatment, tranexamic acid generated additional quality-adjusted life years (QALYs) at an additional cost. Compared with NSAIDs, tranexamic acid generated more QALYs at a lower cost, whereas compared with LNG-IUS, tranexamic acid generated fewer QALYs at a greater cost.[45]

## Conclusion

Tranexamic acid 3.9–4 g/day for 4–5 days is an effective treatment for HMB. It significantly improves QOL relative to placebo or norethisterone, and is significantly more effective in reducing MBL than placebo, NSAIDs, oral cyclical luteal phase progestins, or etamsylate. The levonorgestrel-releasing intrauterine system reduces MBL significantly more than tranexamic acid. An oral progestin administered for 21 days per cycle might be as equally effective in reducing MBL as tranexamic acid, but a significantly larger proportion of women tend to discontinue the treatment due to side effects or lack of response. The presence of moderate-sized uterine fibroids does not seem to compromise the efficacy of tranexamic acid. Tranexamic acid is well tolerated and has a favorable safety profile. Adverse effects are few and they are mainly mild to moderate. The incidence of adverse gastrointestinal effects with the new oral formulation is comparable with that of placebo; even with the older preparations, no strong evidence supports an increase in adverse gastrointestinal effects with the use of tranexamic acid relative to placebo. Thromboembolic events have not been reported in treatment studies, and to date, data from population-based studies do not support the increase in incidence of venous thromboembolisms with the use of tranexamic acid. Treatment of HMB with tranexamic acid seems cost-effective compared with no treatment or NSAIDs, but not when compared with LNG-IUS. Tranexamic acid is non-hormonal, easy to use when needed, and exerts its effect fast. Potential complications caused by surgical procedures can be avoided by favoring medical therapy for HMB.

Studies comparing tranexamic acid with combined oral contraceptives or the combination of tranexamic acid and an NSAID for the treatment of heavy menstrual bleeding are lacking.

## Disclosure

Henri Leminen reports no conflicts of interest. Ritva Hurskainen has received lecture fees from different pharmaceutical companies. No specific funding was obtained. The authors alone are responsible for the content and writing of this paper.

## References

1. Liu Z, Doan QV, Blumenthal P, Dubois RW. A systematic review evaluating health-related quality of life, work impairment, and health-care costs and utilization in abnormal uterine bleeding. *Value Health*. 2007;10(3):183–194.
2. Rees M. Menorrhagia. *Br Med J (Clin Res Ed)*. 1987;294(6574):759–762.
3. Hallberg L, Högdahl AM, Nilsson L, Rybo G. Menstrual blood loss–a population study. Variation at different ages and attempts to define normality. *Acta Obstet Gynecol Scand*. 1966;45(3):320–351.
4. Wyatt KM, Dimmock PW, Walker TJ, O'Brien PM. Determination of total menstrual blood loss. *Fertil Steril*. 2001;76(1):125–131.
5. http://www.fda.gov [homepage on the Internet]. US Food and Drug Administration. Drugs@FDA: Lysteda (tranexamic acid) label information. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022430s002lbl.pdf. Accessed March 19, 2012.
6. Wellington K, Wagstaff AJ. Tranexamic acid: A review of its use in the management of menorrhagia. *Drugs*. 2003;63(13):1417–1433.
7. Taparia M, Cordingley FT, Leahy MF. Pulmonary embolism associated with tranexamic acid in severe acquired haemophilia. *Eur J Haematol*. 2002;68(5):307–309.
8. Woo KS, Tse LK, Woo JL, Vallance-Owen J. Massive pulmonary thromboembolism after tranexamic acid antifibrinolytic therapy. *Br J Clin Pract*. 1989;43(12):465–466.
9. Dawood M, Huang J. Uterine vascular function and menstruation. *Curr Obstet Gynaecol*. 1998;8(2):66–72.
10. Markee JE. Morphological basis for menstrual bleeding; relation of regression to the initiation of bleeding. *Bull N Y Acad Med*. 1948;24(4):253–268.

11. Rogers PA, Lederman F, Taylor N. Endometrial microvascular growth in normal and dysfunctional states. *Hum Reprod Update*. 1998;4(5):503–508.
12. Ferenczy A, Bertrand G, Gelfand MM. Proliferation kinetics of human endometrium during the normal menstrual cycle. *Am J Obstet Gynecol*. 1979;133(8):859–867.
13. Smith SK, Abel MH, Kelly RW, Baird DT. Prostaglandin synthesis in the endometrium of women with ovular dysfunctional uterine bleeding. *Br J Obstet Gynaecol*. 1981;88(4):434–442.
14. Wang IY, Fraser IS, Barsamian SP, et al. Endometrial lysosomal enzyme activity in ovulatory dysfunctional uterine bleeding, IUCD users and post-partum women. *Mol Hum Reprod*. 2000;6(3):258–263.
15. Rybo G. Plasminogen activators in the endometrium. II. Clinical aspects. Variation in the concentration of plasminogen activators during the menstrual cycle and its relation to menstrual blood loss. *Acta Obstet Gynecol Scand*. 1966;45(4):429–450.
16. Hefnawi F, Saleh A, Kandil O, El-Sheikha Z, Hassanein M, Askalani H. Fibrinolytic activity of menstrual blood in normal and menorrhagic women and in women wearing the lippes loop and the cu-T (200). *Int J Gynaecol Obstet*. 1979;16(5):400–407.
17. Gleeson NC, Buggy F, Sheppard BL, Bonnar J. The effect of tranexamic acid on measured menstrual loss and endometrial fibrinolytic enzymes in dysfunctional uterine bleeding. *Acta Obstet Gynecol Scand*. 1994;73(3):274–277.
18. Dockeray CJ, Sheppard BL, Daly L, Bonnar J. The fibrinolytic enzyme system in normal menstruation and excessive uterine bleeding and the effect of tranexamic acid. *Eur J Obstet Gynecol Reprod Biol*. 1987;24(4):309–318.
19. Benoni G, Björkman S, Fredin H. Application of pharmacokinetic data from healthy volunteers for the prediction of plasma concentrations of tranexamic acid in surgical patients. *Clin Drug Invest*. 1995;10(5):280–287.
20. Eriksson O, Kjellman H, Pilbrant A, Schannong M. Pharmacokinetics of tranexamic acid after intravenous administration to normal volunteers. *Eur J Clin Pharmacol*. 1974;7(5):375–380.
21. Pilbrant A, Schannong M, Vessman J. Pharmacokinetics and bioavailability of tranexamic acid. *Eur J Clin Pharmacol*. 1981;20(1):65–72.
22. http://www.ema.europa.eu [homepage on the Internet]. European Medicines Agency. Committee for proprietary medicinal products (CPMP) opinion following an article 10 referral: CYKLO-f (tranexamic acid). Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Cyklo-f/human_referral_000097.jsp&mid=WC0b01ac0580024e9a#. Accessed March 19, 2012.
23. Andersch B, Milsom I, Rybo G. An objective evaluation of flurbiprofen and tranexamic acid in the treatment of idiopathic menorrhagia. *Acta Obstet Gynecol Scand*. 1988;67(7):645–648.
24. Bonnar J, Sheppard BL. Treatment of menorrhagia during menstruation: Randomised controlled trial of ethamsylate, mefenamic acid, and tranexamic acid. *BMJ*. 1996;313(7057):579–582.
25. Callender ST, Warner GT, Cope E. Treatment of menorrhagia with tranexamic acid. A double-blind trial. *Br Med J*. 1970;4(5729):214–216.
26. Freeman EW, Lukes A, VanDrie D, Mabey RG, Gersten J, Adomako TL. A dose-response study of a novel, oral tranexamic formulation for heavy menstrual bleeding. *Am J Obstet Gynecol*. 2011;205(4):319.e1–319.e7.
27. Kouides PA, Byams VR, Philipp CS, et al. Multisite management study of menorrhagia with abnormal laboratory haemostasis: A prospective crossover study of intranasal desmopressin and oral tranexamic acid. *Br J Haematol*. 2009;145(2):212–220.
28. Kriplani A, Kulshrestha V, Agarwal N, Diwakar S. Role of tranexamic acid in management of dysfunctional uterine bleeding in comparison with medroxyprogesterone acetate. *J Obstet Gynaecol*. 2006;26(7):673–678.
29. Lukes AS, Moore KA, Muse KN, et al. Tranexamic acid treatment for heavy menstrual bleeding: A randomized controlled trial. *Obstet Gynecol*. 2010;116(4):865–875.
30. Milsom I, Andersson K, Andersch B, Rybo G. A comparison of flurbiprofen, tranexamic acid, and a levonorgestrel-releasing intrauterine contraceptive device in the treatment of idiopathic menorrhagia. *Am J Obstet Gynecol*. 1991;164(3):879–883.
31. Nilsson L, Rybo G. Treatment of menorrhagia with an antifibrinolytic agent, tranexamic acid (AMCA): A double blind investigation. *Acta Obstet Gynecol Scand*. 1967;46(4):572–580.
32. Preston JT, Cameron IT, Adams EJ, Smith SK. Comparative study of tranexamic acid and norethisterone in the treatment of ovulatory menorrhagia. *Br J Obstet Gynaecol*. 1995;102(5):401–406.
33. Vermylen J, Verhaegen-Declercq ML, Verstraete M, Fierens F. A double blind study of the effect of tranexamic acid in essential menorrhagia. *Thromb Diath Haemorrh*. 1968;20(3):583–587.
34. Hallberg L, Nilsson L. Determination of menstrual blood loss. *Scand J Clin Lab Invest*. 1964;16:244–248.
35. Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *Br J Obstet Gynaecol*. 1990;97(8):734–739.
36. Janssen CA, Scholten PC, Heintz AP. A simple visual assessment technique to discriminate between menorrhagia and normal menstrual blood loss. *Obstet Gynecol*. 1995;85(6):977–982.
37. Lukes AS, Muse K, Richter HE, Moore KA, Patrick DL. Estimating a meaningful reduction in menstrual blood loss for women with heavy menstrual bleeding. *Curr Med Res Opin*. 2010;26(11):2673–2678.
38. Winkler UH. The effect of tranexamic acid on the quality of life of women with heavy menstrual bleeding. *Eur J Obstet Gynecol Reprod Biol*. 2001;99(2):238–243.
39. Muse K, Lukes AS, Gersten J, Waldbaum A, Mabey RG, Trott E. Long-term evaluation of safety and health-related quality of life in women with heavy menstrual bleeding treated with oral tranexamic acid. *Womens Health (Lond Engl)*. 2011;7(6):699–707.
40. Lethaby A, Farquhar C, Cooke I. Antifibrinolytics for heavy menstrual bleeding. *Cochrane Database Syst Rev*. 2000;4:CD000249.
41. Berntorp E, Follrud C, Lethagen S. No increased risk of venous thrombosis in women taking tranexamic acid. *Thromb Haemost*. 2001;86(2):714–715.
42. Rybo G. Tranexamic acid therapy: Effective treatment in heavy menstrual bleeding. Clinical update on safety. *Therapeutic Advances*. 1991;4:1–8.
43. Sundström A, Seaman H, Kieler H, Alfredsson L. The risk of venous thromboembolism associated with the use of tranexamic acid and other drugs used to treat menorrhagia: A case-control study using the General Practice Research Database. *BJOG*. 2009;116(1):91–97.
44. Kirschner R. A cost-benefit analysis of different therapeutic methods in menorrhagia. *Tidsskr Nor Laegeforen*. 1995;115(5):618–621.
45. National Collaborating Centre for Women's and Children's Health (UK). *Heavy Menstrual Bleeding*. London: RCOG Press; 2007.

*Journal of Thrombosis and Haemostasis*, **12**: 1494–1502 DOI: 10.1111/jth.12654

**ORIGINAL ARTICLE**

# Tranexamic acid for epistaxis in hereditary hemorrhagic telangiectasia patients: a European cross-over controlled trial in a rare disease

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**To cite this article:** Gaillard S, Dupuis-Girod S, Boutitie F, Rivière S, Morinière S, Hatron PY, Manfredi G, Kaminsky P, Capitaine AL, Roy P, Gueyffier F, Plauchu H, for the ATERO Study Group. Tranexamic acid for epistaxis in hereditary hemorrhagic telangiectasia patients: a European cross-over controlled trial in a rare disease. *J Thromb Haemost* 2014; **12**: 1494–502.

**Summary.** *Background:* Hereditary hemorrhagic telangiectasia (HHT) is a genetic disorder associated with abnormal angiogenesis and disabling epistaxis. Tranexamic acid (TA) has been widely used in the treatment of these severe bleeds but with no properly designed trial. *Objectives:* To demonstrate the efficacy of TA in epistaxis in HHT patients and to explore its safety of use. *Patients/Methods:* A randomized, placebo-controlled, double-blind, cross-over trial was conducted. Participants were randomized to receive TA (3 g a day) then placebo or the opposite sequence. The main analysis compared intra-individual mean duration of epistaxis under TA vs. placebo on a log scale. The primary outcome was the mean duration of epistaxis per month, assessed with specific grids to be completed by participants. The number of epistaxis episodes was recorded as a secondary outcome. *Results:* A total of 118 randomized patients contributed to the statistical analysis. The mean duration of epistaxis per month was significantly shorter with TA than placebo (0.19 on the log scale; SD = 0.07; $P = 0.005$), corresponding to a decrease of 17.3% (15.7 min) in the duration of epistaxis per month (CI 95%, 5.5–27.6). The median number of epistaxis episodes per month was 22.1 episodes in the placebo arm vs. 23.3 episodes in the TA arm. No thrombophlebitis was observed. *Conclusions:* In the ATERO study, we demonstrated a significant decrease in the duration of epistaxis in HHT patients taking TA. No safety issues were recorded in our cohort of patients.

**Keywords**: epistaxis; hereditary hemorrhagic telangiectasia; Osler-Rendu disease; randomized controlled trial; tranexamic acid.

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Received 22 October 2013
Manuscript handled by: P. de Moerloose
Final decision: F. R. Rosendaal, 15 June 2014

## Introduction

Hereditary Hemorrhagic Telangectasia (HHT) or Rendu-Osler-Weber disease is a rare but ubiquitous condition that affects about 1 in 8000 people [1]. This genetic disorder is characterized by a dominant autosomal hereditary transmission of telangiectasis and arteriovenous fistula. Diagnosis is based on the Curaçao criteria and is considered definite if at least three criteria are present. The criteria are: (i) spontaneous and recurrent epistaxis, (iii)

cutaneo-mucous telangiectasia, (iii) family history and (iv) visceral lesions [2,3]. Three genes are associated with HHT: HHT type 1 results from mutations in *ENG* on chromosome 9 (coding for endoglin) and HHT type 2 results from mutations in *ACVRL1* on chromosome 12 (coding for the activin receptor-like kinase 1, ALK-1) [4,5]. Mutations to either of these genes account for most, but not all, clinical cases. In addition, mutations in *MADH4* (encoding SMAD4) that cause juvenile polyposis/HHT overlap syndrome have also been described [6].

The most apparent expression of the disorder is the occurrence of spontaneous, repeated epistaxis [7]. These epistaxis episodes can be severe and life-threatening. They are often the cause of chronic anemia, and can require continuous iron deficiency treatment and multiple transfusions.

The management of this major symptom is not standardized and often requires local ear, nose and throat (ENT) treatments or medication, the efficacy of which is not sufficiently documented [8,9].

One of these treatments is tranexamic acid (TA), an anti-fibrinolytic agent that has been evaluated several times in poorly designed clinical trials. This has led to wide-scale prescriptions of TA, which seems to be effective in some patients, but with a low level of evidence [10–12]. TA is a competitive inhibitor of plasminogen, reducing the conversion of plasminogen into plasmin (fibrinolysin). Plasmin degrades fibrin clots, fibrinogen and other plasma proteins, including the procoagulant factors V and VIII. TA also directly inhibits plasmin activity, but at higher doses. In an open label study on 14 HHT subjects, Fernandez *et al.* showed that TA stimulates the expression of ALK-1 and endoglin [13].

A high rate of thrombophlebitis was recently reported in HHT patients and the former concept of coagulation disorders or thrombosis led to a restriction in the eligibility criteria and a systematic search for a potential iatrogenic effect [14,15]. It is essential that these prescriptions be based on more reliable data, thereby providing clearer information to patients regarding the expected benefits. The objective of our study was to assess the efficacy of TA in epistaxis in HHT and to explore its safety of use.

## Methods

### *Patients*

Male and female patients with a confirmed diagnosis of HHT, aged 18–80 years and suffering from epistaxis (more than 28 episodes a month or more than 60 min a month as a mean over a 3-month period) were eligible to participate. The main exclusion criteria were: an expected lack of adherence to the daily treatment; a formal indication for TA or a planned ENT treatment; contra-indications to TA such as a history of convulsions, arterial or venous thrombosis, or positivity of venous Doppler ultrasound of the lower limbs; and serum creatinine > 250 μM. Patients treated with anticoagulants or antiplatelet drugs, or those with fibrinolytic conditions following consumption coagulopathy, were not allowed to participate in the study.

Patients had to agree to withdraw their current TA treatment at least 15 days prior to randomization. Informed written consent was obtained from each participant.

### *Study design and oversight*

The ATERO study was a multicenter, randomized, placebo-controlled, double-blind, cross-over trial. It was investigator designed. Twelve French and Italian sites recruited patients for the study. The study was approved by ethics committees recognized by each of the participating centers. The study was declared at the French Agency for the Safety of Health Products (AFSSAPS), registered on ClinicalTrials.gov with the number NCT00355108, and conducted in accordance with the European Guidance for Good Clinical Practice and the Declaration of Helsinki.

### *Randomization and masking*

Potentially eligible patients were identified during a screening period, followed by a 15-day run-in period under placebo. Compliance with treatment and the ability to complete the epistaxis grids were evaluated over this period. Patients were then randomly assigned to a sequence of treatments: TA followed by placebo or the opposite sequence. Size 2 and 4 permutation blocks were used and mixed at random. Randomization was stratified according to study site. A centralized fax system was used to blindly assign treatment sequences. Randomization sequences were generated using SAS software.

### *Study medication and assessment*

Patients received TA then placebo or placebo then TA orally at a dose of 3 g a day (1.5 g twice daily). The placebo used in the ATERO study was indistinguishable from the active treatment. Each cross-over period lasted 3 months.

The duration and number of episodes of epistaxis were recorded by the patients using epistaxis grids throughout the study. Study diaries were used and treatment units were counted to assess compliance with study treatment. A venous Doppler ultrasound of the lower limbs was performed at each visit to search for any signs of thrombophlebitis. Hemoglobin levels were recorded and serum creatinine level was assessed to adjust the study treatment dose.

In compliance with the intent-to-treat (ITT) analysis of the primary endpoint, patients who withdrew early were followed-up until the end of the study.

### Outcome measures

The primary efficacy outcome was the mean duration of nose bleeds per month. The epistaxis grid created by the French Association for Rendu-Osler Disease (AMRO France) and the ENT experts from the French Rendu-Osler Network was systematically given to patients to assess our primary endpoint. Other efficacy outcomes were: the mean number of epistaxis episodes per month recorded on the epistaxis grids; and the patient's improvement assessed by monitoring changes in hemoglobin levels throughout the study.

Tolerance of the treatment was assessed by the incidence of adverse events, particularly infections and abnormalities identified on the venous Doppler ultrasound of the lower limbs.

Quality of life was assessed at each study visit using the Visual Analogical Scale. We asked the participants two questions: one on how satisfied they were with study treatment received during the period (1 = totally dissatisfied to 10 = fully satisfied) and one estimating how comfortable the subject's life was during the period (1 = very poor, 10 = excellent). Questions were asked at baseline and at the end of each cross-over period.

An independent data and safety monitoring board periodically reviewed study outcomes.

### Statistical analysis

The primary hypothesis was that TA reduces the mean intra-individual change in monthly duration of epistaxis by 20% (0.223 on a log scale) compared with placebo. With an intra-individual variance of 0.513 on the log scale, 213 patients were needed to detect this difference with a 90% power at the 5% level.

Epistaxis episodes that were recorded after the theoretical 90-day period were not included in the analysis. To reduce the potential carry-over effect between periods, the first 7 days of each period were excluded from the analysis. Statistical analysis considered all enrolled subjects in their allocated treatment sequence, but was limited to patients who could be assessed for the primary outcome during both treatment periods (modified intent-to-treat analysis, m-ITT).

Each cross-over period was divided into three 30-day intervals. For each patient, the total duration of epistaxis in each interval was divided by the number of daily records and multiplied by 30. The duration of epistaxis per month was then transformed into a logarithm for analysis, with null durations considered as 1 day.

The main analysis compared the intra-individual mean duration of epistaxis under TA vs. placebo using paired data (two periods per patient). Because of the intra-individual variability of repeated measurements (three measurements per period, two periods per patient), a mixed-effect linear regression model was used to estimate treatment effect. Patients were entered into the model as a random effect and the period and treatment as fixed effects.

In order to estimate the rate of epistaxis, the total number of epistaxis episodes was cumulated within each 30-day interval. This outcome was assumed to follow a Poisson distribution, and was analyzed using a generalized linear mixed-effect model, including two fixed effects (treatment and period) and a random patient effect. A log link function was used to relate the outcome to the linear predictor (covariables). An offset was added to the linear predictor to account for the number of epistaxis measurements recorded during the interval (transformed into a log scale).

SAS software was used for all statistical analyses.

## Results

### Patients

Even though the recruitment target (213 randomized patients) was not met at the end of the planned enrolment period, we stopped recruiting patients because not enough patients met eligibility criteria, and the treatment units reached their expiration date. The flow diagram of the study is presented in Fig. 1. Between September 2006 and December 2009, 170 eligible patients entered the run-in period and 135 patients met randomization criteria. Of the non-randomized patients, seven had insufficient epistaxis and one had an abnormal ultrasound with suspected thrombosis. After randomization, 57 patients completed the 'TA-then-placebo' sequence and 61 patients the 'placebo-then-TA' sequence. One hundred and eighteen patients were included in the m-ITT analysis. Seventeen patients were not analyzed. The main reason was the non-availability of epistaxis grids or patients lost to follow-up.

The baseline characteristics of the participants are summarized in Table 1. The mean age of the patients who completed the study was 51.7 years (range, 19.8–73.5 years). A total of 57 (48.5%) were female; 30.5% of the patients had pulmonary arteriovenous malformations, 36.4% had hepatic arteriovenous malformations; 15.2% had digestive arteriovenous malformations and 2.5% had brain arteriovenous malformations.

Following the Summary of the Product Characteristics, only two patients under TA and three patients under placebo received a dose of 1.5 g a day, because of a creatinine level of more than 120 μM. In terms of compliance, 21.2% of patients missed at least 1 day of study treatment under TA vs. 23.7% under placebo ($P = 0.64$). In non-compliers, the mean number of missed treatment days was 8.1 days under TA vs. 6.1 days under placebo ($P = 0.44$).

### Efficacy assessment

The results of the model did not show any interaction (carryover effect) between the period and treatment

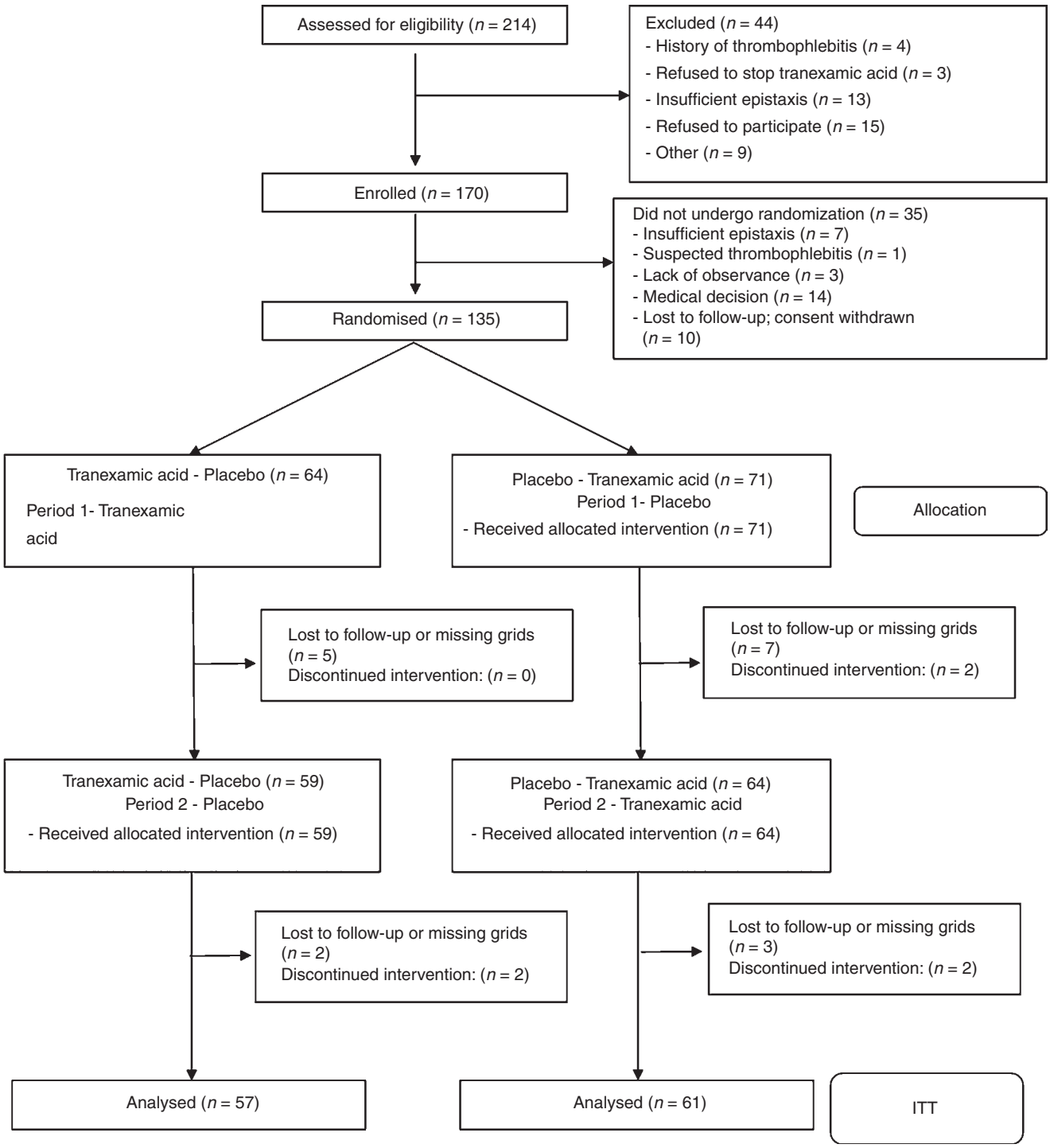


**Fig. 1.** Study flow chart.

effects. There was no period effect detected in the model without interaction. The mean duration of epistaxis per month was estimated to be significantly shorter under TA than placebo (0.19 on the log scale; SD = 0.07; $P = 0.005$). This difference corresponds to a decrease of 17.3% in the duration of epistaxis per month (95% CI, 5.5–27.6) (Table 2).

Over the two periods, the median number (first to third quartiles) of epistaxis episodes per month was 22.1 (13.4–35.1) episodes in the placebo arm vs. 23.3 (11.2–36.5) episodes in the TA arm. The Poisson model on paired data revealed a significant 5.5% decrease in the rate of episodes (95% CI, 2.5–8.1%) in patients under TA as compared with placebo ($P = 0.0005$).

**Table 1** Characteristics of patients at baseline

| | | Sequence of treatment | | |
|---|---|---|---|---|
| | | Tranexamic acid/placebo | Placebo/tranexamic acid | *P* value |
| | *n* | 57 | 61 | – |
| Age | Mean (±SD) years | 53.8 (±11.3) | 49.8 (±11.4) | 0.05 |
| Sex | Male *n* (%) | 29 (50.9) | 32 (52.5) | 1.00 |
| HHT characteristics | Pulmonary AVM (%) | 20 (35.1) | 16 (26.2) | 0.48 |
| | Hepatic AVM (%) | 22 (38.6) | 21 (34.4) | 0.63 |
| | Digestive AVM (%) | 8 (14.0) | 10 (16.4) | 0.85 |
| | Brain AVM (%) | 1 (1.8) | 2 (3.3) | 1.00 |
| DNA (type of mutation) | Missing | 22 | 24 | 1.00 |
| | No mutation (%) | 1 (2.9) | 2 (5.4) | – |
| | ALK 1 mutation (%) | 27 (77.1) | 28 (75.7) | – |
| | ENG mutation (%) | 7 (20.0) | 7 (18.9) | – |
| Age at first epistaxis | Mean (±SD) years | 18.74 (13.24) | 17.35 (11.64) | 0.74 |
| Hemoglobin level | Mean (±SD) g $L^{-1}$ | 123.04 (21.23) | 127.30 (20.76) | 0.32 |
| History of blood transfusion | Yes (%) | 19 (33.3) | 16 (26.2) | 0.43 |
| Iron deficiency treatment | Yes (%) | 41 (71.9) | 37 (60.7) | 0.24 |
| Serum creatinine level | Mean (±SD) μM | 79.57 (14.86) | 80.30 (17.45) | 0.81 |

**Table 2** Efficacy endpoints

| | Period | | | | | |
|---|---|---|---|---|---|---|
| | 1 | | 2 | | All | |
| Duration of epistaxis per month (min) | Placebo | Tranexamic acid | Placebo | Tranexamic acid | Placebo | Tranexamic acid |
| *N* | 61 | 57 | 57 | 61 | 118 | 118 |
| Median | 112.1 | 129.1 | 158.7 | 90.2 | 121.9 | 106.2 |
| 1st quartile | 65.1 | 72.7 | 80.6 | 38.4 | 69.4 | 52.6 |
| 3rd quartile | 208.3 | 226.8 | 236.5 | 195.9 | 231.1 | 212.8 |

| Intra-individual change in duration of epistaxis per month (log) from period 1 to period 2 | Tranexamic acid - placebo | Placebo - tranexamic acid |
|---|---|---|
| 2 | 61 | 57 |
| 2 | −0.11 | 0.31 |
| 2 | 0.95 | 1.08 |

| | Period | | | | | |
|---|---|---|---|---|---|---|
| | 1 | | 2 | | All | |
| Number of epistaxis episodes per month | Placebo | Tranexamic acid | Placebo | Tranexamic acid | Placebo | Tranexamic acid |
| *N* | 61 | 57 | 57 | 61 | 118 | 118 |
| Median | 22.1 | 25.7 | 22.1 | 21.0 | 22.1 | 23.3 |
| 1st quartile | 13.7 | 12.2 | 12.9 | 10.5 | 13.4 | 11.2 |
| 3rd quartile | 34.9 | 36.6 | 35.1 | 34.7 | 35.1 | 36.5 |

Hemoglobin levels did not vary over time, with either TA or placebo. Hemoglobin remained high at a mean value (SD) of 125.7 (18.9) g $L^{-1}$ for TA and 127.2 (19.4) g $L^{-1}$ for placebo, with no variation between periods (Table 3). About two-thirds of the patients required iron-replacement therapy during the study, with no difference between groups (Table 3). ENT medications were used to treat epistaxis in 1.7% of patients taking TA vs. 3.4% of patients taking placebo.

### *Safety assessment*

Table 3 summarizes the non-serious and serious adverse events detected during the study. We did not detect any thrombophlebitis in patients enrolled in this study. There was no difference in the use of iron infusions during study periods (Table 3). During the first period of the study, more patients had vertigo with TA ($n = 10$; 17.5%) than with placebo ($n = 2$; 3.3%); ($P = 0.01$). During the

**Table 3** Evolution of secondary endpoints: hemoglobin level, safety assessments

| | Period 1 | | | Period 2 | | |
|---|---|---|---|---|---|---|
| | Placebo ($n$ = 61) | Tranexamic acid ($n$ = 57) | $P$-value | Placebo ($n$ = 61) | Tranexamic acid ($n$ = 57) | $P$-value |
| Hemoglobin and anemia | | | | | | |
| Hemoglobin level | 127.3 (20.1) | 124.6 (18.5) | 0.49 | 127.2 (18.7) | 126.8 (19.4) | 0.94 |
| Mean (SD) | | | | | | |
| Required infusion (%) | 5 (8.2) | 4 (7.0) | 1.00 | 5 (8.8) | 2 (3.3) | 0.26 |
| Required ENT treatment (%) | 2 (3.3) | 1 (1.8) | 1.00 | 2 (3.5) | 1 (1.6) | 0.61 |
| Required iron therapy (%) | 42 (68.9) | 36 (63.2) | 0.56 | 41 (71.9) | 39 (63.3) | 0.43 |
| Quality of life | | | | | | |
| Satisfaction with study treatment (median, first to third quartiles) | 5.5 (3.0–7.0) | 5.0 (3.0–7.0) | 0.59 | 5.5 (5.0–8.0) | 6.0 (3.0–8.0) | 0.99 |
| Life comfort (median, first to third quartiles) | 6.0 (3.0–8.0) | 5.0 (4.0–7.0) | 0.46 | 5.5 (5.0–7.0) | 6.0 (3.0–8.0) | 0.53 |
| Adverse events | | | | | | |
| Allergies (%) | 1 (1.6) | 1 (1.8) | 1.00 | 1 (1.8) | 0 (0) | 0.48 |
| Deep venous thrombosis (%) | 0 (0) | 0 (0) | – | 0 (0) | 0 (0) | – |
| Superficial venous thrombosis (%) | 0 (0) | 0 (0) | – | 0 (0) | 0 (0) | – |
| Diarrhea (%) | 3 (4.9) | 8 (14.0) | 0.12 | 3 (5.3) | 11 (18.0) | 0.04 |
| Vomiting (%) | 3 (4.9) | 2 (3.5) | 1.00 | 0 (0) | 2 (3.3) | 0.50 |
| Other gastric disorders (%) | 6 (9.8) | 9 (15.8) | 0.41 | 6 (10.5) | 6 (9.8) | 1.00 |
| Vertigo (%) | 2 (3.3) | 10 (17.5) | 0.01 | 4 (7.0) | 4 (6.6) | 1.00 |
| Lipothymia (%) | 2 (3.3) | 1 (1.8) | 1.00 | 0 (0) | 2 (3.3) | 0.50 |
| Convulsions (%) | 0 (0) | 0 (0) | – | 0 (0) | 0 (0) | – |
| Other adverse events (%) | 19 (31.1) | 20 (35.1) | 0.70 | 13 (22.8) | 21 (34.4) | 0.22 |
| Serious adverse events (%) | 5 (8.2) | 5 (8.8) | 1.00 | 6 (10.5) | 4 (6.6) | 0.52 |

second period, there were more cases of diarrhea ($n$ = 11; 18%) with TA than with placebo ($n$ = 3; 5.3%) ($P$ = 0.04). Both events were expected and not more frequent than in the Summary of the Product Characteristics for TA.

### *Quality of life assessment*

No statistical difference in quality of life was found when assessed before, at the end of period 1 or at the end of period 2 (Table 3).

## Discussion

In this prospective randomized cross-over trial, we demonstrated a decrease in the mean duration of epistaxis in HHT patients receiving TA. There was evidence of a significant and clinically moderate treatment effect on both the duration and number of epistaxis episodes per month. The impact of epistaxis on patients' social life is major, so even a moderate improvement is important for the patient. Efficacy of TA in HHT patients had never been studied in a well-designed randomized control trial before. Our study was designed to take into account the inter-individual variability of treatment response, using a cross-over design. The randomization method ensured that study treatment allocation was unpredictable. The double blind procedure was maintained throughout the study for all patients, ensuring an independent evaluation of epistaxis. All analyses were performed on an m-ITT basis and the model applied took into account repeated data over two periods.

In addition to our results, several recent studies have explored the efficacy and safety of using TA in various conditions.

A systematic review of the use of TA in upper gastrointestinal bleeding suggested that TA could reduce all causes of mortality [16]. In the CRASH-2 study, early administration of TA to trauma patients was shown to reduce the risk of death from bleeding (4.9% in the TA group vs. 5.7% in the placebo group; relative risk, 0.85; 95% CI, 0.76–0.96; $P$ = 0.0077) [17].

No cases of thrombophlebitis were detected in the ATERO study, even though they occurred in several French cohorts of patients and are described in a published report [14,18]. We carefully assessed this point during the study. No particular safety issue was encountered. However, the study was not designed to assess this point so we cannot exclude a small increase in risk. In a Spanish study, 14 HHT patients with severe epistaxis were treated with oral TA for a 2- to 25-month period. None of them presented any TA-derived side-effects [13]. In the CRASH-2 study, the risk of vaso-occlusive events was not significantly different between TA and placebo as some events occurred in both arms [17]. Safety data on the use of TA were reported in three trials included in a systematic review of TA for upper gastrointestinal bleeding by Gluud *et al*. [16]. Overall, five out of 522 patients (two myocardial infarctions, two pulmonary embolisms and one cerebral infarction) randomized to TA and four

**Table 4** Distribution of excluded patients per group

| Study completed Frequency % | Nature of treatment | | |
|---|---|---|---|
| | Exacyl-placebo | Placebo-exacyl | Total |
| No | 7 | 10 | 17 |
| | 10.9 | 14.1 | |
| Yes | 57 | 61 | 118 |
| | 89.1 | 85.9 | |
| Total | 64 | 71 | 135 |

| Statistics | DDL | Value | Prob |
|---|---|---|---|
| Chi-square | 1 | 0.3029 | 0.5821 |
| Likelihood ratio test | 1 | 0.3047 | 0.5810 |
| Continuity-adjusted chi-square | 1 | 0.0844 | 0.7714 |
| Mantel-Haenszel chi-square | 1 | 0.3006 | 0.5835 |
| Phi coefficient | | −0.0474 | |
| Contingency coefficient | | 0.0473 | |
| V of Cramer | | −0.0474 | |

| Fisher exact test | |
|---|---|
| Cellul (1,1) Frequency (F) | 7 |
| Pr ≤ F one-sided (left) | 0.3873 |
| Pr ≥ F one-sided (right) | 0.7903 |
| Probability of the table (*P*) | 0.1776 |
| Pr ≤ *P* two-sided | 0.6144 |

Sample size = 135.

out of 526 patients (two myocardial infarctions and two cerebral infarctions) in the placebo group experienced serious thromboembolic events ($P = 0.36$). Six patients in the TA group vs. two patients in the placebo group developed deep venous thrombosis ($P = 0.96$) [16]. In addition, Kakar *et al*. did not observe any deep vein thrombosis in their 50 randomized patients who underwent knee arthroplasty and received either intravenous TA or placebo [19]. Alvarez *et al*. also confirmed the absence of thromboembolic complications in 46 patients who underwent total knee arthroplasty and were randomized to the TA arm [20]. The WOMAN trial is a large, randomized double-blind control trial, currently recruiting postpartum hemorrhage patients to quantify the effects of TA. This large-scale trial should also provide more information on the safety of using TA [21].

Our study had several limitations. The distribution of the primary endpoint revealed a certain number of extreme values during trial follow-ups and several patients with no data available for epistaxis endpoints could not be analyzed. The ATERO study used an mITT analysis instead of an ITT analysis because of missing data for the primary endpoint. In a cross-over design, this method is less deleterious than in parallel groups. The distribution of subjects excluded from analysis per group of treatment showed that exclusion happened equally in both arms (Table 4). We also performed a post-hoc analysis to compare analyzed patients with patients excluded from the mITT analysis (Tables 5). Patients excluded were similar to analyzed patients in terms of main characteristics at inclusion. Patients excluded from analysis had a significantly lower hemoglobin level at inclusion.

A limited number of patients with quite severe epistaxis participated in the ATERO study. We did not reach our recruitment target, so our results do not entirely reflect

**Table 5** Comparison of patients excluded from analysis and analyzed patients

| | | Study completed | | |
|---|---|---|---|---|
| | | No | Yes | *P* value |
| | *n* | 17 | 118 | – |
| Age | Mean (±SD) years | 51.8 (±9.7) | 51.7 (±11.5) | 0.99 |
| Sex | Male *n* (%) | 11 (64.7) | 61 (51.7) | 0.44 |
| HHT characteristics | Missing | 1 | 0 | |
| | Pulmonary AVM (%) | 2 (12.5) | 36 (30.5) | 0.20 |
| | Hepatic AVM (%) | 7 (43.8) | 43 (36.4) | 0.77 |
| | Digestive AVM (%) | 1 (6.3) | 18 (15.3) | 0.66 |
| | Brain AVM (%) | 0 (0.0) | 3 (2.5) | 1.00 |
| DNA (type of mutation) | Missing | 12 | 46 | 1.00 |
| | No mutation (%) | 0 (0.0) | 3 (4.2) | – |
| | ALK 1 mutation (%) | 4 (80.0) | 55 (76.4) | – |
| | ENG mutation (%) | 1 (20.0) | 14 (19.4) | – |
| Age at first epistaxis | Missing | 0 | 1 | 0.78 |
| | Mean (±SD) years | 19.00 (14.56) | 18.03 (12.41) | |
| Hemoglobin level | Missing | 2 | 1 | 0.03 |
| | Mean (±SD) g $L^{-1}$ | 113.13 (21.29) | 125.26 (21.00) | |
| History of blood transfusion | Missing | 3 | 0 | 0.36 |
| | Yes (%) | 6 (42.9) | 35 (29.7) | |
| Iron deficiency treatment | Missing | 3 | 0 | 0.77 |
| | Yes (%) | 10 (71.4) | 78 (66.1) | |
| Serum creatinine level | Missing | 2 | 1 | 0.43 |
| | Mean (±SD) μM | 78.13 (22.11) | 79.95 (16.20) | |

the variability of expression of this symptom in HHT patients. Patients at risk of vaso-occlusive events were not included in this trial. Therefore, the benefit/risk ratio cannot be extrapolated to this population, which represents 7% of HHT patients [14].

Finally, the study failed to meet all of its endpoints, due to slow recruitment related to the 'non-inclusion criteria'.

In conclusion, our randomized control trial demonstrated the significant but moderate efficacy of TA in HHT patients suffering from epistaxis. To date, the role of TA treatment has still not been clearly defined. Epistaxis is one of the most important symptoms of the disease, but none of the treatments used in epistaxis has yet proven to be effective. This result is a step in the right direction towards improving the informed management of epistaxis in HHT patients [22]. The intensity of the effect and its clinical relevance could be discussed. The next step would be to identify the determinants for the response to TA, but this will require a larger thus more powerful dataset. TA safety of use must still be confirmed in trials that are large and powerful enough to assess this concern.

## Addendum

H. Plauchu, F. Gueyffier, S. Rivière and P. Roy conceived and designed the study. The study was managed by H. Plauchu, S. Gaillard and S. Dupuis-Girod. Recruitment was performed by S. Rivière, F. Faure, O. Merrot, S. Morinière, P. Magro, O. Boute, P.-Y. Hatron, E. Buscarini, G. Manfredi, R. Jankowski, P. Kaminsky, L. Pruna, A.-L. Capitaine, B. Gilbert-Dussardier, J.-M. Klossek, P. Delaval, R. Corre, E. Babin, J. Perret, M.-F. Carette, V. Franco-Vidal, P. Duffau and J.-R. Harlé. Results were analyzed by F. Boutitie and P. Roy and interpreted by F. Gueyffier, H. Plauchu, S. Dupuis-Girod and S. Gaillard. All authors reviewed and revised the first draft report, written by S. Gaillard with assistance from S. Dupuis-Girod, H. Plauchu and F. Gueyffier. All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

## Acknowledgements

The authors would like to thank the study nurses and local clinical investigation/research centers that greatly contributed to the study: N. Berthoux, A. Zamora, C. Goudon, M. Hadid and the CICs of Montpellier, Nancy, Poitiers, Paris St Antoine, Tours and Lille. We would also like to thank K. Neal (supported by the French Cochrane Centre) for proofreading the manuscript. The authors are also grateful to the French Association for Rendu-Osler Disease (AMRO France) for helping us recruit patients and its work on the epistaxis grids.

## Funding

The study was sponsored by Hospices Civils de Lyon (France) and the French Ministry of Health (2005 Hospital Clinical Research Programme (PHRC) grant).

## Ethical approval

The ATERO study was approved by an ethics committee in Lyon, France, Le Comité de Protection des Personnes dans la Recherche Biomédicale Sud-Est III, and an ethics committee in Crema, Italy, Il Comitato Etico dell'Azienda Ospedaliera 'Ospedale Maggiore' di Crema.

## Data sharing

Relevant anonymised patient level data are available upon reasonable request from the authors.

## Disclosure of Conflicts of Interest

The authors state that they have no conflict of interest.

## Appendix

### ATERO Study Group

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## References

1 Bideau A, Plauchu H, Brunet G, Robert J. Epidemiological investigation of Rendu-Osler disease in France: its geographical distribution and prevalence. *Popul* 1989; **44**: 3–22.

2 Shovlin CL, Guttmacher AE, Buscarini E, Faughnan ME, Hyland RH, Westermann CJ, Kjeldsen AD, Plauchu H. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). *Am J Med Genet* 2000; **91**: 66–7.

3 Plauchu H, de Chadarevian JP, Bideau A, Robert JM. Age-related clinical profile of hereditary hemorrhagic telangiectasia in an epidemiologically recruited population. *Am J Med Genet* 1989; **32**: 291–7.

4 McAllister KA, Grogg KM, Johnson DW, Gallione CJ, Baldwin MA, Jackson CE, Helmbold EA, Markel DS, McKinnon WC,

Murrell J. Endoglin, a TGF-beta binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangiectasia type 1. *Nat Genet* 1994; **8**: 345–51.
5 Johnson DW, Berg JN, Baldwin MA, Gallione CJ, Marondel I, Yoon SJ, Stenzel TT, Speer M, Pericak-Vance MA, Diamond A, Guttmacher AE, Jackson CE, Attisano L, Kucherlapati R, Porteous ME, Marchuk DA. Mutations in the activin receptor-like kinase 1 gene in hereditary haemorrhagic telangiectasia type 2. *Nat Genet* 1996; **13**: 189–95.
6 Gallione CJ, Repetto GM, Legius E, Rustgi AK, Schelley SL, Tejpar S, Mitchell G, Drouin E, Westermann CJ, Marchuk DA. A combined syndrome of juvenile polyposis and hereditary haemorrhagic telangiectasia associated with mutations in MADH4 (SMAD4). *Lancet* 2004; **363**: 852–9.
7 Haitjema T, Balder W, Disch FJ, Westermann CJ. Epistaxis in hereditary haemorrhagic telangiectasia. *Rhinology* 1996; **34**: 176–8.
8 Karapantzos I, Tsimpiris N, Goulis DG, van Hoecke H, van Cauwenberge P, Danielides V. Management of epistaxis in hereditary hemorrhagic telangiectasia by Nd:YAG laser and quality of life assessment using the HR-QoL questionnaire. *Eur Arch Otorhinolaryngol* 2005; **262**: 830–3.
9 Folz BJ, Tennie J, Lippert BM, Werner JA. Natural history and control of epistaxis in a group of German patients with Rendu-Osler-Weber disease. *Rhinology* 2005; **43**: 40–6.
10 Klepfish A, Berrebi A, Schattner A. Intranasal tranexamic acid treatment for severe epistaxis in hereditary hemorrhagic telangiectasia. *Arch Intern Med* 2001; **161**: 767.
11 Sabba C, Gallitelli M, Palasciano G. Efficacy of unusually high doses of tranexamic acid for the treatment of epistaxis in hereditary hemorrhagic telangiectasia. *N Engl J Med* 2001; **345**: 926.
12 Lozano M. Tranexamic acid in hereditary hemorrhagic telangiectasia. *N Engl J Med* 2002; **346**: 457.
13 Fernandez-L A, Garrido-Martin EM, Sanz-Rodriguez F, Ramirez JR, Morales-Angulo C, Zarrabeitia R, Perez-Molino A, Bernabéu C, Botella LM. Therapeutic action of tranexamic acid in hereditary haemorrhagic telangiectasia (HHT): regulation of ALK-1/endoglin pathway in endothelial cells. *J Thromb Haemost* 2007; **97**: 254–62.
14 Shovlin CL, Sulaiman NL, Govani FS, Jackson JE, Begbie ME. Elevated factor VIII in hereditary haemorrhagic telangiectasia (HHT): association with venous thromboembolism. *J Thromb Haemost* 2007; **98**: 1031–9.
15 Bick RL. Hereditary hemorrhagic telangiectasia and disseminated intravascular coagulation: a new clinical syndrome. *Ann N Y Acad Sci* 1981; **370**: 851–4.
16 Gluud LL, Klingenberg SL, Langholz SE. Systematic review: tranexamic acid for upper gastrointestinal bleeding. *Aliment Pharmacol Ther* 2008; **27**: 752–8.
17 CRASH-2 trial collaborators, Shakur H, Roberts I, Bautista R, Caballero J, Coats T, Dewan Y, El-Sayed H, Gogichaishvili T, Gupta S, Herrera J, Hunt B, Iribhogbe P, Izurieta M, Khamis H, Komolafe E, Marrero MA, Mejía-Mantilla J, Miranda J, Morales C, *et al.* Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010; **376**: 23–32.
18 Rivière S, Pelenc D, Dupuis GirodS, Lorcerie B, Kaminsk P, Lequellec A, Plauchu H, on behalf of the European Network of HHT Disease. Hereditary Hemorrhagic Telanglectasia and Venous Thromboembolism. Proceedings of the 8th International Hereditary Hemorrhagic Telanglectasia Scientific Conference in Santander, Spain. *Hematology Meeting Reports* 2009; **3**: 54.
19 Kakar PN, Gupta N, Govil P, Shah V. Efficacy and Safety of Tranexamic Acid in Control of Bleeding Following TKR: a Randomized Clinical Trial. *Indian J Anaesth* 2009; **53**: 667–71.
20 Alvarez JC, Santiveri FX, Ramos I, Vela E, Puig L, Escolano F. Tranexamic acid reduces blood transfusion in total knee arthroplasty even when a blood conservation program is applied. *Transfusion* 2008; **48**: 519–25.
21 Shakur H, Elbourne D, Gulmezoglu M, Alfirevic Z, Ronsmans C, Allen E, Roberts I. The WOMAN Trial (World Maternal Antifibrinolytic Trial): tranexamic acid for the treatment of postpartum haemorrhage: an international randomised, double blind placebo controlled trial. *Trials* 2010; **11**: 40.
22 Dupuis-Girod S, Ginon I, Saurin JC, Marion D, Guillot E, Decullier E, Roux A, Carette MF, Gilbert-Dussardier B, Hatron PY, Lacombe P, Lorcerie B, Rivière S, Corre R, Giraud S, Bailly S, Paintaud G, Ternant D, Valette D, Valette PJ, *et al.* Bevacizumab in patients with hereditary hemorrhagic telangiectasia and severe hepatic vascular malformations and high cardiac output. *JAMA* 2012; **307**: 948–55.

# Medical interventions for traumatic hyphema (Protocol)

**Savage HI, Gharaibeh A, Mathew MC, Scherer RW**

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**[Intervention Protocol]**

# Medical interventions for traumatic hyphema

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**Editorial group:** Cochrane Eyes and Vision Group.
**Publication status and date:** Edited (no change to conclusions), published in Issue 3, 2009.

**Citation:** Savage HI, Gharaibeh A, Mathew MC, Scherer RW. Medical interventions for traumatic hyphema. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.: CD005431. DOI: 10.1002/14651858.CD005431.



## ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

The objective of this review is to assess the effectiveness of various medical interventions in the management of traumatic hyphema.

# BACKGROUND

## Introduction

Traumatic hyphema is the spillage of blood into the anterior chamber (the space between the cornea and iris) of the eye subsequent to a blow or a projectile striking the exposed parts. Although apparently a minor presentation, traumatic hyphema could be associated with major injuries to the tissues of the eye. Traumatic hyphema is an important clinical entity because of the risks associated with significant initial reduction in vision. In children it could lead to the development of irreversible amblyopia. Complications resulting from secondary hemorrhage such as glaucoma, corneal bloodstaining or optic atrophy could lead to permanent impairment of vision.

## Epidemiology

Traumatic hyphema is usually seen in children with an incidence of approximately 2 per 10,000 children per year (Wright 2003). Males predominate with a male to female ratio of 3:1(Crouch 1993). Sports injuries account for 60% of traumatic hyphemas ( Crouch 1999).

## Presentation and diagnosis

Patients present with a sudden decrease or loss of vision following an injury to the eye. The loss of vision depends on the level of hyphema; a microhyphema may present with moderately blurry vision while a full hyphema might present with complete loss of vision. With time blood in the anterior chamber is forced by gravity to form a level in the bottom of the anterior chamber. Consequently vision clears gradually unless associated injuries or traumatic uveitis contribute to further losses in vision.

The severity of traumatic hyphema varies from microhyphema, where red blood cells are suspended in the anterior chamber, to a layered hyphema where fresh or clotted blood may be observed grossly in the lower anterior chamber.

Recurrent hemorrhage, occurring at a rate of 2% to 38% (Walton 2002), increases the time to visual recovery and may be associated with poorer visual outcomes. Secondary hemorrhage occurs typically three to five days after the incident hyphema and may occur due to clot lysis and retraction of the traumatized vessels.

Hyphema in the setting of sickle cell hemoglobinopathy is particularly dangerous as the naturally hypoxic anterior chamber induces sickling of red blood cells. This in turn prevents egress of those blood cells through the trabecular meshwork. Hyphema patients with sickle cell disease are at a higher risk for glaucoma, corneal bloodstaining and permanent visual sequelae.

The most important sign for diagnosing hyphema is the presence of blood in the anterior chamber assessed by a slit lamp examination. Various grading schemes for hyphema have been proposed. Objective quantitation of the level of hyphema is critical as a sudden increase in the height of a layered hyphema is indicative of 'rebleed'. Measurement of intraocular pressure and a dilated fundoscopy are critical to rule out traumatic retinal tears, dialyses, and detachment.

## Treatment options

Management of traumatic hyphema focuses on preventing repeated eye trauma and rebleed, promoting the settling of blood away from the visual axis, controlling traumatic anterior uveitis, and monitoring of and initiating early treatment for secondary glaucoma. The methods employed in preventing recurrent or iatrogenic trauma include shielding the eye, bedrest, and avoidance of diagnostic interventions such as scleral depression or gonioscopy, which could deform the globe. Elevation of the head while sleeping, topical steroids, and cycloplegic medications are the mainstay in the management of traumatic hyphema. Hospitalization, once a mainstay of enforcing bedrest, has been questioned and is currently advocated only for patients perceived to be at high risk of rebleed or with a risk of noncompliance with bedrest at home.

The use of antifibrinolytic agents such as epsilon-aminocaproic acid and tranexamic acid in traumatic hyphema is controversial. They are reported to have the potential to reduce the rate of recurrent hemorrhage but are known to have several potential side effects such as nausea, vomiting, muscle cramps, conjunctival suffusion, headache, rash, pruritus, dyspnea, toxic confusional states, arrhythmias and systemic hypotension. Epsilon-aminocaproic acid is contraindicated in patients who are pregnant, in patients with coagulopathies or with renal diseases and should be cautiously used in patients with hepatic, cardiovascular or cerebrovascular diseases. A topical gel form of epsilon-aminocaproic acid is awaiting Food and Drug Association (FDA) approval. It appears to have comparable effectiveness with fewer side effects compared with the oral form and this might be used on an outpatient basis. Tranexamic acid (Cyclokapron) is more potent than epsilon-aminocaproic acid and has similar side effects, but with fewer gastric side effects ( Rahmani 1999).

Corticosteroids have also been used to treat hyphema and appear to be effective (Walton 2002). Investigators have studied both topical and systemic corticosteroids, applying these agents for varying lengths of time with or without other interventions such as bedrest or cycloplegics. Topical administration of steroids avoids the side effects of systemic corticosteroid use but it is not known whether topically applied steroids are as effective as systemic steroids in reducing the rate of rebleed. The mechanism of action of corticosteroids is thought to be due to stabilization of the blood ocular barrier and direct inhibition of fibrinolysis (Walton 2002).

Surgical evacuation of hyphema is generally not needed. In the past, surgical evacuation was contraindicated due to the possibility of sudden decreases in intraocular pressure and manipulation of

the damaged iris and ciliary body, increasing the risk of recurrent hemorrhage. However, surgical 'washout' is advocated for managing hyphema in patients with non-clearing hyphema, in whom secondary glaucoma threatens to cause permanent visual loss due to glaucomatous optic neuropathy or facilitation of corneal blood-staining.

### Rationale for a systematic review

Despite the existence of guidelines for the management of traumatic hyphema (Crouch 1999; Rhee 1999) the safety and effectiveness of various therapeutic modalities such as use of antifibrinolytic agents, their routes of administration, use of corticosteroids and hospitalization is controversial. The evidence for the impact of rebleed on visual outcomes, glaucoma, optic atrophy and bloodstaining is limited. Furthermore, rebleed, which is a surrogate outcome, dominates the published literature on management of traumatic hyphema. It is important to examine the impact of the various antifibrinolytic medications, route of administration and dosages used across various populations.

## OBJECTIVES

The objective of this review is to assess the effectiveness of various medical interventions in the management of traumatic hyphema.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

This review will include randomized and quasi-randomized trials.

#### Types of participants

We will include trials in which the study population consisted of people with traumatic hyphema following closed globe trauma. There will be no restrictions regarding age, gender, or severity of the closed globe trauma or level of visual acuity at the time of enrolment.

#### Types of interventions

We will include trials in which:
1) antifibrinolytic agents (epsilon-aminocaproic acid, tranexamic acid) or steroids in any form or dosage with the intention to treat or reduce the symptoms of traumatic hyphema have been compared to other treatment, placebo, or no treatment. There will be no time limit on the duration of treatment;
2) bed rest has been compared to ambulatory management;
3) bilateral patching has been compared with unilateral or no patching;
4) outpatient management has been compared with in-patient management.

#### Types of outcome measures

##### Primary outcomes

The primary outcomes for this review are visual outcomes:

1. visual acuity assessed at short, medium, and long term follow up, defined respectively as two weeks or less; more than two weeks but within two months, and more than two months from the traumatic event. Visual acuity at resolution of hyphema will also be assessed;
2. duration of visual impairment, defined as length of time from onset to resolution.

##### Secondary outcomes

Secondary outcomes for this review are sequelae of traumatic hyphema:

1. incidence of and time to rebleed defined as (a) an increase in height of layered hyphema using the biomicroscopic light caliper or by any other method or (b) the occurrence of fresh (red) blood in the eye with the existing clot;
2. incidence of corneal bloodstaining;
3. incidence of peripheral anterior synechia formation;
4. incidence of glaucoma development;
5. incidence of optic atrophy development.

##### Adverse effects

We will summarize the reported adverse effects related to treatment.

##### Quality of life measures

In addition to examining the time to hyphema resolution we will describe available data on other indicators of quality of life, especially time to best visual acuity.

##### Economic outcomes

We will assess the need for bedrest or hospitalization versus outpatient care. We will also compare length of hospital stay and other economic outcomes as described in the primary reports.

***Follow up***

There will be no restrictions based on length of follow up.

## Search methods for identification of studies

### Electronic searches

At a minimum we will search the Cochrane Central Register of Controlled Trails (CENTRAL) (which contains the Cochrane Eyes and Vision Group Trials Register) in *The Cochrane Library*, MEDLINE and EMBASE. We will also search supplementary information sources as appropriate. There will be no language or date restrictions in the electronic searches.
See Appendix 1 for details of the MEDLINE search strategy. This strategy will be adapted for the other databases.

### Searching other resources

We will search the reference lists of identified trial reports to find additional trials. We will also search the ISI citation index database, Science and Social Science Citation Index/Web of Science Services to find studies that have cited the identified trials. We will contact the primary investigators of identified trials for details of additional trials. We will not conduct manual searches of conference proceeding abstracts specifically for this review.

## Data collection and analysis

### Assessment of search results

Two authors will independently assess the titles and abstracts of all reports identified by the electronic and manual searches as per the 'Criteria for considering studies for this review.' The abstracts will be classified as (a) definitely include, (b) unsure or (c) definitely exclude. Full copies of those classified as (a) or (b) will be obtained and re-assessed as per the 'Criteria for considering studies for this review.' The studies will be classified as (1) included, (2) awaiting assessment or (3) excluded. The concordance between authors will be documented. The third author will resolve disagreements between the two authors. The authors of studies classified as (2) will be contacted for further clarifications and the studies will be re-assessed as per the inclusion criteria as further information becomes available. Studies identified by both authors as (3) will be excluded and documented in the review. Studies identified as (1) will be included and assessed for methodological quality. The authors will be unmasked to the report authors, institutions and trial results during this assessment.

### Assessment of methodological quality

Two authors will assess the sources of systematic bias in trials according to methods set out in Section 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2005). The following parameters will be considered: method of allocation concealment (selection bias), masking of participants and researchers (performance bias), masking of outcome (detection bias), rates of follow up and intention-to-treat analysis (attrition bias). Each of the parameters will be graded as (A) adequate or yes, (B) unclear or not reported, and (C) inadequate or no. Agreement between authors will be documented. A third author will resolve any disagreement. Masking of participants and care providers will be used as a quality criterion only in interventions where masking is feasible. We will contact the authors of trials categorized as 'unclear or not reported' for additional information. If the study authors do not respond we will assign a grade to the trial based on the available information.

### Assessment of study characteristics

In addition to the parameters described above, we will extract data on the study characteristics such as details of participants, the interventions, the outcomes, costs and other relevant information.

### Data collection

Two authors will independently extract the data for the primary and secondary outcomes onto paper data collection forms developed by the Cochrane Eyes and Vision Group. Discrepancies will be resolved by discussion. We will contact primary investigators for missing data. One author will enter all data into Review Manager (RevMan) 4.2. Another author will independently re-enter the data using the double data-entry facility to check for inaccuracies.

### Data synthesis

Data analysis will follow the guidelines in Section 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2005). For dichotomous outcomes we will calculate a summary odds ratio or relative risk. Weighted mean difference will be calculated for continuous outcomes. We will test for statistical heterogeneity. If it is not detected and there is no clinical heterogeneity within the trials we will combine the results in a meta-analysis using a random-effects model. A fixed-effect model will be used if the number of trials is three or less. In case of statistical or clinical heterogeneity we will not combine study results but will present a tabulated summary.
Subgroup analyses according to age, race, presence of sickle cell anemia, presenting intraocular pressure, and severity of hyphema will be performed when sufficient numbers of trials are available.

### Sensitivity analysis

We will conduct sensitivity analyses to determine the impact of excluding studies of lower methodological quality, unpublished studies, and industry-funded studies.

## ACKNOWLEDGEMENTS

We thank Dr Inci Irak, Zbys Fedorowicz, Tianjing Li and Mostafa Elgohary for their comments on this protocol. The Eyes and Vision Group created the search strategies for this protocol. Supported by contract N01-EY-2-1003, National Eye Institute, National Institutes of Health.

## REFERENCES

### Additional references

**Crouch 1993**

Crouch ER Jr, Williams PB. Trauma: Ruptures and Bleeding. In: Tasman W, Jaeger EM editor(s). *Duane's Clinical Ophthalmology*. Vol. **4**, Philadelphia, PA: JB Lippincott, 1993:1–18.

**Crouch 1999**

Crouch ER Jr, Crouch ER. Management of traumatic hyphema: Therapeutic options. *Journal of Pediatric Ophthalmology and Strabismus* 1999;**36**(5):238.

**Higgins 2005**

Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 4.2.4 [updated March 2005]. In: The Cochrane Library, Issue 2, 2005. Chichester, UK: John Wiley & Sons, Ltd.

**Rahmani 1999**

Rahmani B, Jahadi HR. Comparison of tranexamic acid and prednisolone in the treatment of traumatic hyphema. A randomized clinical trial. *Ophthalmology* 1999;**106**(2):375–9.

**Rhee 1999**

Rhee D, Pyfer M. *The Wills Eye Manual.* Lippincott Williams and Wilkins, 1999.

**Walton 2002**

Walton W, Von Hagen S, Grigorian R, Zarbin M. Management of traumatic hyphema. *Survey of Ophthalmology* 2002;**47**(4):297–334.

**Wright 2003**

Wright KW. Pediatric ocular trauma: Pediatric hyphema. In: Wright KW, Spiegel PH editor(s). *Pediatric Ophthalmology and Strabismus.* Vol. **6**, Springer, 2003:79–82.

* *Indicates the major publication for the study*

# APPENDICES

## Appendix 1. MEDLINE search strategy (SilverPlatter on WebSPIRS:5)

#1 explode "Hyphema-" / all SUBHEADINGS in MIME,MJME
#2 explode "Wounds-and-Injuries" / all SUBHEADINGS in MIME,MJME
#3 (eye* in AB) or (eye* in TI)
#4 #2 and #3
#5 "Anterior-Chamber" / injuries in MIME,MJME
#6 explode "Intraocular-Pressure" / all SUBHEADINGS in MIME,MJME
#7 "Eye-Injuries" / complications in MIME,MJME
#8 "Eye-Hemorrhage" / complications ,drug-therapy ,etiology ,prevention-and-control ,therapy in MIME,MJME
#9 "Hemorrhage-" / etiology ,prevention-and-control in MIME,MJME
#10 #3 and #9
#11 ( (hyphem* near3 trauma*) in AB )or( (hyphem* near3 trauma*) in TI )
#12 ( (eye* near3 (injur* or trauma* or wound* or hemorrhag*)) in AB )or( (eye* near3 (injur* or trauma* or wound* or hemorrhag*)) in TI )
#13 #1 or #4 or #5 or #6 or #7 or #8 or #10 or #11 or #12
To identify trials we will combine this search with phases one and two of the Cochrane Highly Sensitive Search Strategy as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2005).

# WHAT'S NEW

| | | |
|---|---|---|
| 7 August 2008 | Amended | Converted to new review format. |

# HISTORY

Protocol first published: Issue 3, 2005

## CONTRIBUTIONS OF AUTHORS

Conceiving the review: HS, A-MG, MM

Designing the review: RS, MM, HS

Coordinating the review: MM

Undertaking manual searches: TBA

Screening search results: HS, A-MG

Organizing retrieval of papers: MM

Screening retrieved papers against inclusion criteria: HS, A-MG, MM

Appraising quality of papers:HS, RS

Abstracting data from papers: A-MG, HS, MM

Writing to authors of papers for additional information: HS, MM

Providing additional data about papers: HS

Obtaining and screening data on unpublished studies: HS, A-MG

Data management for the review: RS, MM

Entering data into RevMan: RS, MM

Analysis of data: RS, MM

Interpretation of data: HS, A-MG, RS

Writing the review: HS, A-MG

Performing previous work that was the foundation of current study: A-MG, HS, RS

## DECLARATIONS OF INTEREST

None known

## SOURCES OF SUPPORT

### Internal sources

- No sources of support supplied

## External sources

- National Eye Institute, National Institutes of Health, USA.
- Brown University, USA.

Received: 4 October 2022 | Accepted: 29 November 2022

DOI: 10.1111/jocd.15561

JCD Journal of Cosmetic Dermatology WILEY

REVIEW ARTICLE

# Oral tranexamic acid in the treatment of hyperpigmentation disorder beyond melasma: A review

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## Abstract

**Background:** Tranexamic acid, a synthetic derivative of the amino acid lysine, is an antifibrinolytic, procoagulant agent approved by the Food and Drug Administration for the treatment of cyclic heavy menstrual bleeding and prevention of bleeding in patients with hemophilia undergoing tooth extraction. Oral tranexamic acid has been used off-label in dermatology in the treatment of melasma and other hyperpigmentation disorders. In a recent study, oral tranexamic acid was reviewed thoroughly in treating melasma, and its effectiveness was demonstrated. Their role in treating other hyperpigmentation disorders has also been tried in several studies.

**Aim:** To review the evidence regarding the use of tranexamic acid in treating different types of hyperpigmentation disorders other than melasma.

**Methodology:** A comprehensive literature review was searched using the electronic online database "PubMed" and "google scholar" using key words "Postinflammatory hyperpigmentation," "lichen planus pigmentosus," "ashy dermatosis," "riehl melanosis". After that, a full-text review of the studies was performed.

**Result:** Oral tranexamic acid has been used in different types of hyperpigmentation disorder, including postinflammatory hyperpigmentation treatment and prevention, lichen planus pigmentosus, ashy dermatosis, and Riehl melanosis in a dose range from 250 mg per day to 1500 mg per day for a period range from 2 weeks to 6 months with variable efficacy and a good safety profile.

**Conclusion:** Oral tranexamic acid is a promising treatment option in a different type of hyperpigmentation disorders refractory to topical treatment. However, more evidence from blinded randomized controlled trials and case–control studies is needed to determine their efficacy in treating various hyperpigmentation disorders.

## 1 | INTRODUCTION

Tranexamic acid (TA), a synthetic derivative of the amino acid lysine, is an antifibrinolytic, procoagulant agent that the Food and Drug Administration approves for the treatment of cyclic heavy menstrual bleeding and prevention of bleeding in patients with hemophilia undergoing tooth extractions.[1]

Oral TA has been used off-label in dermatology in the treatment of melasma and other hyperpigmentation disorders.[2]

In a recent study, oral TA has been reviewed thoroughly in treating melasma, and its effectiveness has been demonstrated.[2] Their role in treating other hyperpigmentation disorders has also been tried in several studies. The present review discusses the emerging role of oral TA in the treatment of hyperpigmentation disorders other than melasma.

## 2 | MECHANISM OF ACTION

Tranexamic acid is known to decrease bleeding by its antifibrinolytic effect by inhibiting the conversion of plasminogen to plasmin involved in fibrin degradation. In addition to its antifibrinolytic effect, TA is thought to have anti-inflammatory, antimelanogenic, and antiangiogenic effects by its potent inhibitory effect on plasmin.[3,4] TA inhibits UV light induces plasmin activation, and decreases plasminogen binding to keratinocyte.[5] Plasmin activation stimulates keratinocytes to release alpha mesh and inflammatory mediators such as alpha-archiedonic acid prostaglandin E2, which in turn result in melanocytes tyrosinase activation, which plays an essential role in skin hyperpigmentation. The antiangiogenic effect of TA is thought to be due to a decrease in plasmin mediate expression of vascular endothelial growth factor and endothelin-1, a significant skin angiogenic factor, which is involved in the vascular theory of the pathogenesis of melasma.[6,7]

## 3 | SIDE EFFECTS

The most common adverse effect include abdominal pain, bloating, nausea and vomiting, numbness or facial pruritus, tinnitus, transient amnesia, tremor, dysmenorrhoea, hair shedding, facial hypertrichosis, lip or periorbital swelling, and palpitations. In the largest retrospective review of patients taking oral TA for melasma, one patient did develop a deep vein thrombosis, but this patient found to have protein S deficiency.[8]

## 4 | CONTRAINDICATIONS

Tranexamic acid is contraindicated in patients allergic to TA, with intracranial bleeding, known defective color vision, history of venous or arterial thromboembolism, or active thromboembolic disease. It is also contraindicated in the patient who is currently taking or have previously taken anticoagulant medications; and in a patient taking oral contraceptive pills, the patient who are pregnant or breastfeeding or are smokers; and those with renal, cardiac, and pulmonary disease.[4,9]

Patients must be screened carefully through careful history for contraindications and risks and given thorough instructions to monitor for side effects before initiating therapy with TA.

## 5 | METHODOLOGY

A comprehensive literature review was searched using the electronic online database “PubMed” and “Google Scholar” using key words “Postinflammatory hyperpigmentation,” “lichen planus pigmentosus,” “ashy dermatosis,” “riehl melanosis”. After that, a full-text review of the studies was performed.

## 6 | LITERATURE REVIEW

Postinflammatory hyperpigmentation (PIH) is a common cosmetic skin condition that occurs after dermatologic procedures, exogenous stimuli like burns or as a sequela of different dermatoses such as acne and eczema. Management of PIH lesions could be challenging as it takes a long time to fully resolve, with or without treatment.[10] Kim et al.[11] used oral TA to treat PIH and found it effective. They report a case of PIH lesions on both malar areas due to intense pulsed light therapy, which was dramatically resolved after 2 weeks of treatment by oral TA 250 mg TID combined with the wet dressing of TA solution three times per week. Another successful outcome in a case of a female with PIH lesions due to allergic contact dermatitis to henna hair dye. The patient underwent low-fluence Q-switched Nd: YAG laser sessions weekly once, combined with 750 mg of oral TA daily for 10 weeks. This combination treatment resulted in significant improvement of the PIH lesions on her forehead and persistent effect after a 1-year follow-up.[12]

Some studies have suggested a preventive and protective role for oral TA in PIH. Lindgren et al. brief communication report give insight into the use of TA in 82 cases in the treatment and prevention of PIH in patients with a high risk of developing PIH before procedures that disturb the epidermis, such as chemical peeling and in the prevention of PIH after injuries to epidermis such as after thermal burn or irritant dermatitis. Lindegran et al. reports two cases in the use of TA prophylaxis with successful outcomes. In the first case, a woman with a significant past medical history of PIH after chemical peeling experienced some irritation after topical anesthetic cream. Therefore, she received oral TA 650 mg daily for 8 weeks and topical clobetasol 0.05% cream twice daily for 1 week. Then after a 16-week follow-up visit, she presented with normal appearing skin. The second case, a case of acne excoriate with PIH, planned to have a series of light chemical peels for her acne-related PIH lesions. As prophylaxis, she was prescribed oral TA 650 mg daily. Over a 2.5-year period, she completed nine exfoliative chemical peels without complications or new PIH lesions despite continued excoriation.[10]

Moreover, the prophylactic role of oral TA post-Q-switched ruby laser treatment was evaluated by Kato et al.[13], who included 32 Japanese women who underwent Q-switched ruby laser treatment for senile lentigines on the face. One group was given 750 mg/day of oral TA for 4 weeks after Q-switched ruby laser treatment, and the other group did not receive TA after Q-switched ruby laser. As a result, there was no significant difference in the incidence of PIH between participants who received oral TA and those who did not.

Similarly, in a trial conducted on 40 patients with solar lentigines treated with Q-switched 532 nm Nd: YAG laser, who were randomly assigned to receive oral TA 1500 mg daily or placebo for 6 weeks. Oral TA appears to be ineffective in preventing PIH post-laser in the treatment group compared with the control group. There were no serious adverse events in either group during the study period. On the other hand, the incidence of dermatoscopic pigmented granules in the TA group was significantly lower than

**TABLE 1** Summary of the studies

| Study | Type of hyperpigmentation | No. of cases | Dose of TA | Duration | Concurrent treatment | Result | Side effect |
|---|---|---|---|---|---|---|---|
| Benchikhi and colleagues[15] | LPP | Case series 11 cases | 500 BID | 3–6 months | Topical hydroquinone, high potent corticosteroid | Good result in three patients, remaining have slight or no improvement | Nil reported |
| Zenjari and colleagues[16] | LPP | Prospective study 20 cases | 250 mg daily | 4–6 months | | Partial improvement in ten patients, no improvement in three patients and seven patients lost follow-up<br>Pruritus disappears in all patients | Nil reported |
| Hyuck H and colleagues[18] | Riehl's melanosis | Prospective Pilot study<br>8 cases | 250 mg | Throughout treatment course | Hydroquinon 4% cream,<br>Multiple laser session (10–18) 3-week interval QS-Nd: YAG 1064 nm<br>1.1–1.3 J/cm$^2$, 10-mm spot size<br>2–3 passes | Almost clear in three patients and marked improvement in the remaining five patient | No serious adverse effect |
| Lee and colleagues[12] | PIH due to allergic contact dermatitis to henna hair dye | Case report | 750 mg per day | 10 weeks | Weekly laser session (10 sessions) QS-Nd: YAG 2–2.2 J/cm$^2$ | Marked substantial improvement, and the patient was very satisfied | Nil reported |
| Kim and colleagues[11] | Treatment of PIH After laser | Case report | 250 mg TID | 3 weeks | Wet dressing using TA solution (3ampules, total 15 ml of TXA) (500 mg /GML) was applied for 20 min three times a week | Significant improvement after 2 weeks<br>After 3 weeks, the facial lesion disappeared | Erythema and burning sensation the site of TA solution application that subsides quickly |
| Wang and colleagues[19] | Melasma, hyperpigmentation, PIH | Retrospective review for safety 206 cases | 650 mg once daily | 1–6 months | Low energy, low density fractional non-ablative 1927 nm laser | | No documented adverse effects, Lack of thromboembolic adverse effect complication |

(Continues)

TABLE 1 (Continued)

| Study | Type of hyperpigmentation | No. of cases | Dose of TA | Duration | Concurrent treatment | Result | Side effect |
|---|---|---|---|---|---|---|---|
| Lindgren and colleagues[10] | Treat and prevent PIH. | Brief communication two cases | 650 mg daily | Until the injury is completely healed and no PIH is present, ranging from 2 weeks to several years with council the patient to stop treatment for 48 h prior to immobility such as flight over 4 h. | | Adding oral TA in the setting of acute injury to prevent PIH in at-risk patients is safe and effective. | Nil reported |
| Rutnin and colleagues[14] | Prevention of PIH after Q switched 532 nm Nd: YAG laser for solar lentigines | Randomized controlled trial Cases: 20 Control: 20 | 1500 mg daily | Given in the first 6 weeks after laser treatment. | | No significant difference in the incidence of PIH between the two groups, but PIH clearance is improved significantly in the treatment group. | Nausea: in four patients in TA group and in three patients in placebo<br>Hypomenorrhea in 3 patients in TA group<br>No incidence of vascular thrombosis in both group. |
| Kato and colleagues[13] | Prevention of PIH after QS- Ruby laser for solar lentigines | Randomized controlled trial Cases: 15<br>Control: 17 | 750 mg daily | Given in the first 4 weeks after laser treatment | | No significant difference in the incidence of PIH between the two groups | Nil reported |

Abbreviations: LPP, lichen planus pigmentosus; PIH, post-inflammatory hyperpigmentation; TA, tranexamic acid.

in the placebo group at the 6th and 12th weeks. This finding might indicate the efficacy of TA in enhancing PIH clearance rather than protection.[14]

Tranexamic acid has also been reported in the treatment of Lichen planus pigmentosus (LPP), a variant of lichen planus manifested as ill-defined oval grayish to brown macules on the sun-exposed area, which represents a real therapeutic challenge with several proposed therapies have limited efficacy. TA has been studied in a case series conducted in North Africa, including 17 patients diagnosed with LPP; 11 were given oral TA 500 mg twice daily for 3 or 6 months. Lesions were mainly in the perioral area, followed by the neck. At follow-up, only three had an excellent result with a complete disappearance of the lesions. The remaining patients have slight or no improvement.[15]

Zenjari et al.[16] demonstrated the therapeutic efficacy of oral TA in 20 patients with LPP; they prescribed 250 mg/daily oral TA for 4–6 months. At follow-up, 10 patients showed partial improvement, three patients had no improvement, and seven patients were lost to follow-up. No severe complications or increased clotting risk were observed.

Moreover, another study conducted on a total of eight Korean patients aimed to evaluate the safety and efficacy of combination therapy (Q-switched Nd: YAG laser, hydroquinone cream, oral TA) in the treatment of recalcitrant Riehl's melanosis, which is a form of contact dermatitis that presents as facial brown or bluish reticulate pigmentation, mainly on the forehead and temporal regions. They were treated with multiple sessions of Q-switched laser for a 3-week interval, daily 4% hydroquinon cream application, and oral TA 250 mg/day throughout treatment courses. Among those eight patients, the majority (five patients) "Marked improvement" grade, and the other three received "Almost clear" grade at final visits. No documented adverse events such as blistering, scarring, or hypopigmentation related to the combination treatment.[17,18]

Regarding TA safety, a 5-year safety review on 206 patients received oral TA with a dose of 650 mg daily for different dermatological conditions, which included melasma (63.9%), hyperpigmentation (43.2%), and/or PIH (10.0%). Most of them had laser procedures combined with oral TA. The duration of therapy ranged from 1 to 6 months, with no noted incidence of vascular thrombosis or other side effects related to oral TA medication.[19]

With that being said, we suggest that combination therapy by oral TA in addition to adjuvant multiple therapeutic modalities for a compelling long-term period could provide several advantages, as shown in melasma treatment.[20]

The literature is summarized in Table 1.

## 7 | CONCLUSION

Oral tranexamic acid is a promising treatment option in a different type of hyperpigmentation disorder refractory to topical treatment. However, more evidence from blinded randomized controlled trials and case–control studies is needed to determine their efficacy in the treatment of the different types of hyperpigmentation disorders.

## AUTHOR CONTRIBUTIONS

Taghreed Mahjoub, contributed to the study conception and design, writing, and reviewing manuscript. Heba Milibary, contributed to writing and reviewing manuscript. All author commented in previous version of the manuscript. All authors read and approved the final manuscript.

## ACKNOWLEDGMENTS

The study has no funding support.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## ETHICAL APPROVAL

Authors declare human ethics approval was not needed for this study.

## REFERENCES

1. Dunn CJ, Goa KL. Tranexamic acid. *Drugs*. 1999;57(6):1005-1032.
2. Karn D, Kc S, Amatya A, Razouria E, Timalsina M. Oral tranexamic acid for the treatment of melasma. *Kathmandu Univ Med J*. 2012;10(4):40-43.
3. Kim S, Park JY, Shibata T, Fujiwara R, Kang H. Efficacy and possible mechanisms of topical tranexamic acid in melasma. *Clin Exp Dermatol*. 2016;41(5):480-485.
4. Chauncey JM, Wieters JS. *Tranexamic Acid*. StatPearls Publishing; 2021.
5. Takashima A, Yasuda S, Mizuno N. Determination of the action spectrum for UV-induced plasminogen activator synthesis in mouse keratinocytes in vitro. *J Dermatol Sci*. 1992;4(1):11-17.
6. Hofman Z, de Maat S, Hack CE, Maas C. Bradykinin: inflammatory product of the coagulation system. *Clin Rev Allergy Immunol*. 2016;51(2):152-161.
7. Kim EH, Kim YC, Lee E-S, Kang HY. The vascular characteristics of melasma. *J Dermatol Sci*. 2007;46(2):111-116.
8. Lee HC, Thng TGS, Goh CL. Oral tranexamic acid (TA) in the treatment of melasma: a retrospective analysis. *J Am Acad Dermatol*. 2016;75(2):385-392.
9. Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. *Circulation*. 2003;107(23_suppl_1):1-9.
10. Lindgren AL, Austin AH, Welsh KM. The use of tranexamic acid to prevent and treat post-inflammatory hyperpigmentation. *J Drugs Dermatol*. 2021;20(3):344-345.
11. Kim JK, Chang SE, Won CH, Lee MW, Choi JH, Moon KC. Dramatic improvement of long lasting post-inflammatory hyperpigmentation by oral and topical tranexamic acid. *J Cosmet Dermatol Sci Appl*. 2012;2(2):62-63.
12. Lee YB, Park SM, Kim J-W, Yu DS. Combination treatment of low-fluence Q-switched Nd: YAG laser and oral tranexamic acid for post-inflammatory hyperpigmentation due to allergic contact dermatitis to henna hair dye. *J Cosmet Laser Ther*. 2016;18(2):95-97.
13. Kato H, Araki J, Eto H, et al. A prospective randomized controlled study of oral tranexamic acid for preventing postinflammatory hyperpigmentation after Q-switched ruby laser. *Dermatol Surg*. 2011;37(5):605-610.

14. Rutnin S, Pruettivorawongse D, Thadanipon K, Vachiramon V. A prospective randomized controlled study of oral tranexamic acid for the prevention of postinflammatory hyperpigmentation after Q-switched 532-nm Nd: YAG laser for solar lentigines. *Lasers Surg Med*. 2019;51(10):850-858.
15. Benchikhi H. Lichen planus pigmentosus in North Africa: a series of 17 cases. *Dermatol Open J*. 2019;4(1):10-14.
16. Zenjari L, Elfetoiki F, Hali F, Skalli H, Chiheb S. Oral tranexamic acid in the Treatment of lichen planus pigmentosus: a prospective study of 20 cases. *Ann Dermatol Venereol*. 2020;47(12):818-822.
17. Wang L, Xu AE. Four views of R iehl's melanosis: clinical appearance, dermoscopy, confocal microscopy and histopathology. *J Eur Acad Dermatol Venereol*. 2014;28(9):1199-1206.
18. Kwon HH, Ohn J, Suh DH, et al. A pilot study for triple combination therapy with a low-fluence 1064 nm Q-switched Nd: YAG laser, hydroquinone cream and oral tranexamic acid for recalcitrant Riehl's melanosis. *J Dermatolog Treat*. 2017;28(2):155-159.
19. Wang JV, Valiga A, Geronemus RG. Real-world experience with oral tranexamic acid and lasers for pigmentary disorders: a 5-year safety review. *Dermatol Surg*. 2021;47(9):1303-1304.
20. Bala HR, Lee S, Wong C, Pandya AG, Rodrigues M. Oral tranexamic acid for the treatment of melasma: a review. *Dermatol Surg*. 2018;44(6):814-825.

**How to cite this article:** Mahjoub TT, Milibary HH. Oral tranexamic acid in the treatment of hyperpigmentation disorder beyond melasma: A review. *J Cosmet Dermatol*. 2023;22:1157-1162. doi:10.1111/jocd.15561

# TRANEXAMIC ACID IN CONTROL OF PRIMARY HEMORRHAGE DURING TRANSURETHRAL PROSTATECTOMY

ANTTI RANNIKKO, ANSSI PÉTAS, AND KIMMO TAARI


## ABSTRACT

**Objectives.** To determine whether short-term treatment of patients about to undergo transurethral resection of the prostate (TURP) with tranexamic acid (TXA) would be beneficial in reducing the associated blood loss.

**Methods.** A prospective and randomized trial was conducted with 136 men requiring TURP for obstructive urinary symptoms. The treatment group received 2 g TXA three times daily on the day of, and first day after, the operation.

**Results.** Short-term TXA treatment significantly reduced the operative blood loss associated with TURP (128 mL versus 250 mL, $P = 0.018$), and this difference was not a result of the amount of tissue resected between the two groups (16 g versus 16 g, $P = 0.415$). In addition, TXA treatment reduced the amount of blood loss per gram of resected tissue (8 mL/g versus 13 mL/g, $P = 0.020$). Furthermore, the volume of irrigating fluid required (15 L versus 18 L, $P = 0.004$) and operating time (36 minutes versus 48 minutes, $P = 0.001$) were also reduced. However, TXA treatment did not influence the number of patients requiring a blood transfusion. Six patients in the treatment group (7.2%) and five in the control group (6.8%) required a transfusion ($P = 0.709$). Moreover, TXA treatment did not affect the duration of catheterization (1 day versus 1 day, $P = 0.342$) or hospitalization (3 days versus 3 days, $P = 0.218$).

**Conclusions.** Short-term TXA treatment is effective in reducing the operative blood loss associated with TURP. UROLOGY **64:** 955–958, 2004. © 2004 Elsevier Inc.


Prostatic hyperplasia is a common condition afflicting older men. Recently, several noninvasive and mini-invasive therapies have gained popularity for the treatment of men with obstructive urinary symptoms; however, transurethral resection of the prostate (TURP) is still the usual treatment of choice for these patients. The main complications of TURP are bleeding and absorption of irrigating fluid. Factors that influence perioperative and postoperative blood loss include prostate weight, weight of the resected tissue, operating time, preoperative urine culture, preoperative finasteride treatment, cancer histologic type, use of acetylsalicylic acid, type of anesthesia, and patient age and blood pressure, although some of these associations remain controversial.[1–6] To reduce the perioperative and postoperative bleeding, several different approaches have been tried, including intravenous administration of estrogens, catheter traction, intraprostatic vasopressin, per os ethamsylate, fibrin adhesive, phenol solution, and, more recently, finasteride. Although these approaches have yielded some promising results, no one technique has gained widespread acceptance and incorporation into surgical routine.[3–5]

TURP results in activation of coagulation and a consequent hypercoagulable state in the patient. This hypercoagulable state is not associated with the amount of tissue resected or amount of perioperative bleeding; however, it may influence the volume of postoperative blood loss.[7,8] Postoperative blood loss is thought to be associated with an increase in urinary fibrinolytic activity. Urine and urothelium contain high concentrations of plasminogen activators that facilitate the lysis of clots.[9] Therefore, administration of antifibrinolytic agents might be beneficial in reducing the amount of postoperative blood loss resulting from TURP.[10,11]

TXA and aminocaproic acid are synthetic derivatives of the amino acid lysine and, in humans, exert an antifibrinolytic activity by reversibly bind-

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*Submitted: May 23, 2003, accepted (with revisions): July 7, 2004*



0090-4295/04/$30.00
doi:10.1016/j.urology.2004.07.008

**TABLE I. *Patient characteristics***

| Variable | Tranexamic Acid (n = 70) | Control (n = 66) | *P* Value |
|---|---|---|---|
| Age (yr) | 71 (67–76) | 68 (63–75) | 0.095* |
| Preoperative hemoglobin (g/L) | 143 (131–153) | 144 (137–155) | 0.284† |
| Prostate size (g) | 50 (35–61) | 51 (40–66) | 0.174* |

*Data presented as median, with 25th to 75th percentiles in parentheses.*
* *t test.*
† *Mann-Whitney U test.*

ing to plasminogen.[12] TXA is approximately 10 times more potent in binding to plasminogen than aminocaproic acid. Previous studies investigating the beneficial effects of these compounds on TURP-associated bleeding have resulted in conflicting conclusions.[13–16] Recently, a growing body of evidence has indicated that TXA is an effective treatment for reducing blood loss in cardiac, orthopedic, and liver surgery. TXA has also been shown to be of benefit in the treatment of secondary hemorrhage associated with TURP.[17–19] However, no report has assessed the effect of TXA on primary hemorrhage. In this report, we investigated the effects of TXA therapy in men undergoing TURP.

## MATERIAL AND METHODS

A total of 200 consecutive patients (between October 2000 and April 2002) requiring TURP for obstructive urinary symptoms were screened for our prospective and randomized study. The local ethics committee approved the study. Patients taking finasteride (n = 32) or with a history of prostate cancer (n = 20) were excluded. Two patients were treated with bladder neck incision instead of TURP and 10 patients' data collection sheets were improperly completed or lost at follow-up and were excluded from the study. Therefore, 136 patients were eligible for participation in our study. All patients had both clinical and laboratory evidence of prostatic enlargement caused by benign prostatic hyperplasia. Prostate size was determined either by transrectal or abdominal ultrasonography. After providing written informed consent, patients were randomized into the treatment group or the control group by a sealed-envelope system. Randomization was done by the nursing staff during the patient's preoperative visit to the department. The surgeons who performed the operations were not informed of the patient grouping. Treatment patients received 2 g TXA (Caprilon, Leiras, Finland) orally three times daily on the operative and first postoperative day. Control group patients received no medication, because identical placebo tablets were not available.

Patients taking acetylsalicylic acid or warfarin medication discontinued their treatment 7 and 2 days before surgery, respectively. All TURPs were performed under spinal anesthesia. We used a 26F to 28F continuous irrigating resectoscope and warm irrigating fluid (Somanol + 1% ethanol, Braun, Germany). All irrigating fluid used was collected and measured. Surgical blood loss was determined by the amount of hemoglobin in the irrigating fluid using a photometer (HemoCue Low Hemoglobin Photometer, HemoCue, Dronfield, United Kingdom), as described previously.[6] The measuring sensitivity and range of the photometer is 0.3 to 30.0 g/L of hemoglobin in the irrigating fluid. We defined the operating time as the start of resection until hemostasis was complete. All resected tissue was weighed and underwent histologic evaluation.

The statistical analyses were performed with NCSS 2000 statistical software. Correlations between the parameters were analyzed using the Spearman's rank order test. Differences between groups were analyzed with the two-tailed two-sample *t* test, Mann-Whitney *U* test, or chi-square test, as appropriate. Finally, correlations were ranked by multiple regression analyses.

## RESULTS

The treatment and control groups were comparable in age, preoperative hemoglobin concentration, and prostate size (Table I). In addition, no statistically significant difference was found between the two groups in the amount of tissue resected (median 16 g versus 16 g, $P = 0.415$).

A strong correlation was observed between the amount of surgical blood loss and prostate size ($r = 0.549$, $P < 0.001$), irrigating fluid volume ($r = 0.744$, $P < 0.001$), resected weight ($r = 0.725$, $P < 0.001$), and operating time ($r = 0.795$, $P < 0.001$; Spearman's rank order test). According to multiple regression analyses, only the resected weight and operating time were independent variables. Age was not associated with the other variables.

During TURP, the treatment group had significantly less bleeding than the control group (median 128 mL versus 250 mL, $P = 0.018$; Table II). To control for the amount of tissue resected, we divided the amount of surgical bleeding by the weight of the prostate resected in each case. The difference in blood loss between the two groups was still statistically significant (median 8 mL/g versus 13 mL/g, $P = 0.020$). In addition, we observed a slight decrease in the blood hemoglobin concentration on the first (median 12 g/L versus 13 g/L, $P = 0.109$) and second (median 12 g/L versus 17 g/L, $P = 0.055$) postoperative days (Table II). However, the treatment and control groups had similar postoperative blood transfusion rates, 7.2% (6 patients) and 6.8% (5 patients; $P = 0.709$), respectively.

TXA treatment reduced the operative time (median 36 minutes versus 48 minutes, $P = 0.001$) and the volume of irrigating fluid used (median 15 L versus 18 L, $P = 0.004$). However TXA treatment

**TABLE II. *Comparison of treatment group and control group***

| Variable | Tranexamic Acid (n = 70) | Control (n = 66) | *P* Value |
|---|---|---|---|
| Operative blood loss (mL) | 128 (43–338) | 250 (95–500) | 0.018* |
| Blood loss per gram of resected tissue (mL/g) | 8 (4–17) | 13 (7–22) | 0.020* |
| Decrease in Hb on first postoperative day (g/L) | 12 (6–19) | 13 (7–21) | 0.172† |
| Decrease in Hb on second postoperative day (g/L) | 12 (7–19) | 17 (9–28) | 0.087† |
| Volume of irrigant fluid (L) | 15 (8–21) | 18 (12–30) | 0.004* |
| Weight of resected tissue (g) | 16 (9–24) | 16 (10–25) | 0.415* |
| Operating time (min) | 36 (19–52) | 48 (32–73) | 0.001* |
| Length of catheterization (days) | 1 (1–2) | 1 (1–2) | 0.342* |
| Length of hospitalization (days) | 3 (2–4) | 3 (2–3) | 0.218* |

*KEY: Hb = hemoglobin.*
*Data presented as median, with 25th to 75th percentiles in parentheses.*
** Mann-Whitney U test.*
*† t test.*

had no effect on the duration of catheterization or hospitalization (Table II).

## COMMENT

The current treatment of choice for obstructive urinary symptoms caused by prostatic enlargement is TURP, although the procedure is associated with complications such as blood loss and irrigating fluid absorption. Finasteride pretreatment, for at least 2 weeks, reduces perioperative blood loss, but does not affect other clinically relevant parameters such as the postoperative blood transfusion rates or duration of catheterization.[3] Despite statistically significant reductions in operative bleeding and operative time, we found that, as with finasteride, short-term administration of TXA did not affect the numbers of patients requiring blood transfusion or shorten the hospitalization time. Finasteride is thought to act by mediating androgen-dependent growth factors that regulate angiogenesis in the prostate.[20] TXA, in contrast, accumulates in the extracellular space of tissues where it inhibits tissue fibrinolysis. The consequent stabilization of the blood clots is not associated with laboratory signs of excessive fibrinolysis.[21]

Postoperative TURP-associated blood loss has been correlated with an increase in urinary fibrinolytic activity. Administration of antifibrinolytic drugs may be beneficial in reducing postoperative bleeding.[11] We continued TXA treatment to include the first postoperative day and observed a decrease in the blood hemoglobin concentration on the second postoperative day. However, this decrease was not statistically robust. Nevertheless, our results are in accordance with the findings that short-term aminocaproic acid treatment reduced the immediate postoperative bleeding associated with TURP.[13] Because finasteride and TXA have different mechanisms of action, their co-administration may have an additive effect in reducing TURP bleeding and could possibly have wider clinical benefits. However, we should not underestimate the significance of surgical skill. The strong correlation between the amount of blood loss and the weight of the resected tissue is associated with physical damage (severing of blood vessels) and, therefore, reflects the importance of the surgical technique.

Long-term postoperative TXA treatment (3 weeks) has been shown to reduce the incidence of secondary hemorrhage, which can occur within 4 weeks after the operation.[19] However, the effect of short-term TXA treatment on the incidence of secondary hemorrhage was not within the scope of this study and remains to be investigated.

In addition to reducing operative blood loss, we were surprised to observe a statistically significant decrease in the operative time and volume of irrigating fluid required. Reduced bleeding during TURP as a result of TXA treatment may lead to better surgical conditions and, as a consequence, shorter operative times and lower irrigating fluid volumes. This is an intriguing finding, because absorption of irrigating fluid is another concern with TURP and is associated with increased operative time and blood loss.[5,22] Therefore, TXA treatment may have the additional benefit of reducing irrigating fluid absorption. None of our 136 patients had clinical signs of irrigating fluid absorption (transurethral resection syndrome). However, because of the lack of detailed postoperative follow-up, strict conclusions could not be drawn. The frequency of transurethral resection syndrome varied from

0.18% to 10.9% in recent studies[23–25]; therefore, we would have required a much larger pool of patients to detect any statistically significant differences.

Several studies have demonstrated that TXA treatment does not predispose a patient to thromboembolic complications.[26–28] Accordingly, we did not observe any severe thromboembolic complications. However, it must be noted that controlled clinical trials are not ideal for detecting rare drug-related adverse events.[29] Moreover, we did not observe indissoluble intravesical blood clots in patients receiving TXA that would have hampered resection, as has been suggested.[30] Furthermore, because the operating time and volume of irrigating fluid needed were reduced in our treatment group, it was unlikely that TXA treatment had any detrimental effects on the operation.

## CONCLUSIONS

We have shown that short-term TXA treatment significantly reduces surgical bleeding during TURP. Additional studies are needed to investigate whether co-administration of TXA with finasteride can further reduce TURP-associated bleeding, the blood transfusion rate, and other objectively measurable clinical parameters. Our findings of a reduction in the operative time and irrigating fluid requirement are intriguing and merit future study.

## REFERENCES


1. Mebust WK, Holtgrewe HL, Cockett ATK, *et al:* Transurethral prostatectomy: immediate and postoperative complications. Cooperative study of 13 participating institutions evaluating 3,885 patients. J Urol **141:** 243–247, 1989.
2. Borboroglu PG, Kane CJ, Ward JF, *et al:* Immediate and postoperative complications of transurethral prostatectomy in the 1990s. J Urol **162:** 1307–1310, 1999.
3. Donohue JF, Sharma H, Abraham R, *et al:* Transurethral prostate resection and bleeding: a randomized, placebo controlled trial of the role of finasteride for decreasing operative blood loss. J Urol **168:** 2024–2026, 2002.
4. Hagerty JA, Ginsberg JD, Harmon JD, *et al:* Pretreatment with finasteride decreases perioperative bleeding associated with transurethral resection of the prostate. Urology **55:** 684–689, 2000.
5. Sandfeldt L, Bailey DM, and Hahn RG: Blood loss during transurethral resection of the prostate after 3 months of treatment with finasteride. Urology **58:** 972–976, 2001.
6. Ekengren J, and Hahn RG: Blood loss during transurethral resection of the prostate as measured by the Hemocue photometer. Scand J Urol Nephrol **27:** 501–507, 1993.
7. Nielsen JD, Gram J, Holm-Nielsen A, *et al:* Bleeding and activation of coagulation during and after transurethral prostatectomy: importance of the acute-phase response and prostate specific antigen? BJU Int **83:** 990–995, 1999.
8. Bell CRW, Murdock PJA, Pasi KJ, *et al:* Thrombotic risk factors associated with transurethral prostatectomy. BJU Int **83:** 984–989, 1999.
9. Nielsen JD, Gram J, Fabrin A, *et al:* Lack of correlation between blood fibrinolysis and the immediate or post-operative blood loss in transurethral resection of the prostate. Br J Urol **80:** 105–110, 1997.
10. Andersson L, Nilsson IM, Colleen S, *et al:* Role of urokinase and tissue activator in sustaining bleeding and the management thereof with EACA and AMCA. Ann NY Acad Sci **146:** 642–658, 1968.
11. Nielsen JD, Gram J, Holm-Nielsen A, *et al:* Post-operative blood loss after transurethral prostatectomy is dependent on *in situ* fibrinolysis. Br J Urol **80:** 889–893, 1997.
12. Mannucci PM: Hemostatic drugs. N Engl J Med **339:** 245–253, 1998.
13. Madsen PO, and Strauch AE: The effect of aminocaproic acid on bleeding following transurethral prostatectomy. J Urol **96:** 255–256, 1966.
14. Smart CJ, Turnbull AR, and Jenkins JD: The use of frusemide and epsilon-amino-caproic-acid in transurethral prostatectomy. Br J Urol **46:** 521–525, 1974.
15. Smith RB, Riach P, and Kaufman JJ: Epsilon aminocaproic acid and the control of post-prostatectomy bleeding: a prospective double-blind study. J Urol **131:** 1093–1095, 1984.
16. Sharifi R, Lee M, Ray P, *et al:* Safety and efficacy of intravesical aminocaproic acid for bleeding after transurethral resection of prostate. Urology **27:** 214–219, 1986.
17. Erstad BL: Systemic hemostatic medications for reducing surgical blood loss. Ann Pharmacother **35:** 925–934, 2001.
18. Porte RJ, and Leebeek FW: Pharmacological strategies to decrease transfusion requirements in patients undergoing surgery. Drugs **62:** 2193–2211, 2002.
19. Miller RA, May MW, Hendry WF, *et al:* The prevention of secondary haemorrhage after prostatectomy: the value of antifibrinolytic therapy. Br J Urol **52:** 26–28, 1980.
20. Hahn RG, and Ekengren JC: Patterns of irrigating fluid absorption during transurethral resection of the prostate as indicated by ethanol. J Urol **149:** 502–506, 1993.
21. Berntorp E, Follrud C, and Lethagen S: No increased risk of venous thrombosis in women taking tranexamic acid. Thromb Haemost **86:** 714–715, 2001.
22. Levi M, Cromheecke ME, de Jong E, *et al:* Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints. Lancet **354:** 1940–1947, 1999.
23. Ruel MA, Wang F, Bourke ME, *et al:* Is tranexamic acid safe in patients undergoing coronary endarterectomy? Ann Thorac Surg **71:** 1508–1511, 2001.
24. Kaufman DW, and Shapiro S: Epidemiological assessment of drug-induced disease. Lancet **356:** 1339–1343, 2000.
25. Ward MG, and Richards B: Complications of antifibrinolysis therapy after prostatectomy. Br J Urol **51:** 211–212, 1979.
26. Berger AP, Wirtenberger W, Bektic J, *et al:* Safer transurethral resection of the prostate: coagulating intermittent cutting reduces hemostatic complications. J Urol **171:** 289–291, 2004.
27. Kolmert T, and Norlen H: Transurethral resection of the prostate: a review of 1111 cases. Int Urol Nephrol **21:** 47–55, 1989.
28. Koshiba K, Egawa S, Ohori M, *et al:* Does transurethral resection of the prostate pose a risk to life? 22-year outcome. J Urol **153:** 1506–1509, 1995.
29. Puchner PJ, and Miller MI: The effects of finasteride on hematuria associated with benign prostatic hyperplasia: a preliminary report. J Urol **154:** 1779–1782, 1995.
30. Verstraete M: Clinical application of inhibitors of fibrinolysis. Drugs **29:** 236–261, 1985.

Original Report

# An Open-Label, Single-Arm, Efficacy Study of Tranexamic Acid in Adolescents with Heavy Menstrual Bleeding

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A B S T R A C T

*Study Objective:* Heavy menstrual bleeding (HMB) occurs in up to 40% of adolescent girls, significantly affecting their daily activities. Identifying alternative treatment strategies for HMB is particularly important for adolescents who prefer not to take hormonal contraception. Our objective was to determine whether use of tranexamic acid (TA) would increase health-related quality of life and decrease menstrual blood loss (MBL) in adolescents with HMB.

*Design, Setting, Participants, Interventions, and Main Outcome Measures:* In an open-label, multi-institutional, single-arm, efficacy study, patients 18 years of age or younger with HMB were treated with oral TA 1300 mg 3 times daily during the first 5 days of menses and monitored over the course of 4 menstrual cycles (1 baseline; 3 treatment cycles). Assessment of MBL was performed using the Menorrhagia Impact Questionnaire (MIQ) and the Pictorial Blood Assessment Chart. The MIQ includes Likert scale items, validated to assess the influence of HMB on quality of life. In previous studies, a 1-point decrease or more in score correlated with clinically significant improvement.

*Results:* Thirty-two patients enrolled in the study, and 25 had sufficient follow-up data to be deemed evaluable. The mean age of the participants was 14.7 years (range, 11-18 years). There was an overall improvement in all items of the MIQ, with a greater than 1-point improvement in the MIQ perceived blood loss scale. When using TA, mean Pictorial Blood Assessment Chart score improved by 100 points. There were no medication-related serious adverse events.

*Conclusion:* Use of TA in female adolescents with HMB is well tolerated and leads to clinically meaningful reduction in MBL.

*Key Words:* Heavy menstrual bleeding, Menorrhagia, Tranexamic acid, Menorrhagia Impact Questionnaire

## Introduction

Heavy menstrual bleeding (HMB) is commonly encountered in adolescents.[1] In population-based studies, 1 in 4 women experience HMB at some point during their reproductive years[2] and HMB has a significant detrimental effect on their quality of life.[3–5] HMB has a multifactorial etiology, with up to 20% of patients having an underlying bleeding disorder.[6,7] Commonly used treatment approaches include the use of combined oral contraceptives, levonorgestrel-releasing intrauterine devices, and cyclical progestin.[8,9]

Tranexamic acid (TA), a competitive plasminogen inhibitor (antifibrinolytic), has been used for the treatment of HMB outside of the United States for decades,[10] and has established efficacy in reducing menstrual blood loss (MBL) in adults. A new oral formulation of TA with increased absorption time (Lysteda; Ferring Pharmaceuticals) was approved by the US Food and Drug Administration in 2009 for women 18 years of age and older with cyclic HMB. In a study of adult women, those receiving 3900 mg/d of TA for up to 5 days per menstrual cycle had significantly greater reduction in MBL compared with the placebo group. Similar safety and efficacy data are lacking for adolescents, for whom identifying alternative treatment strategies is particularly important. Although oral contraceptives are often the first-line treatment for HMB, barriers to effective use of oral contraceptives in young adolescents include difficulties with compliance, concerns about side effect profile, hesitancy to commit to a daily medication in an otherwise healthy young woman, as well as religious and cultural influences on willingness to use a "birth control pill." For these patients, TA is a potential alternative to oral contraceptives.

The primary objective of this study was to assess the efficacy of TA in decreasing MBL and increasing health-related quality of life (HRQoL) in adolescents with HMB.

## Materials and Methods

The presented study was a prospective, multicenter, single-arm, efficacy study of TA for the treatment of HMB in

The authors indicate no conflicts of interest.

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1083-3188/$ - see front matter 
https://doi.org/10.1016/j.jpag.2019.01.009

**Table 1**
Study Inclusion and Exclusion Criteria

| |
|---|
| Study inclusion criteria |
| • Menstruating and between 10 and 19 years of age<br>• Nonsmoker<br>• Negative pregnancy test<br>• Menstrual cycles occur every 21-60 days<br>• Either sexually inactive or agree to use a barrier method with spermicide throughout the study period |
| Study exclusion criteria |
| • Severe anemia (hemoglobin <8 g/dL)<br>• Active thromboembolic disease, history of thromboembolic disease, known inherited thrombophilia, or family history of thrombosis in a first-degree relative<br>• Severe medical or psychiatric illness<br>• Severe bleeding disorder (patients with mild bleeding disorders such as von Willebrand disease type 1, platelet storage pool or release defects, and bleeding tendency due to Ehlers-Danlos syndrome were included in the study)<br>• Pregnancy in the past 6 months or breastfeeding<br>• Use of estrogen- and/or progesterone-containing hormonal contraception within 3 months of study entry<br>• Use of systemic steroids within 1 month of study entry<br>• History of subarachnoid hemorrhage<br>• History of hepatitis B, C, or HIV<br>• Baseline creatinine >20% above the upper limit of normal for age |

female adolescents. Its primary goal was to assess whether the use of TA during the first 5 days of menses decreased MBL and improved HRQoL defined by a 1 point or more improvement in the Menorrhagia Impact Questionnaire (MIQ) score.[11]

*Patients*

Young women aged 10-19 years were eligible to be enrolled during regularly scheduled visits to pediatric hematology clinics for evaluation or management of HMB. Four children's hospitals participated in the study (Nationwide Children's Hospital, Columbus, OH; Akron Children's Hospital, Akron, OH; Rainbow Babies and Children's Hospital, Cleveland, OH; Riley Hospital for Children at Indiana University Health, Indianapolis, IN). At Nationwide Children's Hospital (primary study site), a system-wide electronic mail message to employees and the publication of the study advertisement on an online, publicly available, searchable database of clinical trials was also used to augment recruitment. For study inclusion, the diagnosis of HMB was on the basis of the medical judgement of the principal or the site investigator, although patients did need to have baseline cycles occurring every 21-60 days to be eligible (Table 1). Participants with and without previously diagnosed bleeding disorders were eligible for inclusion. Participants were excluded if they had used hormonal contraception (estrogen or progestin) within 3 months of study entry or had an anticipated need to initiate hormonal contraception during the study period. The study was approved by the institutional review board of each participating site. Written informed consent was obtained from the legal guardian of each participant and written informed assent was obtained from each participant.

*Study Protocol and Data Collection*

Upon enrollment, participants underwent a study entrance medical history, physical examination, and baseline laboratory testing (Table 2). The study period consisted of 1 pretreatment baseline menstrual cycle, 3 on-treatment menstrual cycles (cycles 1, 2, and 3), and a study exit visit. Study staff kept in contact with families via phone, e-mail, or text messaging reminders (on the basis of the selected patient preference at time of enrollment). At the end of each cycle, participants returned a completed Pictorial Blood Assessment Chart (PBAC) and medication administration log. Study staff administered the MIQ to each participant over the phone within 7 days of completion of each menses. Adverse event data were collected for each participant throughout the 4-month study period at clinic visits and during follow-up phone calls. Participants were considered evaluable if at least 2 of the 3 treatment cycles, in addition to the baseline cycle, were completed.

Upon successful completion of data collection for the first and third treatment cycle and study exit visit, each participant received a small monetary compensation. There was an additional small monetary incentive for returning PBACs, subject diaries, and unused medication.

*Medication Acquisition and Administration*

Ferring Pharmaceuticals supplied 3600 Lysteda tablets (650 mg) for the purpose of this study. In 2013, Ferring Pharmaceuticals stopped the production of Lysteda and after October 2014, all patients enrolled on this study received generic TA. Participants were instructed to take 2

**Table 2**
Study Schema

| | Study Entry | Baseline (Pretreatment) | Cycle 1 | Cycle 2 | Cycle 3 | Study Exit* |
|---|---|---|---|---|---|---|
| | | | Treatment with TA | | | |
| History and physical | × | | | | | × |
| MIQ and PBAC | | × | × | × | × | |
| Complete blood count | ×† | | | | | × |
| Ferritin | ×† | | | | | × |
| Creatinine | ×† | | | | | |
| Urine pregnancy test | × | | | | | |
| Phone call | | ×‡ | ×‡ | ×‡ | ×‡ | |

MIQ, Menorrhagia Impact Questionnaire; PBAC, Pictorial Blood Assessment Chart; TA, tranexamic acid.
* Study exit visit to occur within 30 days of the end of the fourth menses.
† Study laboratory tests completed at study entry or within 60 days before initiation of study medication treatment.
‡ Study phone call to occur within 7 days of the end of the menses (MIQ administered).

tablets (1300 mg) of TA 3 times a day (3900 mg/d) for a maximum of 5 days during monthly menstruation (15 total doses). If menses lasted less than 5 days, participants were instructed to stop the medication when menses ended.

Compliance was defined as adhering to prescribed therapy two-thirds of the time or more. To meet this definition, participants who completed 2 treatment cycles had to use 40 or more of the 60 expected tablets and participants who completed 3 treatment cycles had to use 60 or more of the 90 expected tablets. Compliance was assessed by study personnel, who reviewed participant study diaries and counted returned tablets.

### *Study End Points*

The primary study end point was predetermined to be an improvement in HRQoL as defined by a 1 point or more decrease (improvement) in the individual items of the MIQ score.

The MIQ is a validated, disease-specific patient-reported outcome measurement tool used in patients with HMB for subjective assessment of blood loss, limitations in work (school attendance in the case of adolescents), limitations in social/leisure and physical activities, as well as an overall assessment of the meaningfulness of any observed changes in quality of life (Table 3).[11] The overall respondent burden, as noted in the validation study, is an average of 2 minutes. A change in the MBL measured according to PBAC scores, as well as change in hemoglobin and ferritin concentrations, were defined as secondary end points for this study. Investigators have shown that a PBAC score of 150-185 or more correlates with 80 mL or more of MBL measured using the alkaline hematin test.[12,13] The PBAC has not been well studied in adolescents with HMB, but one study reported a correlation between PBAC scores and self-identification among adolescents as having heavy, normal, or light menses.[14]

### *Statistical Considerations*

An efficacy analysis was conducted using data from a modified intent-to-treat population, defined as participants with sufficient data from the pretreatment phase and 2 or more treatment cycles. Changes in the MIQ scores were measured across the treatment cycles using a Friedman test. As hypothesized, no differences were observed across treatment cycles so the average MIQ scores during treatment cycles were compared with the pretreatment value for each MIQ item using paired *t* tests. Sample size calculation was on the basis of the assumption of a 25% dropout rate and greater than 90% power to detect an improvement in MIQ score of 1 or more point using an $\alpha$ of 0.05 and assuming that the SD of the difference would be 1.4 or less. If the data were not normally distributed, a Wilcoxon signed rank test was used with resulting power of 89%. A paired *t* test was used to analyze intraparticipant changes in PBAC scores, hemoglobin, and ferritin. A McNemar $\chi^2$ test was used to compare the change in the percentage of patients who reported heavy/very heavy bleeding from baseline to treatment cycle 3 (MIQ-1). Demographic and safety data are described using summary statistics.

**Table 3**
Menorrhagia Impact Questionnaire[8]

| MIQ Question | Response Scale |
|---|---|
| 1. During your most recent menstrual period, your blood loss was: | 1. Light<br>2. Moderate<br>3. Heavy<br>4. Very heavy |
| 2. How much did your bleeding limit your school attendance? | 1. Not at all<br>2. Slightly<br>3. Moderately<br>4. Quite a bit<br>5. Extremely |
| 3. How much did your bleeding limit you in your physical activities? | |
| 4. How much did your bleeding limit your social or leisure activities? | |
| 5/5a/5b. Compared with your previous menstrual period, would you say your blood loss during this period was: | 0. About the Same<br>1. Better<br>2. Worse (if better or worse, patient given 7-point response scale):<br>1. Almost the same, hardly better/worse at all<br>2. A little better/worse<br>3. Somewhat better/worse<br>4. An average amount better/worse<br>5. A good deal better/worse<br>6. A great deal better/worse<br>7. A very great deal better/worse |
| 6. Was this a meaningful or important change for you? | 0. No<br>1. Yes |

MIQ, Menorrhagia Impact Questionnaire.

## Results

A total of 32 subjects were enrolled in this study from June 2013 to July 2016. Of these, 2 were screen failures. Of the remaining 30 patients, 25 patients completed at least 2 of the 3 treatment cycles and were included in the final analysis (16 subjects: 3 treatment cycles; 9 subjects: 2 treatment cycles). Patients were enrolled across all participating sites, with most (21/25) enrolled at Nationwide Children's Hospital.

The mean age of the participants was 14.7 years (range, 11-18 years). Most (78%) of enrolled subjects were 1-year or more postmenarche (and 63% ≥2 years) at the time of study enrollment. Ninety-one percent described their baseline cycles as “monthly” or between 24 and 35 days in duration. Ten participants (40%) had an identified bleeding disorder. Baseline demographic characteristics for the 25 patients included in the analysis are described in Table 4. Of these 25 patients, 21 patients met the study definition of therapy compliance, on the basis of the number of tablets left at study exit visit.

At baseline, 4 of the 25 patients (16%) had a hemoglobin concentration of less than 12 g/dL. However, 11 (44%) subjects had reduced bodily iron stores with ferritin concentration of less than 20 ng/dL. Twenty-one subjects (84%) noted heavy or very heavy MBL as measured by a MIQ-1 score of 3 or more. Four girls (16%) reported that heavy

**Table 4**
Description of the Study Population (n = 25)

| Variable | Value |
|---|---|
| Mean age | 14.7 years (range, 11-18 years) |
| Mean weight | 71.5 kg (range, 45.9-110.4 kg) |
| Race, n (%) | |
| White non-Hispanic | 13 (52) |
| White Hispanic | 1 (4) |
| Black non-Hispanic | 7 (28) |
| Biracial | 3 (12) |
| Asian | 1 (4) |
| Bleeding disorder, n (%) | |
| Platelet function defect | 6 (24) |
| Joint hypermobility | 3 (12) |
| von Willebrand disease type 1 | 1 (4) |

MBL led to at least moderate limitations on school activities (MIQ-2 ≥ 3), 9 (36%) reported that it limited their physical activities (MIQ-3 ≥3) and similarly, 9 (36%) reported that heavy MBL led to at least moderate limitations on their social and leisure activities (MIQ-4 ≥3).

*MIQ-1: Perceived Blood Loss*

For the 25 patients analyzed in this study, the mean MIQ-1 score improved from 3.0 at baseline to 1.91 on average across the treatment cycles ($P < .001$; difference = 1.09; 95% confidence interval [CI], 0.76-1.42; Fig. 1), fulfilling the primary end point of a 1-point or more improvement (median MIQ-1 changed from 3 at baseline to 2 across treatment cycles; $P = <.001$). When evaluated individually, 17 patients (68%) had an average 1-point or more improvement in their MIQ-1 score during the treatment cycles compared with their baseline cycle. All 17 patients (17/17; 100%) reported that this change was clinically meaningful (MIQ-6 score 1). The number of patients reporting heavy/very heavy blood loss decreased from 84% at baseline to 23% with the use of TA ($P < .001$; Fig. 2). In a subanalysis of patients with and without identified bleeding disorders, we did not note a statistically significant difference in change in MIQ-1 scores between these 2 populations.

*MIQ-2, 3, and 4: Limitations on School Attendance, Physical, Social, and Leisure Activities*

At baseline, the mean MIQ-2 score (limitations on school attendance) was 1.64 (range, 1-5), with only 6 of the 25 (24%) patients reporting any limitations on school attendance during their monthly menses (MIQ-2 score ≥2). The mean score did not change significantly with use of TA ($P = .134$; difference = 0.37; 95% CI, −0.12 to 0.87). Pre- and post median MIQ-2 scores were 1 and 1, respectively ($P = .25$).

The MIQ-3 score, reflective of limitations on physical activities, changed from a mean of 2.08 at baseline to 1.40

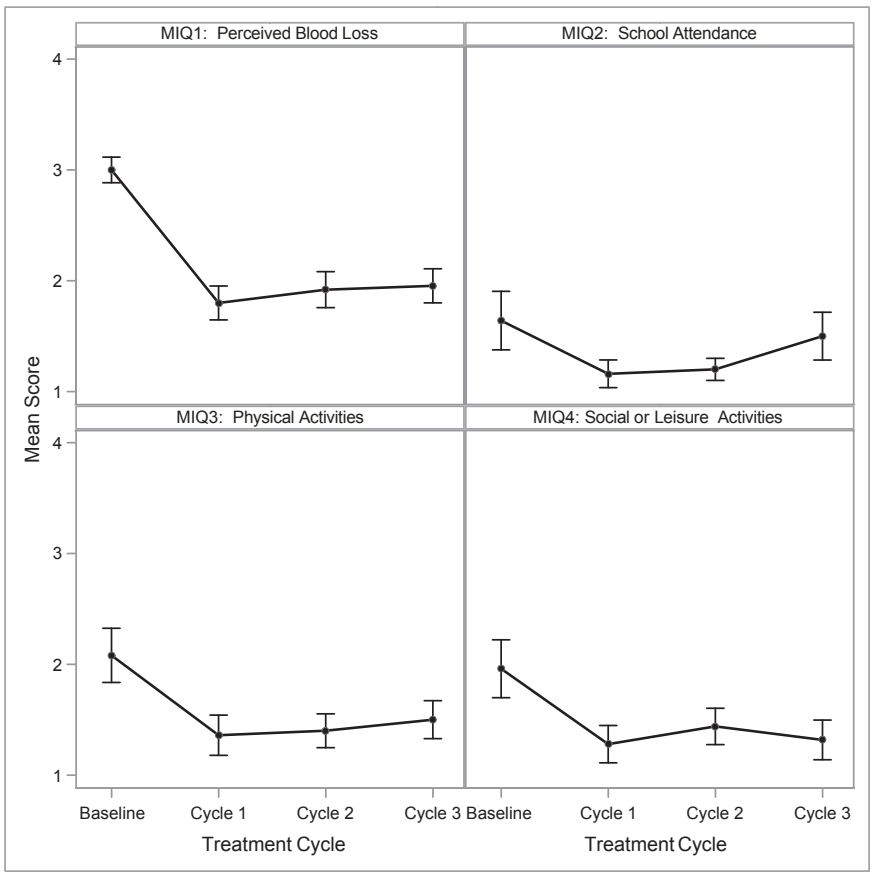


**Fig. 1.** Health-related quality of life scores at baseline and during treatment with tranexamic acid (TA) using the Menorrhagia Impact Questionnaire (MIQ) tool. For item 1 (MIQ1), there was a greater than 1 point improvement in the average score with the use of TA ($P < .001$). For items 2, 3, and 4 (MIQ2, 3, and 4), the change in average score was <1, however, the improvement in scores was statistically significant for MIQ3 ($P = .002$) and MIQ4 ($P = .009$).

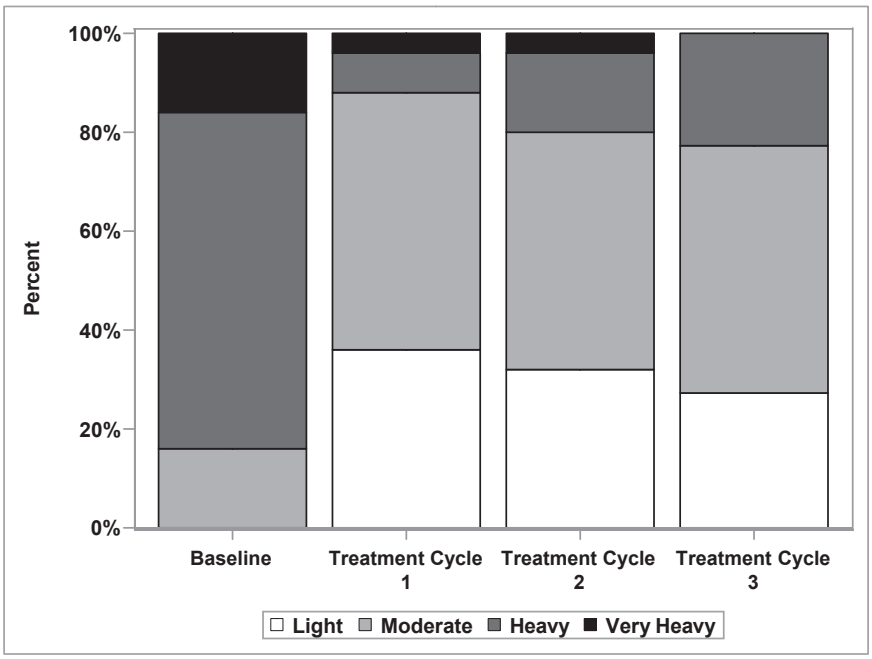


**Fig. 2.** Patient-reported reduction in menstrual blood loss (MBL) with use of tranexamic acid (TA), assessed according to responses to the first item of the Menorrhagia Impact Questionnaire (perceived blood loss). A 60% reduction in the number of patients reporting heavy/very heavy MBL was noted with the use of TA ($P < .001$).

averaged over 3 treatment cycles ($P = .002$; difference = 0.68; 95% CI, 0.28-1.08). Median MIQ-3 score changed from 2 to 1 ($P = .002$). Nine patients (36%) had a MIQ-3 score of 3 or more at baseline, indicating significant restrictions on physical activities because of HMB. For this subset of patients, the MIQ-3 score improved to an average of 1.74 over 3 treatment cycles, with a 1-point or more improvement in this item of the MIQ with the use of TA.

At study entry, 10 of 25 patients (40%) reported that HMB limited their social and leisure activities, of which 9 of 25 (36%) had an MIQ-4 score of 3 or more at baseline, indicating significant restrictions on social/leisure activities because of HMB. Overall, the MIQ-4 score changed from a mean of 1.96 to 1.33 ($P = .009$; difference = 0.63; 95% CI, 0.17-1.08), and pre- and post median MIQ-4 scores were 1 and 1, respectively ($P = .006$). However, for patients with significant restrictions on social/leisure activities, treatment with TA improved the MIQ-4 score from an average of 3.5 to 1.76 ($P = .002$; difference = 1.74; 95% CI, 0.86-2.62), showing a greater than 1-point improvement with treatment.

*PBAC Scores*

PBAC scores were available for 24 of the 25 subjects. Twenty (83%) subjects reported a PBAC score greater than 100 (abnormal) at baseline and 19 (79.2%) subjects reported an improvement in their PBAC scores during treatment with TA. Overall, the PBAC score improved from an average of 255.1 to 154.6 ($P < .001$; difference = 100.5; 95% CI, 46.3-154.7).

*Hemoglobin and Ferritin Concentrations*

No significant changes in hemoglobin or ferritin were observed over time. The average hemoglobin at study entry was 12.7 g/dL (n = 25; range, 10.4-15.3 g/dL) and during treatment with TA was 12.8 g/dL (n = 22; range, 10.6-14.7 g/dL; $P = .94$). The average ferritin concentration at baseline was 25.9 ng/dL (n = 25; range, 4-82 ng/dL). With TA treatment, the average ferritin was 26.3 ng/dL (n = 22; range, 5-59 ng/dL; $P = .61$).

*Adverse Events*

During the course of this study, a total of 2 serious adverse events were reported. These were 2 episodes of suicidal ideation (1 around the time of baseline assessment and 1 after TA initiation) that occurred in the same patient, who had a history of psychiatric illness. Neither event was thought to be related to the study drug. Most adverse events noted were known side effects of TA, and were mild to moderate in severity (Table 5). The most common adverse events reported were sinonasal symptoms (nasal

**Table 5**
Frequency of Adverse Events Reported with Tranexamic Acid Treatment

| Event, n (%) |
|---|
| Sino-nasal symptoms: 17 (21) |
| Cough, sore throat, earache, mouth pain: 8 (10) |
| Fatigue: 8 (10) |
| Musculoskeletal pain: 7 (8.75) |
| Abdominal pain: 7 (8.75) |
| Headache: 7 (8.75) |
| Diarrhea, constipation, bloating, gastroenteritis: 5 (6.25) |
| Nausea, vomiting: 4 (5) |
| Menstrual discomfort and cramps: 3 (3.75) |
| Passage of blood clots with menses: 3 (3.75) |
| Prolonged bleeding: 3 (3.75) |
| Fever: 2 (2.5) |
| Anxiety: 2 (2.5) |
| Suicidal ideation: 2 (2.5) |
| Dizziness: 1 (1.25) |
| Urinary tract infection: 1 (1.25) |
| Yeast infection: 1 (1.25) |

Total number of adverse events noted in 25 patients = 81.

congestion, headache, sinus pain). Other side effects noted during the study, notably musculoskeletal pain (back, abdomen), menstrual cramps, nausea, etc, were likely related to the underlying HMB. No thrombotic events were noted during the study period and none of the participants reported any ocular adverse effects.

## Discussion

This prospective, open-label clinical study was designed to evaluate the usefulness of a newer formulation of TA in decreasing menstrual blood flow and improving HRQoL in adolescent girls with HMB. In our study cohort of 25 patients ranging in age from 11 to 18 years, the use of TA led to qualitative and quantitative improvement in MBL measured according to the MIQ and PBAC, respectively. Most of our subjects noted significant improvement in their MIQ-1 (perceived blood loss) and PBAC scores during treatment with TA. For most of these young girls, this improvement was noticeable during their first treatment cycle with TA, and was maintained over the course of the study period.

The improvements seen in items 3 (physical activity) and 4 (social activities) of the MIQ were statistically significant, but failed to meet our primary end point of a 1-point or more improvement in the average score during treatment with TA. For the one-third of patients who reported baseline severe restrictions on physical or social activities because of HMB, the use of TA did lead to significant improvement in their ability to participate.

In contrast to adult women, in whom a study of TA showed that most reported baseline moderate-severe limitations on work inside or outside of the home due to heavy menstrual blood flow,[15] only a small proportion of our study participants reported major restrictions on school attendance or participation due to heavy menses. This might reflect parental and societal pressure to attend school, despite significant physical discomfort, or it is possible that our study population had milder heavy menses at baseline.

Iron deficiency, with or without anemia, occurs commonly in young women with HMB.[16–18] None of our study participants were severely anemic at baseline, although nearly half of them had reduced bodily iron stores (serum ferritin $<20$ ng/dL), further substantiating that iron deficiency without anemia can be unrecognized if screening is performed with hemoglobin and red cell indices alone.[17] These participants were not routinely prescribed iron supplements, and because of the short duration of our study period, there was no significant change noted in the average hemoglobin or ferritin concentrations with the use of TA.

TA was generally well tolerated and most of the adverse events noted during the course of the study were mild to moderate in severity. The most common side effects reported were symptoms commonly reported with menses (headache, cramps) or otherwise unlikely to be study drug related (nasal congestion and other upper respiratory symptoms).

In a study of adult women, those who received 3900 mg TA per day for up to 5 days per menstrual cycle, showed clinically meaningful and significantly greater reduction in menstrual blood flow compared with women who received placebo.[15] Ferring Pharmaceuticals has also performed a pharmacokinetic study of Lysteda (Ferring Pharmaceuticals) in 20 female adolescents (12-16 years of age) with HMB (http://clinicaltrials.gov/ct2/show/results/NCT01190150), which showed that 3900 mg/d is also an appropriate dosage for this age group. Because our study population was similarly aged, we chose this dosing strategy. Because TA is sold as 650-mg tablets in the United States, this approach is suitable for all patients who weigh 40 kg or more.

Our study design was not without limitations, most notably the lack of a comparator (hormonal contraception, for example) or placebo-controlled arm. We selected a single-arm study design because of the numerous patient-level, parent-level, and cultural factors that affect decision-making regarding the use of hormonal contraception in young adolescents, and the ethical issues of the use of placebo in this setting. It was determined that a randomized design would be a major barrier to study feasibility. It is also true that dysfunctional bleeding due to anovulatory cycles will improve with time over the first 12-18 months after menarche. However, because of the relatively short duration of our study (4 months), and the fact that most enrolled subjects were 1 year or more post-menarche at the time of study enrollment, we do not believe natural history played a substantial role in the clinical improvements seen with use of TA.

Another limitation of our methodology is that the primary study end point was change in MIQ as opposed to a more objective change in measured blood loss.[19] However, a major factor that motivates patients with HMB to seek medical care is the negative effect of HMB on daily life.[20–22] Quality of life is an integral part of the National Institute for Health and Clinical Excellence definition of HMB, and HMB is defined by the International Federation of Gynecology and Obstetrics as excessive MBL that interferes with the woman's physical, emotional, social, and material quality of life.[23,24] The selection of change in MIQ as our primary outcome served to enhance the feasibility of our study (actual menstrual blood flow is quite burdensome to measure) and the clinical meaningfulness of our results. This study also included adolescents with and without an underlying bleeding disorder. However, none of the subjects with an identified bleeding disorder were treated with nasal desmopressin or replacement factor products during the study period, decreasing the heterogeneity of our study population.[25]

In conclusion, the use of TA in adolescent girls (with and without bleeding disorders) with cyclic HMB led to clinically meaningful reduction in the MBL and improvement in HRQoL. A small percentage of the patients reported mild/moderate side effects, and TA was generally well tolerated. TA offers a safe and efficacious first-line treatment option for young girls with cyclic HMB.

## Acknowledgments

The authors thank Ferring pharmaceuticals (Parsippany, NJ) for the supply of 3600 Lysteda tablets that were provided to the patients as part of this study. This work was

supported by a grant from the Hemostasis and Thrombosis Research Society, United States (Clinical Research Award to S.H.O). S.S. was the recipient of the Joan Fellowship in Pediatric Hemostasis and Thrombosis at Nationwide Children's Hospital, 2016-2017.

## References


1. James AH, Ragni MV, Picozzi VJ: Bleeding disorders in premenopausal women: (another) public health crisis for hematology? Hematology Am Soc Hematol Educ Program 2006;474
2. Fraser IS, Mansour D, Breymann C, et al: Prevalence of heavy menstrual bleeding and experiences of affected women in a European patient survey. Int J Gynaecol Obstet 2015; 128:196
3. Cote I, Jacobs P, Cumming D: Work loss associated with increased menstrual loss in the United States. Obstet Gynecol 2002; 100:683
4. Pawar A, Krishnan R, Davis K, et al: Perceptions about quality of life in a school-based population of adolescents with menorrhagia: implications for adolescents with bleeding disorders. Haemophilia 2008; 14:579
5. Shankar M, Chi C, Kadir RA: Review of quality of life: menorrhagia in women with or without inherited bleeding disorders. Haemophilia 2008; 14:15
6. Zia A, Rajpurkar M: Challenges of diagnosing and managing the adolescent with heavy menstrual bleeding. Thromb Res 2016; 143:91
7. Vo KT, Grooms L, Klima J, et al: Menstrual bleeding patterns and prevalence of bleeding disorders in a multidisciplinary adolescent hematology clinic. Haemophilia 2013; 19:71
8. Pai M, Chan A, Barr R: How I manage heavy menstrual bleeding. Br J Haematol 2013; 162:721
9. Srivaths LV, Dietrich JE, Yee DL, et al: Oral tranexamic acid versus combined oral contraceptives for adolescent heavy menstrual bleeding: a pilot study. J Pediatr Adolesc Gynecol 2015; 28:254
10. Callender ST, Warner GT, Cope E: Treatment of menorrhagia with tranexamic acid. A double-blind trial. Br Med J 1970; 4:214
11. Bushnell DM, Martin ML, Moore KA, et al: Menorrhagia Impact Questionnaire: assessing the influence of heavy menstrual bleeding on quality of life. Curr Med Res Opin 2010; 26:2745
12. Janssen CA, Scholten PC, Heintz AP: A simple visual assessment technique to discriminate between menorrhagia and normal menstrual blood loss. Obstet Gynecol 1995; 85:977
13. Zakherah MS, Sayed GH, El-Nashar SA, et al: Pictorial blood loss assessment chart in the evaluation of heavy menstrual bleeding: diagnostic accuracy compared to alkaline hematin. Gynecol Obstet Invest 2011; 71:281
14. Sanchez J, Andrabi S, Bercaw JL, et al: Quantifying the PBAC in a pediatric and adolescent gynecology population. Pediatr Hematol Oncol 2012; 29:479
15. Lukes AS, Moore KA, Muse KN, et al: Tranexamic acid treatment for heavy menstrual bleeding: a randomized controlled trial. Obstet Gynecol 2010; 116: 865
16. Wang W, Bourgeois T, Klima J, et al: Iron deficiency and fatigue in adolescent females with heavy menstrual bleeding. Haemophilia 2013; 19:225
17. Johnson S, Lang A, Sturm M, et al: Iron deficiency without anemia: a common yet under-recognized diagnosis in young women with heavy menstrual bleeding. J Pediatr Adolesc Gynecol 2016; 29:628
18. Sharma R, Stanek JR, Koch TL, et al: Intravenous iron therapy in non-anemic iron-deficient menstruating adolescent females with fatigue. Am J Hematol 2016; 91:973
19. Lukes AS, Muse K, Richter HE, et al: Estimating a meaningful reduction in menstrual blood loss for women with heavy menstrual bleeding. Curr Med Res Opin 2010; 26:2673
20. Shapley M, Jordan K, Croft PR: Abnormal bleeding patterns associated with menorrhagia in women in the community and in women presenting to primary care. Fam Pract 2007; 24:532
21. Kulkarni R: Improving care and treatment options for women and girls with bleeding disorders. Eur J Haematol 2015; 95(Suppl 81):2
22. Shapley M, Jordan K, Croft PR: Why women consult with increased vaginal bleeding: a case-control study. Br J Gen Pract 2002; 52:108
23. National Institute for Health and Clinical Excellence: Heavy Menstrual Bleeding. London, England, National Institute for Health and Clinical Excellence, 2007
24. Munro MG, Critchley HO, Fraser IS: The FIGO systems for nomenclature and classification of causes of abnormal uterine bleeding in the reproductive years: who needs them? Am J Obstet Gynecol 2012; 207:259
25. Kouides PA, Byams VR, Philipp CS, et al: Multisite management study of menorrhagia with abnormal laboratory haemostasis: a prospective crossover study of intranasal desmopressin and oral tranexamic acid. Br J Haematol 2009; 145:212

*Int. J. Oral Maxillofac. Surg. 2003; 32: 504–507*
doi:10.1054/ijom.2002.0414, available online at http://www.sciencedirect.com

International Journal of
Oral & Maxillofacial Surgery

Clinical Paper
Oral Medicine

# Tranexamic acid mouthwash—A prospective randomized study of a 2-day regimen *vs* 5-day regimen to prevent postoperative bleeding in anticoagulated patients requiring dental extractions

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*G. Carter, A. Goss: Tranexamic acid mouthwash—A prospective randomized study of a 2-day regimen* vs *5-day regimen to prevent postoperative bleeding in anticoagulated patients requiring dental extractions. Int. J. Oral Maxillofac. Surg. 2003; 32: 504–507.* 

*Abstract.* This prospective randomized study analyses the use of a prescribed 4.8% tranexamic acid post-operative mouthwash over 2 days *vs* 5 days to prevent bleeding in patients taking warfarin who require dental extractions. Eighty-five patients therapeutically anticoagulated with warfarin for various conditions, ranging in age from 21 to 86 years and requiring dental extractions, were randomly divided into two groups. Group A postoperatively received a 4.8% tranexamic acid mouthwash to be used over a 2-day period. Group B received the same mouthwash and instructions postoperatively, to be taken over 5 days. All procedures were performed on an ambulatory basis under local anaesthetic by the same surgeon. Patients were reviewed 1, 3, and 7 days postoperatively to assess bleeding. Eighty-two of the 85 patients encountered no postoperative problems. Two patients in group A and one in group B had minor postoperative bleeds that required minor ambulatory intervention to control. This study shows that a 2-day postoperative course of a 4.8% tranexamic acid mouthwash is as equally effective as a 5-day course in controlling haemostasis post-dental extractions in patient's anticoagulated with warfarin.

Key words: tranexamic acid; warfarin; dental extractions.

Accepted for publication 13 March 2003

Warfarin, the most commonly prescribed oral anticoagulant, is a vitamin K antagonist that impairs the synthesis of coagulation factors II, VII, IX, and X and endogenous proteins C and S in the liver, resulting in impaired fibrin formation. This coagulation defect is used to prevent thromboembolism in various recognized conditions[7]

0901-5027/02/000504+04 $30.00/0 

such as atrial fibrillation and valvular heart disease. Its effects are at the same time however, associated with an increased risk of haemorrhage.

There remains no general consensus on the appropriate peri-operative management of anticoagulation for patients who have been receiving long-term warfarin therapy[10]. In recent years, continuation of anticoagulant therapy in minor oral surgical procedures has gained more attention in the literature, emphasizing the role of local haemostasis[1–4,6,8,9,11].

The majority of postoperative bleeding episodes in anticoagulated patients, who have undergone oral surgery, tend to occur 2 or 3 days after the initial surgery, presumably secondary to increased concentrations of plasminogen and plasminogen activators in the external oral environment with subsequent fibrinolysis. The significant haemostatic effect of local fibrinolysis inhibition in the oral cavity has been demonstrated by utilizing a 4.8% tranexamic acid solution as a postoperative mouthwash[8]. Classically the mouthwash has been prescribed over a 7-day period postoperatively yet some authors have used shorter duration regimens[9]. The shorter course has the benefit of increased compliance and decreased cost.

In this single-blind, prospective randomized study, the effect of a 2-day *vs* 5-day regimen of a 4.8% tranexamic acid mouthrinse on patients who were therapeutically anticoagulated with warfarin and requiring dental extractions were evaluated.

## Materials and methods

Patients older than 18 years of age, therapeutically anticoagulated with warfarin in the range of 2.0 to 4.0 according to the International Normalized Ratio (INR), who were referred for simple tooth extraction (single or multiple), or surgical removal of a retained tooth (single or multiple), were included in the study. Each patient gave signed informed consent as required by the institutional ethical clearance for this study. The patients were treated on an ambulatory basis with exodontia performed under local anaesthetic in the out-patient clinic. They were randomly allocated through the Royal Adelaide Hospital Pharmacy Unit by a computer-generated randomization chart to receive either a 2-day or 5-day course of a 4.8% tranexamic acid (Cyclokapron®, Pharmacia) solution to aid with haemostasis post-dental extraction. The following patients were excluded from the study:

1. Those that did not give informed consent
2. Those that were unable to comprehend the English language
3. Those that were psychiatrically or mentally impaired to give consent
4. Those who had taken aspirin or non-steroidal anti-inflammatory agents within 14 days before surgery
5. Those who had a known haemorrhagic diathesis
6. Those with a known hypersensitivity to the proposed medications including local anaesthetics used in the study

Any patient who consented to participate in the trial had the right to withdraw at any stage and was excluded from the statistical analysis.

The patient's medical history was obtained at the first visit and a standardized form was completed for each patient to record the relevant clinical data. Blood samples were taken on the day of surgery for analysis of the vitamin K-dependent coagulation factors (II+VII+IX+X), calculating the INR utilizing thromboplastin with a known international sensitivity index. The same surgeon treated all of the patients. Patients with cardiac valvular disease received prophylactic antibiotic cover according to the institutional protocol[12].

At surgery, the number of extracted teeth, number of surgically treated teeth, and type of surgery performed were recorded, as well as the duration of surgery and any complications in connection with the procedure. The analgesic drugs used in this study were paracetamol or paracetamol/codeine. All patients received local anaesthetic (2% lignocaine with epinephrine 1/80 000).

Immediately after tooth extraction, but before suturing, the surgically treated region was irrigated with an active 4.8% tranexamic acid mouthwash solution produced by the Royal Adelaide Hospital Pharmacy Department. An oxidized cellulose mesh (Surgicel®, Johnson & Johnson) was soaked in the tranexamic acid solution and then placed in the base of each tooth socket. Resorbable (4.0 Vicryl®, Ethicon) sutures were then placed over the individual sockets.

Before leaving the facility, the patients received a bag containing either 8 or 20 plastic containers each containing 10 ml of the tranexamic acid solution, a supply of analgesics, and gauze pads, postoperative instructions and a list of review appointments (1, 3 and 7 days after surgery). The patients were instructed to use the mouthwash by rinsing for 2 min four times daily, expectorating after use until all containers supplied to them were finished. They were asked not to eat or drink during the first hour after using the mouthwash, and to maintain a liquid diet on the first day after surgery.

Efficacy was monitored by: the recording of subjective bleeding; the need for further intervention to control haemostasis (e.g. alternative haemostatic agents, pharmacological control); other complications; and patient acceptance to the regimen. The monitoring of safety involved ensuring all patients fit the selection criteria, reporting any adverse side effects immediately to the Oral and Maxillofacial Surgery Unit or on-call resident. If postoperative bleeding developed that could not be controlled by compression with a gauze pad for a 20 min period with the patient sitting upright, the patient was reviewed and irrigation of the bleeding surgical site with a 4.8% tranexamic acid solution for 2 min and application of a gauze pad soaked in the solution with compressive biting force for a period of 20 min was instituted.

At the final review visit, all patients were asked whether any discomfort had developed in connection with the mouthwash. The occurrence of haematoma, oedema, and pain was recorded, as well as the ingestion of any drug not previously recorded. For a test of compliance of the mouthwash protocol, the patients were asked to return unused containers of the tranexamic acid solution.

Differences in the treatment groups with respect to postoperative bleeding necessitating intervention were analysed by the $\chi^2$ test.

## Results

Eighty-five patients, 54 males and 31 females ranging from 21 to 86 years of age, underwent a total of 152 dental extractions without cessation or dose modification of their warfarin therapy. The reasons for anticoagulation are presented in Table 1. The patient's demographics and results are presented in Table 2.

Statistically there was no significant difference at the 5% probability level in

*Table 1.* Indications for anticoagulant therapy in the present group of patients ($n=85$)

| Diagnosis | No. | % |
|---|---|---|
| Atrial fibrillation | 14 | 16 |
| Valvular disease | 33 | 39 |
| Arterial thromboembolism | 1 | 1 |
| Venous thromboembolism | 20 | 24 |
| Cerebrovascular disease | 10 | 12 |

postoperative bleeding between the two groups in our trial ($P=0.57$). The observed postoperative bleeding incidence of 4% in our trial is in keeping with that recorded in non-medically compromised patients undergoing routine dental extractions. The postoperative bleeding noted in three cases in our study were all associated with the presence of severe localized bone loss consistent with adult periodontitis in maxillary teeth. All patients tolerated the procedures under local anaesthetic as an outpatient. Post-surgical complications were minimal with only three cases of delayed bleeding occurring, two in group A and one in group B. All cases occurred in the first 48 hours after surgery whilst the patients were still using the mouth rinse, and involved solitary posterior maxillary tooth sockets, in teeth that were routinely delivered with forceps extraction. The common factor in all three cases was severe periodontitis as the indication for extraction, and it is possible the infection in the surrounding soft tissues and local inflammation may have contributed to these bleeds. In all three cases, the bleeding was a persistent ooze of venous origin and haemostasis was achieved by irrigating the sockets with tranexamic acid for 2 min and applying compressive biting pressure for 20 min with a gauze pack soaked in the solution. No case required resuturing, vitamin K or the infusion of fresh frozen plasma. The INR recorded on the day of the bleed was within the therapeutic range for all three patients (3.4, 2.4, 3.7).

## Discussion

This study shows a similar low bleeding rate for a 2-day postoperative course of a 4.8% tranexamic acid mouthrinse as compared to the 5-day regimen.

In Sindet-Pedersen's original article[8], anti-coagulant-treated patients undergoing oral surgery, were prescribed a 4.8% aqueous solution of tranexamic acid for seven days post-surgery to prevent re-bleeding secondary to fibrinolysis of the wound clot. Indeed, the same protocol has been employed in our unit for several years and the significant haemostatic effectiveness of the mouthwash has been confirmed. Interestingly, in a study reported by SOUTO et al.[9], patients rinsed postoperatively for a period of only two days with a similar low incidence of bleeding. This study however, included small numbers of patients, reducing the possibilities of drawing useful conclusions from the data. The results of the present study confirm that anticoagulation treatment with warfarin need not be withdrawn prior to dental extractions, provided that the patients do not have a preoperative INR value greater than 4.0, and local measures including antifibrinolytic therapy is instituted.

Recently some authors have recommended that most anticoagulated patients are capable of withstanding routine, limited, oral surgery procedures without additional medical intervention such as an antifibrinolytic mouthwash provided a good surgical technique is employed[4]. However, they limit acceptable INR values for this proposal to 3.0 or less when clearly there are patients with therapeutic levels higher than 3.0 and this group tends to comprise those most at risk of serious thromboembolic events if their anticoagulation is temporarily discontinued or decreased such as prosthetic mitral valve replacement.

All patients in our study had INR measurements performed by the hospital laboratory prior to treatment, a process that required planning to avoid delays in management. The use of point-of-care-assays to monitor warfarin therapy has received attention recently, claiming several advantages over standard hospital laboratory testing[9].

We chose to use Surgicel® in this study because it is widely available, easy to handle, inexpensive and acts as a good delivery vehicle for the tranexamic acid deep into the base of the tooth sockets and subsequent blood clot after surgery. Surgicel is an oxidized regenerated cellulose preparation whose local haemostatic action depends on the binding of haemoglobin to oxycellulose, allowing the dressing to expand into a gelatinous mass, which in turn acts both as a scaffolding for clot formation and a clot stabilizer[6,7]. The material is completely absorbable and does not interfere with healing or bone regeneration.

The common factor in the three recorded cases of postoperative bleeding in our study was severe periodontitis as the indication for extraction, and it is possible the infection in the surrounding soft tissues and local inflammation may have contributed to these bleeds. Similar findings have been noted in a recent previous study[2] confirming that severe local infection with its increased vascularity is a predominant risk factor for bleeding most likely by enhancing local fibrinolysis.

A 4.8% tranexamic acid mouthwash is effective in controlling local haemostasis in anticoagulated patients undergoing dental extractions. Statistically there appears to be no difference between a prescribed two-day *vs* a five-day course.

*Table 2.* Demographics and statistical results of tranexamic acid mouthwash (TAMW) study 2 days *vs* 5 days

| | TAMW 2 days—Group A | TAMW 5 days—Group B | Total |
|---|---|---|---|
| Gender | | | |
| Male | 22 | 32 | 54 |
| Female | 21 | 10 | 31 |
| Age range | 21–77 | 24–86 | |
| Median age | 65.2 | 65.7 | |
| No extractions | | | |
| Mandible | 49 | 62 | 111 |
| Maxilla | 48 | 42 | 90 |
| Range | 1–13 | 1–16 | |
| Reason for exodontia | | | |
| Periodontal disease | 47 | 41 | 88 |
| Caries | 48 | 61 | 109 |
| Other | 3 | 1 | 4 |
| INR Mean | 2.7 | 2.8 | |
| Postop bleed* | | | |
| Mandible | 0 | 0 | 0 |
| Maxilla | 2 | 1 | 3 |

*Statistical method=$\chi^2$, df=1.0, 0.32.

*Acknowledgments.* This research was supported financially by a grant provided by the Australian and New Zealand Association of Oral and Maxillofacial Surgeons research and education foundation.

## References

1. Beirne OR, Koehler JR. Surgical management of patients on warfarin sodium. J Oral Maxillofacial Surg 1996: **54**: 1115–1118.
2. Blinder D, Manor Y, Martinowitz U, Taicher S. Dental extractions in patients maintained on continued oral anticoagulant: comparison of local haemostatic modalities. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999: **88**: 137–140.
3. Borea G, Montebugnoli L, Capuzzi P, Magelli C. Tranexamic acid as a mouthwash in anticoagulant-treated patients undergoing oral surgery. An alternative method to discontinuing anticoagulant therapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1993: **75**: 29–31.
4. Campbell JH, Alvarado F, Murray RA. Anticoagulation and minor oral surgery: Should the anticoagulation regimen be altered? J Oral Maxillofacial Surg 2000: **58**: 131–135.
5. Dajani AS, Taubert KA, Wilson W, et al. Prevention of Bacterial Endocarditis: Recommendations by the American Heart Association. JAMA 1997: **277**: 1794–1801.
6. Devani P, Lavery KM, Howell CJT. Dental extractions in patients on warfarin: is alteration of anticoagulant regime necessary? Br J Oral Maxillofac Surg 1998: **36**: 107–111.
7. Halfpenny W, Fraser J, Adlam D. Comparison of 2 haemostatic agents for the prevention of postextraction haemorrhage in patients on anticoagulants. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001: **92**: 257–259.
8. Kearon C, Hirsh J. Management of anticoagulation before and after elective surgery. N Eng J Med 1997: **336**: 1506–1511.
9. Reiss R, Haas C, Griffis D, Porter B, Tara M. Point-of-care versus laboratory monitoring of patients receiving different anticoagulant therapies. Pharmacotherapy 2002: **22**: 677–685.
10. Sindet-Pedersen S, Ramstrom G, Bernvil S, Blomback M. Haemostatic effect of tranexamic acid mouthwash in anticoagulant-treated patients undergoing oral surgery. N Engl J Med 1989: **320**: 840–843.
11. Souto JC, Oliver A, Zuazu-Jausoro I, et al. Oral surgery in anticoagulated patients without reducing the dose of oral anticoagulant: a prospective randomised study. J Oral Maxillofac Surg 1996: **54**: 27–32.
12. Wahl MJ. Dental Surgery in anticoagulated patients. Arch Intern med 1998: **158**: 1610–1616.
13. Webster K, Wilde J. Management of anticoagulation in patients with prosthetic heart valves undergoing oral and maxillofacial operations. Br J Oral Maxillofac Surg 2000: **38**: 124–126.

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# Long-term prophylaxis in hereditary angio-oedema: a systematic review

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**To cite:** Costantino G, Casazza G, Bossi I, *et al*. Long-term prophylaxis in hereditary angio-oedema: a systematic review. *BMJ Open* 2012;**2**:e000524. doi:10.1136/bmjopen-2011-000524

► Prepublication history for this paper is available online. To view this file please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2011-000524).

Received 21 October 2011
Accepted 27 April 2012



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## ABSTRACT

**Objective:** To systematically review the evidence regarding long-term prophylaxis in the prevention or reduction of attacks in hereditary angio-oedema (HAE).

**Design:** Systematic review and meta-analysis.

**Data sources:** Electronic databases were searched up to April 2011. Two reviewers selected the studies and extracted the study data, patient characteristics and outcomes of interest.

**Eligibility criteria for selected studies:** Controlled trials for HAE prophylaxis.

**Results:** 7 studies were included, for a total of 73 patients and 587 HAE attacks. Due to the paucity of studies, a meta-analysis was not possible. Since two studies did not report the number of HAE attacks, five studies (52 patients) were finally included in the summary analysis. Four classes of drugs with at least one controlled trial have been proposed for HAE prophylaxis. All those drugs, except heparin, were found to be more effective than placebo. In the absence of direct comparisons, the relative efficacies of these drugs were determined by calculating a RR of attacks (drug vs placebo). The results were as follows: danazol (RR=0.023, 95% CI 0.003 to 0.162), methyltestosterone (RR=0.054, 95% CI 0.013 to 0.163), ε-aminocaproic acid (RR=0.095, 95% CI 0.025 to 0.356), tranexamic acid (RR=0.308, 95% CI 0.195 to 0.479) and C1-INH 0.491 (95% CI 0.395 to 0.607).

**Conclusions:** Few trials have evaluated the benefits of HAE prophylaxis, and all drugs but heparin seem to be effective in this setting. Since there are no direct comparisons of HAE drugs, it was not possible to draw definitive conclusions on the most effective one. Thus, to accumulate evidence for HAE prophylaxis, further studies are needed that consider the dose–efficacy relationship and include a head-to-head comparison between drugs, with the active group, rather than placebo, as the control.

## ARTICLE SUMMARY

### Article focus

- To find evidence regarding long-term prophylaxis in the prevention or reduction of attacks in HAE.

### Key messages

- Four classes of drugs have been proposed for HAE prophylaxis: androgen derivatives, antifibrinolytics, C1-inhibitor and heparin.
- All, except heparin, have been shown to be more effective than placebo.
- To accumulate evidence supporting HAE prophylaxis, further studies, including head-to-head comparisons between drugs, are needed, with the active group rather than placebo as the control.

### Strengths and limitations of this study

- This is the first systematic review on this topic.
- Only seven studies were retrieved, for a total of 73 patients and 587 HAE attacks; there were no direct comparisons between drugs.
- It was not possible to draw definitive conclusions on the most effective drug.

## INTRODUCTION

Hereditary angio-oedema (HAE) is a rare genetic disorder resulting from an inherited deficiency or dysfunction of C1 inhibitor (C1-INH). It is characterised by recurrent episodes of angio-oedema, without urticaria or pruritus, and primarily affects the skin or the mucosal tissues of the upper respiratory and gastrointestinal tracts. The inheritance of HAE is autosomal dominant, but only a few affected individuals are homozygous for the defect.[1] The prevalence of the disease in the general population is estimated at one individual per 50 000, with reported ranges from 1:10 000 to 1:150 000 and no racial differences.[2–5] The two most common forms of HAE (types I and II) result from either a deficiency or a dysfunction of C1-INH. In the former, antigenic and functional levels of C1-INH are below 50% of normal, while in the latter (ie, in type II), antigenic levels are normal to elevated, but function is low.[6 7] Nearly 90% of patients suffer from both cutaneous and abdominal attacks, while 50% also experience laryngeal/pharyngeal oedema.[8–10] Attacks typically involve one site at a time, but the simultaneous involvement of multiple sites is not common.[10] Symptoms usually increase in severity over a period of 24 h and then subside over the next 24–72 h. The frequency of recurrences has an

extremely high intrasubject and intersubject variability, ranging from less than once a year up to every 3–4 days.[11] Laryngeal recurrences are less common, accounting for 6% of all angio-oedema episodes.[12] The socioeconomic consequences of HAE are significant, as patients with frequent attacks may miss up to 100–150 days of work each year.[10]

Although HAE-induced swelling is self-limited, laryngeal involvement may cause asphyxiation. In fact, the mortality rate of patients not properly diagnosed or treated is reportedly as high as 30%. In addition to the risk of death, the burden of the disease is related to the symptom-derived disability, which, in turn, is a function of the frequency and severity of the attacks.

Two therapeutic strategies can ameliorate this burden: (1) prophylactic therapy, aimed at reducing the number of attacks, and (2) treatment of the attacks to reduce their severity and duration. Their common end point is a reduction of the duration of angio-oedema-related disability and the risk of asphyxiation induced by laryngeal oedema.

The controlled studies of HAE carried out thus far were designed to evaluate the efficacy and safety of single drugs; none compared either the different drugs or the different therapeutic approaches (eg, prophylaxis vs treatment of attacks). To the best of our knowledge, there are no meta-analyses of these studies. Hence, existing consensus documents support treatment recommendations primarily based on expert opinion rather than on a systematic review of the evidence.[4] Therefore, the aim of this study was to systematically review the evidence regarding the efficacy of HAE long-term prophylaxis.

## METHODS

### Data sources

Relevant primary studies were identified by searching the MEDLINE and EMBASE databases, the Cochrane Library and the http://Clinicaltrials.gov database (to identify ongoing trials yet to be reported in the literature) until April 2011. Both the reference lists included in the clinical guidelines and the proceedings of relevant meetings were also considered. The search strategy was based on the target disease (hereditary angioedema, C1 inhibitor and synonyms) and the type of study (controlled trial and synonyms according to the Cochrane collaboration guidelines). No language restrictions were applied.

Eligible studies were controlled trials evaluating long-term prophylactic therapies for HAE.

All the evaluated studies were included if they had a placebo or comparison group. Cross-over and parallel group designs were also included.

Observational studies, single-arm studies and studies with historical controls were excluded.

Two reviewers (GCo and IB) independently screened titles and abstracts to identify relevant publications. Full texts were retrieved and evaluated by the same two reviewers (GCo and IB), and a final decision regarding the inclusion or exclusion of the paper was made. Discrepancies were resolved by discussion; in case of disagreement, the final decision was made by a clinical expert (MC).

### Data extraction

Two reviewers (IB and GCo) extracted the data, which were recorded in an electronic spreadsheet. Extracted data consisted of the study characteristics (first author, journal and year of publication, drug name, number of patients enrolled/included, primary end point with its statistical significance, study duration), some of the patient characteristics (mean age, proportion of men) and the outcome of interest.

### Quality assessment of primary studies

The quality of the included studies was assessed based on the five-item Jadad score, which takes into account several of the methodological characteristics of clinical studies, such as blinding, randomisation and dropouts.[13] Studies with a score <3 were considered of low quality.

### Outcome of interest

The outcome of interest was the number of HAE attacks during prophylaxis treatment. In this study, two different end points were considered: the number of attacks per course of therapy and the number of attacks per month. Studies without at least one of these end points were not considered in the analysis.

### Data analysis

For each included study in which the data were reported as number of courses with and without attacks, the attack rate was calculated by dividing the number of HAE attacks by the total number of courses of treatment. For studies in which the data were reported as the number of attacks and the number of months of treatment, the attack rate was defined as the ratio between the number of HAE attacks and the total number of months of treatment. The attack rate was calculated separately for the drug and the control groups. To obtain a summary measure of efficacy for use in the analysis, a RR with 95% CI was calculated as the ratio of the attack rates in the drug and control groups.[14]

Pooled RRs with their 95% CIs for the same type of drug were calculated, when appropriate, using a random-effects model (DerSimonian and Laird method) for RRs.[15] Graphical representation of the study results was obtained by plotting RR estimates with their 95% CIs in a Forest plot.

In the absence of a direct comparison, an indirect comparison (for descriptive purposes) between drugs was done simply by comparing the estimates (95% CIs) of those drugs.[16] All the analyses were performed with STATA software, release V.11.0.

## RESULTS

### Descriptive analysis

From the 11 412 references identified by the search strategy, 11 344 were excluded after title/abstract review.

Of the remaining 68 references, 61 were excluded after a full-text evaluation: 43 articles reported studies that were not trials, four studies were duplicate publications, three studies had no end point, one article was a trial with retrospective controls and the focus of 10 studies was on therapy only, not on prophylaxis. Thus, seven studies were eligible for descriptive analysis (figure 1). The total number of patients enrolled in the seven studies was 73 (range 4–22). The efficacy evaluation was based on HAE attack recurrences, with 587 recurrences registered by the studies. Two of the seven studies[17 18] did not report the number of attacks; thus five studies (52 patients) were considered for the analysis.[19–23]

All the studies were designed to evaluate the efficacy of a single dose of a specific drug. The main characteristics of the included studies are summarised in table 1. The first study was published in 1972 and the last one in 2010. All were cross-over designed and the control group was placebo. In all but one study,[17] a statistically significant result was achieved for the primary end point. Three different classes of drugs were evaluated: antifibrinolytics (one study with ε-aminocaproic acid and one with tranexamic acid), androgen derivatives (one study with danazol and one with methyltestosterone), plasma-derived C1-INH (one study with a vapour-heated preparation and one with a pasteurised, nanofiltered preparation) and heparin (one study). The duration of treatment ranged from a minimum of 1 month to a maximum of 16 months. No major side effects were reported in any of the studies.

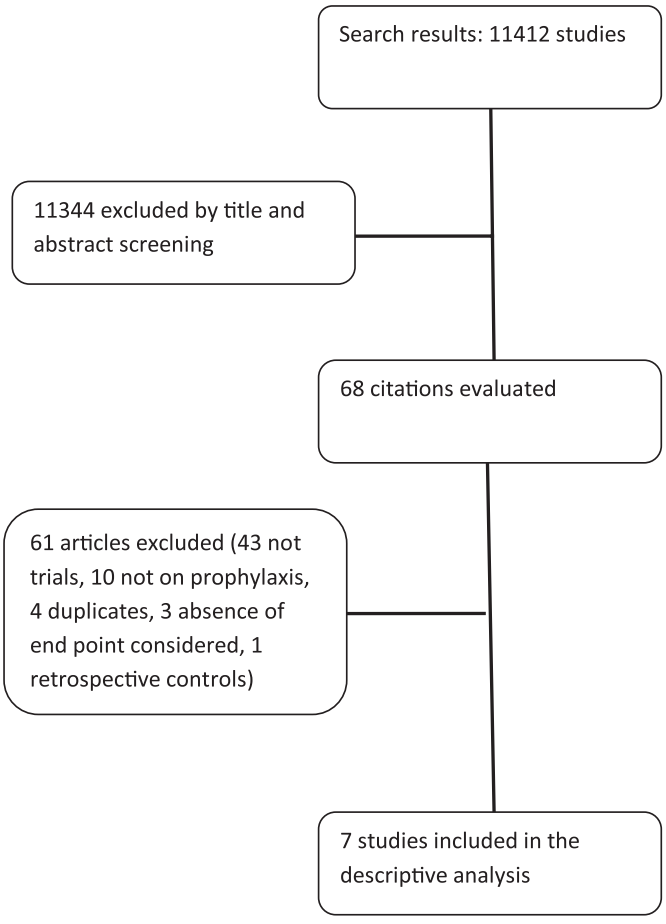


**Figure 1** Search history.

Primary efficacy end points, against placebo, were the number of courses (a course terminated whenever an attack occurred or after 1 month) with and without attacks (two studies), the number of attacks per month (two studies), the average flare intensity (one study), the daily score of disease activity (one study) and the number of attacks normalised for the number of days (one study).

According to the Jadad score, six out of the seven trials were high-quality studies (Jadad score range: 1–5).

## Summary of the results

Due to the paucity of studies retrieved and to the substantial heterogeneity between them (study design, definition of end points), it was not appropriate to perform any meta-analyses.

For the studies considered in the analysis, the number of enrolled patients, the end points and the frequency of attacks in the treatment and control groups are summarised in table 2 and figure 2.

*Antifibrinolytics.* Two antifibrinolytics were analysed in two separate studies (17 patients, 121 HAE attacks), with both drugs shown to be better than placebo. The estimates of RR differed greatly between studies (figure 2).

*Androgens.* Two studies compared androgen derivatives with placebo in 13 patients who registered five and 63 attacks, respectively. In both studies, the drugs were more effective than placebo and the RR values of the two studies were similar (figure 2).

*C1-inhibitor.* Data were available for only one study, which reported that in 22 patients C1-INH and placebo had an average period-specific normalised attack rate of 6.26 and 12.73, respectively. The estimated RR was 0.491 (95% CI 0.395 to 0.607).

*Heparin.* The only data provided by the one study were those for flare intensity, which did not significantly differ between active and control groups. While no data were published on the number of attacks, the authors did state that these numbers were not significantly different between the drug and the placebo groups.

*Indirect comparison.* In the absence of head-to-head comparisons and due to the very limited number of studies, the differences between the drugs were estimated in informal descriptive comparisons.

Based on the studies in which the number of attacks and the number of courses of treatment with drug or placebo were the primary end points, danazol (RR=0.023, 95% CI 0.003 to 0.162) seemed to be comparable to ε-aminocaproic acid (RR=0.095, 95% CI 0.025 to 0.356). In the studies that reported the number of attacks per month, methyltestosterone (RR=0.054, 95% CI 0.013 to 0.163) seemed to be better than tranexamic acid (RR=0.308, 95% CI 0.195 to 0.479). Finally, an indirect comparison between all treatments involving drugs of the same pharmacological class and not separated for end point suggested that androgen

**Table 1** Characteristics of the included studies

| First author | Drug | Dose | Number of patients included | Mean age (years) | Minimum number attacks for month | Mean attacks for month controls | Primary end point | Randomised | Jadad score |
|---|---|---|---|---|---|---|---|---|---|
| Frank (1972)[19] | Aminocaproic acid | 16 g/day | 5 | 35.6 | 1 | – | No. of courses with and without attacks in drug and placebo | No | 4 |
| Sheffer (1972)[20] | Tranexamic acid | 3 g/day | 12 | 12–72 | – | 1.1 | No. of attacks for month | No | 1 |
| Gelfand (1976)[21] | Danazol | 600 mg/day | 9 | 34.9 | 1 | – | No. of courses with and without attacks in drug and placebo | Yes | 5 |
| Sheffer (1977)[22] | Methyltestosterone | 10 mg/day | 4 | – | 1 | 1.6 | No. of attacks for month | Yes | 3 |
| Weiler (2002)[17] | Heparin | 400 U/kg/day | 15 | 32.6 | 1 | – | Average flare intensity | Yes | 5 |
| Waytes (1996)[18] | V-H C1 inhibitor | 25 plasma unit/kg/every 3 days | 6 | – | 0.5 | – | Daily score for disease activity | Yes | 5 |
| Zuraw (2010)[23] | C1 inhibitor | 1000 U/every 3–4 days | 22 | 38.1 | 2 | 4.24 | No. of attacks normalised for the number of days | Yes | 5 |

V-H, Vapour-heated.

**Table 2** Summary of results of the included studies

| Drug | No. of patients | Treatment No. of attacks/ No. of courses | Ratio | Control No. of attacks/ No. of courses | Ratio | RR treatment/control (95% CI) |
|---|---|---|---|---|---|---|
| Studies considering number of attacks per therapeutic course | | | | | | |
| Aminocaproic acid[19] | 5 | 2/21 | 0.10 | 24/24 | 1.00 | 0.095 (0.025 to 0.356) |
| Danazol[21] | 9 | 1/46 | 0.02 | 44/47 | 0.94 | 0.023 (0.003 to 0.162) |
| **Drug** | **No. of patients** | **Treatment No. of attacks/ No. of months** | **Ratio** | **Control No. of attacks/ No. of months** | **Ratio** | **RR treatment/control (95% CI)** |
| Studies considering number of attacks per months | | | | | | |
| Tranexamic acid[20] | 12 | 32/94 | 0.34 | 63/57 | 1.11 | 0.308 (0.195 to 0.479) |
| Methyltestosterone[22] | 4 | 4/46 | 0.09 | 19/12 | 1.61 | 0.054 (0.013 to 0.163) |
| C1 inhibitor[23] * | 22 | 131/63 | 2.07 | 267/63 | 4.24 | 0.491 (0.395 to 0.607) |

*Number of attacks (expressed as attacks per month) was derived from the attack rate (expressed as attacks per 12 weeks) as reported in the study.

derivatives are more effective than C1-INH, while the efficacy of antifibrinolytics is midway between that of androgens and C1-INH.

*Heterogeneity*. As clearly seen in the Forest plot (figure 2), the point estimates of each study were very imprecise, with wide-ranging variability between the primary studies.

Figure 3 allows a quick visual comparison, for every study, of the number of attacks experienced by each patient during courses of treatment with placebo or with active drug. A reduction in the frequency of attacks was achieved during active treatment in all but four patients: one on tranexamic acid and three on C1-INH.

## DISCUSSION

This systematic review identified four classes of drugs used for HAE prophylaxis: androgen derivatives, antifibrinolytics, heparin and C1-INH. The drugs were tested in at least one controlled trial and, with the exception of heparin, all of them were shown to be better than placebo in reducing the frequency of attacks. The small number of patients in each trial explains the low precision of the estimates of RR (see figure 2), which, in turn, were at least partly responsible for the observed variability of the RRs between studies. As seen in figure 2, the RR point estimates are quite different, but almost all the 95% CIs overlap, indicating high interstudy and intrastudy variability. The observed heterogeneity could be due to several factors, the most important of which may have been the fact that five different primary end points were considered across the seven primary studies. Moreover, the year of publication ranged from 1972 to 2010. During this interval, there have been many changes in the diagnosis and management of HAE. The inclusion criteria also varied from study to study, but even when they were similar, as for average attack frequency, the respective placebo groups still behaved differently. The mean number of attacks for the placebo group was higher in the C1-INH study[23] than in the other (four vs two attacks per month, respectively). This suggests that disease severity differed in the patients recruited for the examined studies. Finally, the large variability in follow-up duration (from 1 month to 16 months) is another relevant

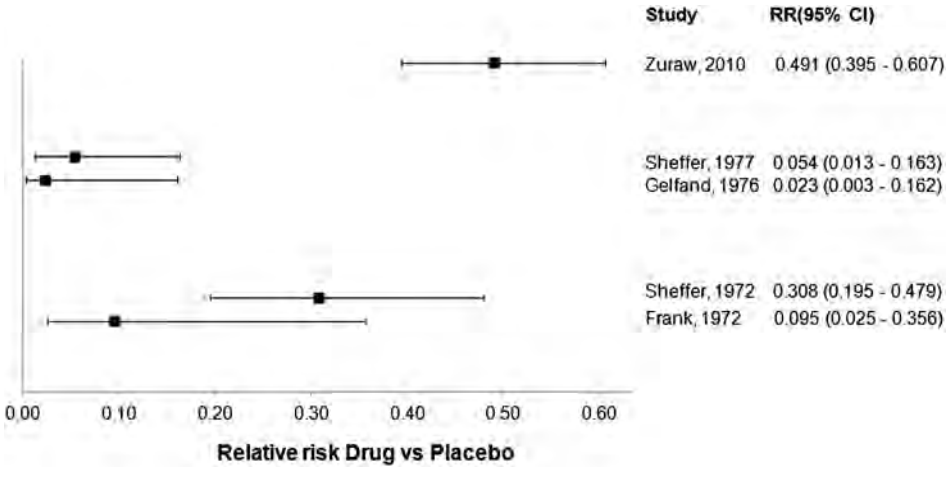


**Figure 2** RR of drugs analysed compared with placebo.

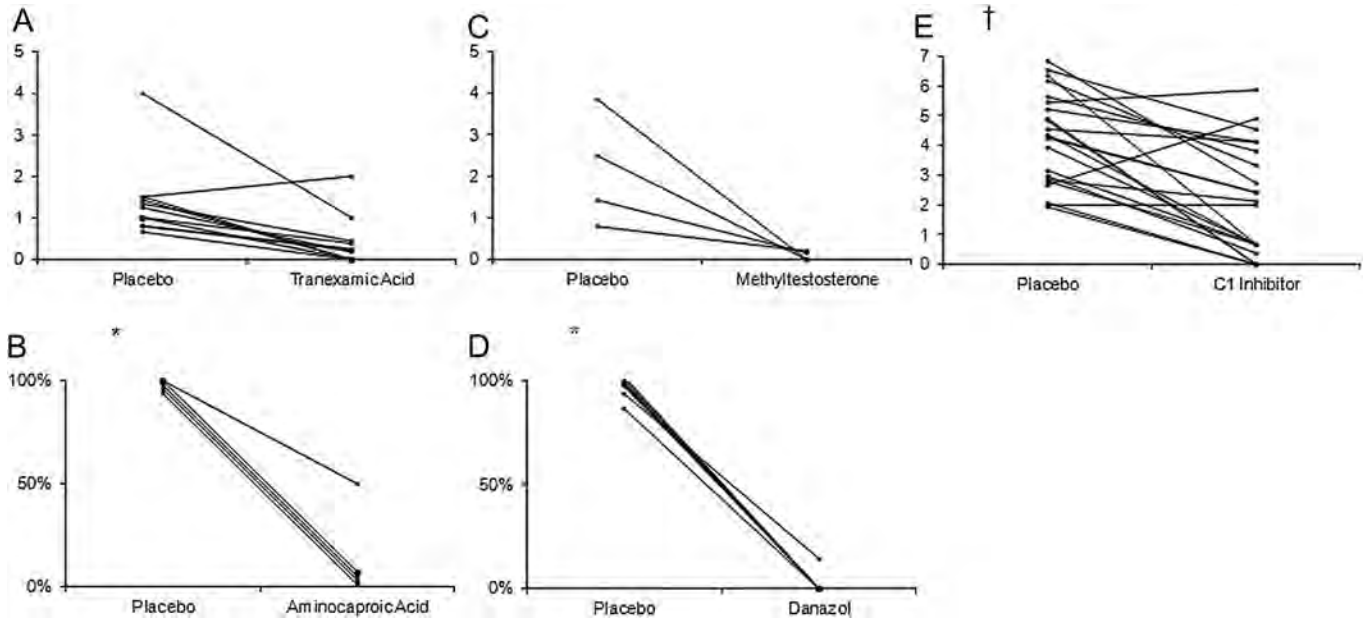


**Figure 3** (A) Single patient data of placebo versus tranexamic acid study (attacks per months); (B) single patient data of placebo versus aminocaproic acid study (cycle of therapy with attacks vs total number of cycles); (C) single patient data of placebo versus methyltestosterone study (attacks per months); (D) single patient data of placebo versus danazol study (cycle of therapy with attacks vs total number of cycles); (E) single patients data of placebo versus C1 inhibitor study (attacks per months). For explanation, see text. *For graphical purposes, some patients' values have been slightly modified. †Data retrieved from figure 2 of the original paper.

important difference that no doubt contributed to the observed heterogeneity.

All trials considered for this analysis were published in core medical journals, reflecting the high clinical interest in HAE. Nevertheless, it should be noted that the studies on androgens and antifibrinolytics were conducted in the 1970s. While no serious side effects were reported in the included trials, randomised clinical trials are not the best study design to investigate side effects, particularly for long-term treatments. Indeed, extensive clinical experience has since accumulated with attenuated androgens and antifibrinolytics, and side effects are well known from observational studies.[3] C1-INH, used for 30 years in the treatment of attacks, was only recently recognised as indicated for prophylaxis. A close look at the early trials from the vantage point of current clinical experience reveals important side effects of androgens used at doses of 600 mg/day, as was the case in those clinical trials. Over time, clinical practice has shown that much lower doses maintain clinical efficacy and with fewer side effects, allowing treatment to be continued over the very long term.[24 25] Nevertheless, the level of efficacy at these lower doses has never been quantified in a controlled study. In addition, while the efficacy of antifibrinolytics in long-term prophylaxis was confirmed, clinical experience showed that there are no doses that can lead a large number of patients to have significant benefit. Thus, today, only a small minority of patients with HAE continue to use these drugs. In fact, according to the most recently released consensus document on HAE treatment, antifibrinolytics are not considered as a relevant agent.[26] Although we do not have large documented clinical experience with C1-INH, the available data suggest the importance of individually titrating effective doses in order to establish the 'minimal effective dose'; this is current practice with danazol.[27 28] The problem of effective dose has never been addressed in clinical trials. This is a major limitation particularly for prophylactic treatments in which the risk–benefit balance is crucial as the relevant drug is likely to be taken life-long. Increasing awareness of HAE can be expected to focus on this issue, but its resolution will require long-ranging clinical experience.

One of the aims of our systematic review was to compare therapies, which could only be done indirectly. However, we were unable to single out a superior therapy due to the small number of patients enrolled in the studies and the broad CIs of the point estimates. Indeed, an indirect comparison of the studies considering the same end point showed that while methyltestosterone seems to be more effective than tranexamic acid, danazol does not differ from ε-aminocaproic acid.[19–22] For a more specific comparison of the different trials, the response of each patient in each trial, both in the placebo group and in the active group, was analysed (figure 3). The results showed that all 13 patients treated with androgens had a marked reduction in the number of attacks, suggesting a uniform efficacy of this drug among patients. By contrast, a reduction was not achieved by one of 17 patients in the antifibrinolytic group and three of 22 patients in the C1-INH group. A first and obvious explanation of these differences is the extremely small number of patients included in some of the studies, such that the variability of the HAE

population could not be adequately determined. Another possibility, already highlighted, is that in the absence of convincing dose-finding studies, the respective drugs may have been overdosed or underdosed.

## Limitations

The major limitation of our systematic review was the very small number of patients enrolled in the original studies and the heterogeneity between the studies considered. Moreover, there was no consensus on the definition of the primary end point, as in some studies it was the number of courses with and without attacks, and in others, it was the number of attacks per month or the average flare intensity.

Given the paucity of studies published in the literature, to obtain useful evidence we opted to compare results from different studies, irrespective of the heterogeneity arising from differences in the designs of the primary studies (ie, definition of primary end point, drugs considered).

Another limitation is related to the statistical analysis. In each original study, we considered the number of months (or courses) and the number of attacks in both the placebo and the active group as if they were independent. Since all were cross-over trials, with this analyses, the correlation within patients is ignored.

In conclusion, our systematic review supports the use of certain drugs in the prophylaxis of attacks in patients with HAE, but we were unable to determine whether one prophylactic therapy is better than another. Clearly, there is a compelling need for more trials, with head-to-head comparisons, to provide convincing evidence of the benefit and safety of a specific, potentially life-long prophylactic regimen.

**Contributors** GCo, GCa, PD and MC designed the study. GCa and PD wrote the statistical analysis plan and analysed the data. GCo and IB screened titles and abstracts to identify relevant publications and extracted the data. All authors participated in drafting the paper and in its subsequent revision.

**Funding** This research was supported by a grant from Telethon (No. GGP08223).

**Competing interests** MC has a consultancy agreement and/or has been an invited speaker for the following companies that produce treatments for hereditary angio-oedema: CSL Behring, Shire, Dyax, Viro Pharma, Pharming. The other authors declare no conflict of interest.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** No additional data are available.

## REFERENCES

1. Blanch A, Roche O, Urrutia I, *et al*. First case of homozygous C1 inhibitor deficiency. *J Allergy Clin Immunol* 2006;118:1330–5.
2. Lopez-Lera A, Favier B, Mena de la Cruz B, *et al*. A new case of homozygous C1-inhibitor deficiency suggests a role for Arg378 in the control of kinin pathway activation. *J Allergy Clin Immunol* 2010;126:1307–10.
3. Roche O, Blanch A, Caballero T, *et al*. Hereditary angioedema due to C1 inhibitor deficiency: patient registry and approach to the prevalence in Spain. *Ann Allergy Asthma Immunol* 2005;94:498–503.
4. Bowen T, Cicardi M, Farkas H, *et al*. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy Asthma Clin Immunol* 2010;6:24.
5. Bygum A. Hereditary angio-oedema in Denmark: a nationwide survey. *Br J Dermatol* 2009;161:1153–8.
6. Tosi M. Molecular genetics of C1 inhibitor. *Immunobiology* 1998;199:358–65.
7. Prada AE, Zahedi K, Davis AE 3rd. Regulation of C1 inhibitor synthesis. *Immunobiology* 1998;199:377–88.
8. Bork K, Meng G, Staubach P, *et al*. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. *Am J Med* 2006;119:267–74.
9. Bork K, Staubach P, Eckardt AJ, *et al*. Symptoms, course, and complications of abdominal attacks in hereditary angioedema due to C1 inhibitor deficiency. *Am J Gastroenterol* 2006;101:619–27.
10. Agostoni A, Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine (Baltimore)* 1992;71:206–15.
11. Gompels MM, Lock RJ, Abinun M, *et al*. C1 inhibitor deficiency: consensus document. *Clin Exp Immunol* 2005;139:379.
12. Zanichelli A, Vacchini R, Badini M, *et al*. Standard care impact on angioedema because of hereditary C1 inhibitor deficiency: a 21-month prospective study in a cohort of 103 patients. *Allergy* 2011;66:192–6.
13. Jadad AR, Moore RA, Carroll D, *et al*. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1–12.
14. Altman DG. *Practical Statistics for Medical Research*. London: Chapman & Hall, 1991.
15. Egger M, Davey Smith G, Altman DG. *Systematic Reviews in Health Care: Meta-Analysis in Context*. London: BMJ Books, 2003.
16. Glenny AM, Altman DG, Song F, *et al*. Indirect comparisons of competing interventions. *Health Technol Assess* 2005;9:26.
17. Weiler JM, Quinn SA, Woodworth GG, *et al*. Does heparin prophylaxis prevent exacerbations of hereditary angioedema? *J Allergy Clin Immunol* 2002;109:995–1000.
18. Waytes AT, Rosen FS, Frank MM. Treatment of hereditary angioedema with a vapor-heated C1 inhibitor concentrate. *NEJM* 1996;334:1630–4.
19. Frank MM, Sergent JS, Kane MA, *et al*. Epsilon aminocaproic acid therapy of hereditary angioneurotic edema. A double-blind study. *NEJM* 1972;286:808–12.
20. Sheffer AL, Austen KF, Rosen FS. Tranexamic acid therapy in hereditary angioneurotic edema. *NEJM* 1972;287:452–4.
21. Gelfand JA, Sherins RJ, Alling DW, *et al*. Treatment of hereditary angioedema with danazol. Reversal of clinical and biochemical abnormalities. *NEJM* 1976;295:1444–8.
22. Sheffer AL, Fearon DT, Austen KF. Methyltestosterone therapy in hereditary angioedema. *Ann Intern Med* 1977;86:306–8.
23. Zuraw BL, Busse PJ, White M, *et al*. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *NEJM* 2010;363:513–22.
24. Sloane DE, Lee CW, Sheffer AL. Hereditary angioedema: safety of long-term stanozolol therapy. *J Allergy Clin Immunol* 2007;120:654–8.
25. Bork K, Bygum A, Hardt J. Benefits and risks of danazol in hereditary angioedema: a long-term survey of 118 patients. *Ann Allergy Asthma Immunol* 2008;100:153–61.
26. Cicardi M, Bork K, Caballero T, *et al*; HAWK (Hereditary Angioedema International Working Group). Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. *Allergy* 2012;67:147–57.
27. Kreuz W, Martinez-Saguer I, Aygören-Pürsün E, *et al*. C1-inhibitor concentrate for individual replacement therapy in patients with severe hereditary angioedema refractory to danazol prophylaxis. *Transfusion* 2009;49:1987–95.
28. Agostoni A, Cicardi M, Martignoni GC, *et al*. Danazol and stanozolol in long-term prophylactic treatment of hereditary angioedema. *J Allergy Clin Immunol* 1980;65:75–9.

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*BMJ Open* 2012 2:
doi: 10.1136/bmjopen-2011-000524

Current Medical Research and Opinion

ISSN: 0300-7995 (Print) 1473-4877 (Online) Journal homepage: https://www.tandfonline.com/loi/icmo20

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**To cite this article:** Andrew Zakhari, Ari Paul Sanders & Meir Jonathon Solnik (2019): Tranexamic acid in gynecologic surgery, Current Medical Research and Opinion, DOI: 10.1080/03007995.2019.1708533

**To link to this article:** https://doi.org/10.1080/03007995.2019.1708533

Accepted author version posted online: 21 Dec 2019.

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## Transparency

***Declaration of funding***
No sponsorship/funding was required for the completion of this project

***Declaration of financial/other relationships***
AZ has received honoraria from Hologic. APS is a consultant and on the speaker bureau for Hologic and is a consultant for Medtronic. MJS is a consultant for Medtronic and sits on the advisory board of Abbvie, Allergan, and FelixForYou. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

***Author contributions***
All authors agree to be accountable for all aspects of the work. AZ: design, literature review, manuscript preparation. APS: conception and design, literature review, manuscript preparation. MJS: manuscript preparation.

***Acknowledgements***
No assistance in the preparation of this article is to be declared.

***Previous presentations***
This article has been presented in abstract form at the 2019 ACSC conference in Halifax, Canada, and as a virtual poster at the 2019 CanSAGE4 conference in Ottawa, Canada.

**Abstract**

***Objective*:** To review the mechanism of action, pharmacology, dosing, and complications of tranexamic acid (TXA) and consolidate current evidence for TXA in gynecologic surgery.

***Methods*:** A literature search of PubMed, Ovid (MEDLINE), Google Scholar, and Elsevier was performed, in addition to a targeted search of cited references involving TXA and gynecologic surgery. Preference was given to systematic reviews and randomized control trials (RCTs).

***Results*:** TXA reversibly binds to plasminogen, preventing clot degradation. RCTs on hysterectomy, myomectomy, cervical conisation, hysteroscopy, and surgery for cervical and ovarian cancer were identified, as were case reports on TXA use for ectopic pregnancy. During hysterectomy, TXA reduces blood loss (two RCTs, n=432, mean difference -66.0mL and 180mL), blood transfusion (1 RCT, n=100, 12% versus 42%, p<0.00001). For myomectomy, a systematic review and meta-analysis showed a statistically significant decrease in blood loss with TXA (two RCTs, mean difference -213.1mL, 95% CI: -242.4mL to -183.7mL). Following cervical conisation, TXA decreased the risk of delayed hemorrhage (four RCTs, RR 0.23, 95% CI: 0.11 – 0.50). A single RCT for cervical and ovarian cancer surgery demonstrated a decrease mean blood loss of 120mL – 135mL and 210mL, respectively, and fewer blood transfusions for the latter (OR 0.44, upper 95% CI: 0.97, p=0.02). Less robust data suggest a possible benefit from TXA during hysteroscopy and surgery for ectopic pregnancies. Most commonly, 1g of intravenous TXA is given intraoperatively.

***Conclusion*:** TXA is a safe adjunct that can be considered in a variety of gynecologic surgeries to decrease blood loss and risk of blood transfusion.

**Keywords:** blood loss; hysterectomy; myomectomy; surgery; tranexamic acid

## Introduction

Intraoperative hemorrhage is a surgical complication that has the potential for significant morbidity or even mortality in gynecology [1-3]. Particularly in gynecology, many patients awaiting surgery may have pre-existing anemia secondary to their underlying gynecologic disorder, such as abnormal uterine bleeding (AUB). Preoperative anemia can compound the deleterious effects of surgical blood loss and predispose the patient to a preventable blood transfusion. Many interventions aimed at reducing intra-operative blood loss for different gynecological procedures have been described in the literature, including the pre-operative use of gonadotropin releasing hormone agonist (GnRH-a), misoprostol, vasopressin, use of a peri-cervical tourniquet, and uterine artery occlusion [4-8]. In this article, we seek to review the mechanism of action, pharmacology, and reported uses of tranexamic acid (TXA), a systemic antifibrinolytic agent, in gynecologic procedures.

### *History and Mechanism of Action*

Discovered in the search for a hemostatic molecule to treat post-partum hemorrhage, TXA was patented by Dr. S. Okamoto in 1957, who later published on its use in collaboration with her research partner and husband [9, 10]. TXA was found to be significantly more potent than a precursor molecule known as epsilon-amino-caproic acid (EACA). Both work in a similar fashion; as lysine-analogues, they reversibly bind to plasminogen, preventing its activation to plasmin and subsequent degradation of the fibrin clot complex [11]. For this reason, TXA is commonly referred to as an anti-fibrinolytic, or clot-stabilizer. It has also been shown to decrease inflammatory markers and mitigate hyperfibrinolysis-driven coagulopathy [9, 12].

### *Pharmacology*

Tranexamic acid, known also by the brand name Cyklokapron (Pfizer, New York, NY) or Lysteda (Ferring, Parsippany, NJ), is available in both oral and injectable formulations. The oral bioavailability of TXA is incomplete (40%). Peak serum levels are reached at approximately 3 hours following ingestion, with a short half-life of approximately 1-2 hours [13-15]. The drug is cleared renally in an almost entirely unchanged form, with near complete elimination by 24 hours. Due to relatively little binding to albumin or other plasma proteins apart from plasminogen, TXA has a high volume of distribution and readily diffuses into tissue compartments, such as across the blood-brain barrier, into joint fluid, placental tissue and umbilical cord blood in pregnant patients. However, TXA reaches a significantly lower concentration in breast milk (approximately one one-hundredth maternal serum levels). Reproductive animal studies have not revealed any adverse fetal effects, although human data is limited (pregnancy category B).

## Methods

A literature search was performed using PubMed, Ovid (MEDLINE), Google Scholar, and Elsevier, in addition to a search of cited references for articles discussing TXA use in gynecologic surgery. The search was performed from database inception to January 2019, and results were limited to full-text English language articles. Although preference for selection was given to systematic reviews and randomized control trials, due to the dearth of available publications, no limits on publication type were set. Additionally, articles discussing TXA pharmacology and complications were included. Current literature was grouped and synthesized based on gynecologic procedure and is presented here as such. Given the review nature of this article, Institutional Review Board approval was not required for the completion of this project.

## Results

### *Current Uses*

*Office Gynecology*

Evidence in the literature for TXA in the treatment of heavy menstrual bleeding dates back decades. A Cochrane review in 2018 compared antifibrinolytic therapy with TXA to other medical options such as progestogens, non-steroidal anti-inflammatory drugs (NSAIDs), and the levonorgesterel-releasing intra-uterine system (LNG-IUS) among others, in the management of heavy menstrual bleeding [16]. The authors concluded that TXA resulted in a significant reduction in bleeding (mean reduction of 40-50%) and was superior to other comparator groups in reducing blood loss, except when compared with the LNG-IUS. Moreover, TXA is recommended as an initial management strategy for heavy menstrual bleeding in several national society guidelines such as the Society of Obstetricians and Gynecologists of Canada (SOGC) and the American College of Obstetricians and Gynecologists (ACOG) [17, 18].

*Obstetrics*

True to its first intended application, TXA has proven to be an effective agent in the management of post-partum hemorrhage. A recent Cochrane review showed that timely administration of TXA in patients with post-partum hemorrhage following delivery by any route resulted in not only reduced total blood loss, but also decreased maternal mortality due to hemorrhage (relative risk RR 0.81; 95% C1: 0.65 – 1.00) [19].

Studies have also looked at the prophylactic administration of TXA at time of caesarean section [20]. Results show significant decreases in surgical blood loss, rates of post-partum hemorrhage, post-operative drops in hemoglobin, and risk of requiring a blood transfusion. In these studies, there were no reported adverse events of statistical significance such as deep-vein thrombosis (DVT), pulmonary embolism, stroke, or seizure. In contrast to these findings, the multicenter, double-blind, TRAAP RCT by Sentilhes et al published in 2018 failed to show any benefit to prophylactic TXA at the time of vaginal delivery [21].There are case reports documenting exceedingly rare thrombotic complications such as an aortoiliac thrombosis at the time of caesarean/hysterectomy for invasive placentation, however with concomitant use of occlusive iliac artery balloons – a known inciting risk factor [22].

*Other Disciplines*

In fields other than obstetrics and gynecology, TXA has been used heavily in the perioperative setting, particularly in cardiac and orthopedic surgery. In a Cochrane review from 2011, TXA use across surgical specialties in the perioperative setting has been shown to decrease total blood loss (mean difference per patient -414.06mL; 95% CI: -525.19mL to -302.92mL) and reduce the relative risk of allogenic blood transfusion by 39% [23]. Another review of all randomized controlled trials (RCTs) across surgical domains examining the effect of TXA on blood transfusion, thromboembolic events, and mortality in both elective and emergency surgical cases was published in the British Medical Journal in 2012 [24]. Results showed that patients receiving TXA had one third the risk of blood transfusion compared to controls, with no increased risk of thromboembolic events (myocardial infarction, stroke, or pulmonary embolism). Although there were fewer deaths in the TXA group, the statistical significance was lost when restricting the analysis to studies with adequate concealment (TXA and surgical bleeding). Similar findings were reproduced in a Cochrane review investigating the effect of TXA on blood transfusion and mortality rates in adult emergency surgery, with a 30% reduction in risk of blood transfusion although no clear reduction in mortality [25]. In contrast however, the multinational randomized placebo-controlled trial CRASH-2 showed that early administration of TXA in bleeding trauma patients significantly reduced both all-cause mortality and risk of death due to bleeding [26].

***Uses in Gynecologic Surgery***

*Hysterectomy*

Hysterectomy is among the most frequently performed major surgeries in North America, with a growing trend towards minimally invasive approaches and same-day discharge [27]. The most common indication for hysterectomy is uterine fibroids, often associated with heavy menstrual bleeding – making this an at-risk population for pre-operative iron deficiency anemia. A double-blind RCT from 2016 conducted in Denmark and published in the American Journal of Obstetrics and Gynecology evaluated the prophylactic administration of TXA compared to placebo at the time of hysterectomy for benign indications [28]. The majority of hysterectomies in both groups were performed laparoscopically or robotically (TXA n=115, placebo n=114). Those in the treatment arm received 1g of TXA at the beginning of surgery. Results showed lower incidences of blood loss exceeding 500mL (6 vs. 21 patients, p=0.003) and re-operation due to postoperative hemorrhage (4.2%, n=7 vs. 10.8%, n=18 patients; p=0.024) in the TXA group. There was a statistically significant decrease in estimated blood loss (EBL) both objectively by sponge weights (mean difference 36.4mL, p=0.006) and subjectively (mean difference -66.0mL, p=0.004). No thrombotic events or deaths were reported in either group. There was no significant difference in blood transfusion rate between groups (2/164 vs. 7/167 patients, RR 0.29; 95% CI: 0.06 – 1.38), although the absolute risk was demonstrably low. Similar results have been replicated in another randomized double-blind, placebo-controlled trial evaluating TXA in women undergoing abdominal hysterectomy in India. [29]. This study included 50 patients in each arm, and found prophylactic TXA led to statistically significant reductions in blood loss (360.16±107.1mL vs. 540.22±121.9mL, p<0.00001), rates of blood transfusion (12% vs. 42%; p<0.00001), and mean operative time (127.86mins vs. 148.64mins; p<0.00001).

*Myomectomy*

Blood loss at time of myomectomy is a common concern among gynecologists, and a variety of approaches, both medical and surgical, have been described to mitigate surgical bleeding [8]. Among medical options, pre-treatment with a gonadotropin-releasing hormone agonist (GnRHa) has proven beneficial in terms of operative blood loss, as have other medications such as intravaginal prostaglandins, vasopressin, and oxytocin. A systematic review and meta-analysis from 2018 which included three RCTs of women undergoing abdominal myomectomy evaluated the efficacy of intraoperative TXA compared to placebo or no treatment [30]. These three studies originated from Kenya, Turkey, and Egypt, and enrolled 34, 100, and 132 patients respectively, equally divided between treatment and control groups. After meta-analysis, the latter two studies showed a statistically significant mean difference in blood loss (-213.1mL; 95% CI: -242.4mL to -183.7mL), with no significant difference in the rate of blood transfusion. Two of the three studies reported a significant reduction in operative time among patient receiving TXA, with a mean difference of approximately ten minutes. Although one study reported higher rates of nausea and vomiting in patients who received TXA, there were no other significant differences in adverse events between the two groups. Similar findings were reported in a study from Egypt published the subsequent year on TXA at time of myomectomy. Mean total blood loss in patients receiving 1g of intravenous TXA prophylactically was significantly reduced compared to controls (721.71±211.78mL, n = 35 vs. 1080.00±126.07mL, n = 35; p=0.0001), and a lower rate of blood transfusion was also observed (17.1% vs. 54.3%, p=0.001) [31]. The authors also investigated a third arm comprised of 35 patients who received 2g of TXA topically through a soaked sponge applied to the myoma bed for 5 minutes. Compared to controls, this group had a statistically significant decrease in total blood loss (683.61±214.92mL vs. 1080.00±126.07mL; p=0.0001), and incidence of blood transfusion (20.0% vs. 54.3%, p=0.003).

*Cervical Conisation*

A variety of hemostatic options at time of surgery for cervical intraepithelial neoplasia have been described and summarized in a Cochrane review from 2013 [32]. Interventions include the application of Monsel's solution, cervical vasopressin injection, vaginal packing, and TXA. A total of four studies examining the role of the latter were included in this review, originating from Denmark and Sweden. A meta-analysis including two of these studies failed to show any effect on the rate of primary hemorrhage (occurring within 24 hours) during knife or laser cone biopsy (RR 1.24; 95% CI: 0.04 – 38.1). However, a meta-analysis of the four trials showed that prophylactic TXA administration combined with a post-operative oral course significantly reduced the rate of secondary hemorrhage (occurring within 14 days) with a relative risk of 0.23 (95% CI: 0.11 – 0.50). Although the exact dosages varied between studies, a common trend was administering a single gram intravenously during the procedure, followed by 12 to 14 days of 1.5g of oral TXA three times daily. A significant decrease in mean post-operative blood loss was also noted, with a mean difference of -55.6mL (95% CI: -94.61mL to -16.29mL) compared to controls.

*Cervical cancer*

Worldwide, cervical cancer ranks as the fourth most commonly diagnosed malignancy in women, disproportionately affecting those in low and middle income countries [33]. Primary surgery remains the treatment of choice for the management of early-stage cervical cancer [34]. One study originating from Turkey investigated TXA use at time of surgery for cervical cancer. In this prospective, double-blind, randomized trial during open, type III hysterectomy for stage I–II cervical cancer, Celebi et al compared four groups: crystalloid fluid replacement, colloid fluid replacement, crystalloid fluids with 10mg/kg IV TXA, and crystalloids with 100mg/kg IV EACA [35]. Patients with significant medical comorbidities or those requiring blood transfusion during surgery were excluded. There were no significant differences between the four groups in terms of age, BMI, duration of surgery, or baseline hemoglobin values. Although no significant differences were seen in hemoglobin concentration at 12 and 24 hours post-operatively, the TXA group (n = 27) had significantly lower EBL compared to the other three groups (mean EBL for TXA 270±40mL vs. crystalloid 405±40mL n = 26, colloid 390±35mL n = 26, EACA 355±40mL n = 26; p=0.005), as calculated by surgical suction volume, sponge counting, and drain output over the first 24 hours postoperatively.

*Ovarian cancer*

Ovarian cancer remains a diagnostically challenging malignancy that is typically identified at an advanced stage, and often requires primary surgery for diagnosis, staging, cytoreduction, and guiding adjuvant therapy [36, 37]. Blood transfusion in the setting of malignancy has been shown to be associated with decreased survival and time to recurrence [38-41]. In a retrospective cohort study by De Oliveira Jr. et al, perioperative blood transfusion in patients with advanced ovarian cancer undergoing cytoreductive surgery was associated with a significantly shorter disease-free interval and poorer overall survival, with a median time to recurrence of 11 months (95% CI: 8 –14 months) vs. 17 months (95% CI: 6 – 27; p=0.03), and median survival of 36 months (95% CI: 28 – 44 months) vs. 58 months (95% CI: 43 – 73; p=0.04).

A Cochrane review from 2016 assessing the effects of TXA in reducing blood loss during cytoreductive surgery for ovarian cancer included only a single study [42]. This study by Lundin et al was a multicenter, prospective randomised placebo-controlled double-blind trial that took place in Sweden [43]. One hundred women scheduled for radical debulking for presumed ovarian cancer were randomized to either a single dose of 15mg/kg IV TXA or placebo immediately pre-operatively. Data on blood loss and transfusion rates between the two groups was compared. Results showed that women who received

TXA had significantly less intra-operative blood loss (median EBL 520mL vs. 730mL; p=0.03) and lower rates of blood transfusion (15 vs. 22 patients; OR 0.44; upper 95% CI: 0.97; p=0.02) than women receiving placebo.

A proposed bundled intervention to optimize blood transfusion practices in open gynecological cancer surgery was published by Wallace et al in Obstetrics and Gynecology in 2018 [44]. In this retrospective study from the U.S., a historical cohort, managed in the usual fashion, was compared to a blood-conservation intervention cohort. The intervention applied was a bundled hemostasis package with clear, standardized transfusion guidelines, a surgical hemostasis checklist, as well as evidence-based administration of TXA. Patients were predominantly operated on for ovarian cancer, however a minority of patients had advanced endometrial cancer (47/226, 20.8%). Tranexamic acid was used in 60.7% of patients in the intervention group, at a dose of 15mg/kg IV. Among patients with ovarian cancer, the intervention group had a 60.3% risk reduction in blood transfusion compared to the historical cohort (16.2% vs. 40.8%; p<0.001), a difference which remained significant after propensity matching. In contrast, among the minority with endometrial cancer, no significant difference was observed. Overall, between the intervention and historical cohorts, there was a significant reduction in median estimated blood loss (300mL vs. 500mL; p=0.009) as well as mean operative time (241.7mins vs. 279.3mins; p=0.01).

*Ectopic Pregnancy*

The incidence of ectopic pregnancy in the general population is approximately 1 – 2% of all pregnancies [45, 46]. Blood transfusions are required in up to 10% of patients undergoing surgical management of ectopic pregnancies [47]. Authors have described the use of intraoperative autologous blood transfusion when significant hemoperitoneum is present as a means of reducing the rate of allogenic blood use, however this remains an uncommon practice [48, 49].

There is little published data on the use of TXA in the management of ectopic pregnancy and most originates from case reports. One such case from Ireland pertains to a Jehovah's Witness patient who presented with significant anemia (Hgb 57g/L) and 1.5L of hemoperitoneum [50]. Declining all blood products, the patient ultimately consented to surgery with use of cell salvage, and received 1g of IV TXA intraoperatively. Three other case reports detail the use of TXA in the context of cervical ectopic pregnancies, which pose a high risk of hemorrhage. In two of these cases, originating from Nigeria and Italy, TXA was given intravenously, either prophylactically in conjunction with methotrexate prior to surgical evacuation or during treatment of hemorrhage related to the cervical ectopic [51, 52]. In the latter case, control of massive hemorrhage was facilitated with the use of a double-balloon cervical ripening catheter to tamponade the bleeding. A third case from the U.S. describes cervical packing with TXA imbibed iodoform gauze in conjunction with transvaginal suture ligation of the cervicovaginal branches of the uterine artery [53]. Blood transfusion was still required, illustrating the high risk of significant hemorrhage inherent to cervical ectopic pregnancies.

*Hysteroscopy*

Evidence for the use of TXA in the context of hysteroscopic surgery is relatively sparse. A prospective randomized trial from Turkey published in 2012 evaluated the effect of TXA administration at time of resectoscopic endometrial ablation (REA) on postoperative bleeding in a group of 60 patients [54]. Those in the intervention group (n = 30) were given 500mg of TXA during the procedure, followed by 250mg one hour later. There were no intraoperative or postoperative outcomes reported in this study. Nevertheless, results showed that the Pictorial Blood loss Assessment Chart (PBAC) scores on post-

operative day 1 suggested less bleeding in the TXA group than in the controls, albeit without reaching statistical significance.

In a prospective, randomized control trial from Egypt, 50 patients undergoing resectoscopic myomectomy with a monopolar loop electrode were randomized to intravenous infusion of either oxytocin or TXA [55]. Compared between the two groups were intraoperative hemodynamic measures (central venous pressure (CVP), mean arterial blood pressure (MBP), heart rate (HR), and oxygen saturation) and postoperative laboratory measures (hemoglobin concentration, hematocrit, and serum sodium concentration). Patients who received TXA were significantly more likely to have increased CVP, lower MBP, and lower HR throughout the procedure. Despite having comparable baseline values, they also had statistically significant drops in post-operative hemoglobin (10.18±0.62g/dL vs. 11.13±0.7g/dL; $p<0.001$), hematocrit (32.68% vs. 38.16%; $p<0.001$), and serum sodium (45mins from start of resection: 131.3meq/L vs. 138.96meq/L; $p<0.001$) compared to the oxytocin group. There was no significant difference in the rate of blood transfusion between the two groups. These findings led the authors to conclude that the uterotonic effects of oxytocin were more effective than TXA at reducing blood loss while simultaneously protecting against excessive fluid absorption, evidenced by the difference in post-operative serum sodium levels.

A case report from Belgium on hysteroscopic myomectomy describes intrauterine application of 1000mg of TXA, along with intrauterine foley catheter, in the management of immediate post-operative hemorrhage with good effect and resolution of bleeding [56]. Two similar studies explore the use of intrauterine EACA. One prophylactically added EACA to the distending medium, while the other involved intrauterine injection of EACA in the management of intractable bleeding. Subjective reductions in blood loss based on surgeons' visual assessment were appreciated in both instances [57, 58].

***Dosing***

As outlined in the U.S. product monograph, the recommended dose of oral TXA for cyclic heavy menstrual bleeding in those with normal renal function is 1300mg orally three times a day (total dose 3900mg/day) for a maximum of 5 days [59]. Parenteral dosing is approved for dental extraction in patients with hemophilia at a dose of 10mg/kg body weight intravenously three to four times daily for up to 8 days in those with normal renal function [60]. The Canadian monograph includes hereditary angioneurotic oedema as an indication, in addition to clinical situations of hyperfibrinolysis such as epistaxis, hyphaema, dental extractions in patients with coagulopathies, and in gynecology for conization of the cervix and heavy menstrual bleeding [61]. Approved Canadian dosing recommends 2-3 tabs of 500mg every 8-12 hours for up to 12 days. Intravenous dosing is identical, at 10mg/kg body weight, not to exceed an administration rate of 50mg/min.

Various dosing regimens have been reported in the literature, a selection of which pertaining to gynecologic surgery have been summarized in Table 1. TXA is most commonly administered either as a single dose of 1000mg IV pre-operatively, or weight based at 10-15mg/kg IV. Less commonly, infusions of 1mg/kg/hr may follow an initial administration. A recent prospective, double-blind control trial investigated two different dosing regimens of TXA for patients undergoing laparotomy for various abdomino-pelvic indications [62]. Patients were randomized to either a single dose of TXA pre-operatively (1000mg IV, group 1), a bolus dose followed by a 4-hour infusion of TXA (10mg/kg IV x 1, then 1mg/kg/hr, group 2), or a bolus of saline (group 3). While there was no difference in intraoperative blood loss between the groups, those receiving TXA had higher hemoglobin values at 24-48 hours post-operatively (mean hemoglobin ±- standard deviation for group 1: 10.5±1.1g/L; group 2: 10.8±1.3g/L; group 3: 9.7±0.8g/L; $p=0.003$). A randomised, double-blind trial comparing a single intravenous bolus

dose (30mg/kg) compared to a loading dose followed by an infusion (10mg/kg, then 2mg/kg/h) in patients undergoing total knee arthroplasty failed to detect any difference in blood loss or transfusion requirements between the two regimens [63]. Overall, the published literature in gynecologic surgery supports intraoperative prophylactic administration of tranexamic acid for hysterectomy, myomectomy, cervical conisation, and open surgery for cervical and ovarian cancer. The most common dosing of TXA in this setting is 1g intravenously at the onset of surgery, and in the case of cervical conisation may include a post-operative oral course of 1.5g three times a day for 12 to 14 days. See Table 2.

***Complications of use***

Given the mechanism of action of TXA, it would be logical to expect an increased risk of thrombotic events. However, the literature attests to the overwhelmingly positive safety profile of TXA and the exceedingly rare incidence of thrombosis. A systematic review and meta-analysis on the safety and efficacy of lysine-analogues in pelvic surgery failed to show any statistically significant increased risk of thrombosis for lysine analogues, either collectively or individually by drug [64]. Similarly, another systematic review and meta-analysis focusing on prophylactic TXA use prior to benign uterine surgery (caesarean section or abdominal myomectomy) did not show any increased risk of thrombotic events [65]. Indeed, clinical trials from trauma, orthopedic, cardiac, and general surgery all attest to the low risk of thrombotic complications with TXA use [24-26, 66, 67].

At higher doses, TXA has been associated with seizures, perhaps due to an interaction with GABA receptors in the central nervous system[9]. Published evidence from the cardiac surgery literature suggests that moderate to high dose regimens are associated with non-ischemic seizures [68]. A 2016 meta-analysis showed a dose-response relationship between TXA use and risk of seizure, with the highest risk found in the high dose group (30-109 mg/kg loading dose, infusion of 15 mg/kg/h) [69]. Although, an increased risk of seizure was seen even in the low dose group, it is important to note the relatively higher dose of TXA reported in this group compared to the common dosing used in gynecology (24-50mg/kg vs. 10mg/kg).

Reversible visual disturbances, including altered colour perception and temporary blindness, have been reported with tranexamic acid [70, 71]. For this reason, acquired defective color vision has been listed as a contraindication in the product monograph, as this prevents detection of a potential early sign of toxicity. The exact mechanism between TXA use and visual disturbances, however, remains to be fully elucidated. Additionally, other contraindications include hypersensitivity, active intravascular clotting, thromboembolic disease, and concomitant use of combined hormonal contraceptives. Overall, TXA is generally well tolerated by patients, with the most frequently reported adverse events being nausea, vomiting, or other gastrointestinal disturbances [72].

**Conclusion**

Since its discovery, tranexamic acid has proven to be a valuable resource across surgical specialties, demonstrating considerable benefit in terms of both morbidity and mortality. While most gynecologists are likely familiar with the use of TXA in the outpatient management of heavy menstrual bleeding, the prophylactic and therapeutic use in gynecologic surgery may be less well known. This review highlights a growing body of literature supporting the use and safety of TXA in gynecologic surgery for procedures such as hysterectomy, myomectomy, cervical conisation, ovarian cancer debulking, and intrauterine surgery. A single intravenous dose of 1000mg of tranexamic acid pre-operatively for patients undergoing myomectomy and other procedures in which excessive bleeding may be encountered can be considered as a safe adjunctive measure to decrease total blood loss and minimize the risk of peri-operative blood transfusion.

**References**


1. McPherson K, Metcalfe M, Herbert A, Maresh M, Casbard A, Hargreaves J, et al. Severe complications of hysterectomy: the VALUE study. BJOG: An International Journal of Obstetrics & Gynaecology 2004;111(7):688-94.
2. Mäkinen J, Brummer T, Jalkanen J, Heikkinen A-M, Fraser J, Tomás E, et al. Ten years of progress—improved hysterectomy outcomes in Finland 1996–2006: a longitudinal observation study. BMJ open 2013;3(10):e003169.
3. LaMORTE AI, Lalwani S, Diamond MP. Morbidity associated with abdominal myomectomy. Obstetrics and gynecology 1993;82(6):897-900.
4. Crosignani PG, Vercellini P, Meschìa M, Oldani S, Bramante T. GnRH agonists before surgery for uterine leiomyomas. A review. The Journal of reproductive medicine 1996;41(6):415-21.
5. Sanders AP, Chan WV, Tang J, Murji A. Surgical outcomes after uterine artery occlusion at the time of myomectomy: systematic review and meta-analysis. Fertility and Sterility 2019;111(4).
6. Zakhari A, Sanders AP, Murji A. Uterine artery occlusion at myomectomy. Fertility and sterility 2019;111(5):1030-31.
7. Kalogiannidis I, Xiromeritis P, Prapas N, Prapas Y. Intravaginal misoprostol reduces intraoperative blood loss in minimally invasive myomectomy: a randomized clinical trial. Clinical and experimental obstetrics & gynecology 2011;38(1):46-49.
8. Hickman LC, Kotlyar A, Shue S, Falcone T. Hemostatic techniques for myomectomy: an evidence-based approach. Journal of minimally invasive gynecology 2016;23(4):497-504.
9. Ng WCK, Jerath A, Wasowicz M. Tranexamic acid: a clinical review. Anaesthesiology intensive therapy 2015;47(4):339-50.
10. Watts G. Utako Okamoto. The Lancet 2016;387(10035):2286.
11. Okamoto S, Hijikata-Okunomiya A, Wanaka K, Okada Y, Okamoto U. Enzyme-controlling medicines: introduction. Seminars in thrombosis and hemostasis; 1997: Copyright© 1997 by Thieme Medical Publishers, Inc.; 1997. p. 493-501.
12. Jimenez JJ, Iribarren JL, Lorente L, Rodriguez JM, Hernandez D, Nassar I, et al. Tranexamic acid attenuates inflammatory response in cardiopulmonary bypass surgery through blockade of fibrinolysis: a case control study followed by a randomized double-blind controlled trial. Critical Care 2007;11(6):R117.
13. BRAMSEN T. Serum and aqueous humour concentration of tranexamic acid after peroral administration. Acta ophthalmologica 1979;57(3):455-60.
14. Pilbrant Å, Schannong M, Vessman J. Pharmacokinetics and bioavailability of tranexamic acid. European journal of clinical pharmacology 1981;20(1):65.
15. Andersson L, Nilsson IM, Niléhn JE, Hedner U, Granstrand B, Melander B. Experimental and clinical studies on AMCA, the antifibrinolytically active isomer of p-aminomethyl cyclohexane carboxylic acid. Scandinavian journal of haematology 1965;2(3):230-47.
16. Bryant-Smith AC, Lethaby A, Farquhar C, Hickey M. Antifibrinolytics for heavy menstrual bleeding. Cochrane Database of Systematic Reviews 2018(4).
17. Singh S, Best C, Dunn S, Leyland N, Wolfman WL. No. 292-Abnormal Uterine Bleeding in Pre-Menopausal Women. Journal of Obstetrics and Gynaecology Canada 2018;40(5):e391-e415.
18. ACOG committee opinion no. 557: Management of acute abnormal uterine bleeding in nonpregnant reproductive-aged women. Obstetrics and gynecology 2013 Apr;121(4):891-6.
19. Beaumont D, Pavord S, Gayet-Ageron A, Ker K, Mousa HA, Shakur H. Antifibrinolytic drugs for treating primary postpartum haemorrhage. The Cochrane database of systematic reviews 2018;2018(2).

20. Simonazzi G, Bisulli M, Saccone G, Moro E, Marshall A, Berghella V. Tranexamic acid for preventing postpartum blood loss after cesarean delivery: a systematic review and meta-analysis of randomized controlled trials. Acta obstetricia et gynecologica Scandinavica 2016;95(1):28-37.
21. Sentilhes L, Winer N, Azria E, Sénat M-V, Le Ray C, Vardon D, et al. Tranexamic acid for the prevention of blood loss after vaginal delivery. New England Journal of Medicine 2018;379(8):731-42.
22. Hajmurad OS, Choxi AA, Zahid Z, Dudaryk R. Aortoiliac thrombosis following tranexamic acid administration during urgent cesarean hysterectomy: a case report. A&A Practice 2017;9(3):90-93.
23. Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane database of systematic reviews 2011(3).
24. Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. Bmj 2012;344:e3054.
25. Perel P, Ker K, Uribe CHM, Roberts I. Tranexamic acid for reducing mortality in emergency and urgent surgery. Cochrane Database of Systematic Reviews 2013(1).
26. Roberts I, Shakur H, Coats T, Hunt B, Balogun E, Barnetson L, et al. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. Health technology assessment (Winchester, England) 2013;17(10):1.
27. Hammer A, Rositch AF, Kahlert J, Gravitt PE, Blaakaer J, Søgaard M. Global epidemiology of hysterectomy: possible impact on gynecological cancer rates. American journal of obstetrics and gynecology 2015;213(1):23-29.
28. Topsoee MF, Bergholt T, Ravn P, Schouenborg L, Moeller C, Ottesen B, et al. Anti-hemorrhagic effect of prophylactic tranexamic acid in benign hysterectomy—a double-blinded randomized placebo-controlled trial. American journal of obstetrics and gynecology 2016;215(1):72. e1-72. e8.
29. Arthi P N, B J, S G. Effect of prophylactic tranexamic acid on blood conservation in Indian women undergoing abdominal hysterectomy. International Journal of Reproduction, Contraception, Obstetrics and Gynecology 2018;7(9):3538-45.
30. Fusca L, Perelman I, Fergusson D, Boutet M, Chen I. The effectiveness of tranexamic acid at reducing blood loss and transfusion requirement for women undergoing myomectomy: a systematic review and meta-analysis. Journal of Obstetrics and Gynaecology Canada 2018.
31. Shady NW, Sallam HF, Fahmy H. Reducing blood loss during open myomectomy with intravenous versus topical tranexamic acid: A double-blinded randomized placebo-controlled trial. Middle East Fertility Society Journal 2018;23(3):225-31.
32. Martin-Hirsch PPL, Bryant A. Interventions for preventing blood loss during the treatment of cervical intraepithelial neoplasia. Cochrane Database of Systematic Reviews 2013(12).
33. Vu M, Yu J, Awolude OA, Chuang L. Cervical cancer worldwide. Current Problems in Cancer 2018 2018/09/01/;42(5):457-65.
34. Bansal N, Herzog TJ, Shaw RE, Burke WM, Deutsch I, Wright JD. Primary therapy for early-stage cervical cancer: radical hysterectomy vs radiation. American journal of obstetrics and gynecology 2009 Nov;201(5):485.e1-9.
35. Celebi N, Celebioglu B, Selcuk M, Canbay O, Karagoz AH, Aypar U. The role of antifibrinolytic agents in gynecologic cancer surgery. Saudi medical journal 2006;27(5):637-41.
36. Reid BM, Permuth JB, Sellers TA. Epidemiology of ovarian cancer: a review. Cancer biology & medicine 2017;14(1):9.
37. Elattar A, Bryant A, Winter-Roach BA, Hatem M, Naik R. Optimal primary surgical treatment for advanced epithelial ovarian cancer. The Cochrane database of systematic reviews 2011 Aug 10(8):Cd007565.

38. Amato A, Pescatori M. Perioperative blood transfusions and recurrence of colorectal cancer. Cochrane Database of Systematic Reviews 2006(1).
39. Rosenberg SA, Seipp CA, White DE, Wesley R. Perioperative blood transfusions are associated with increased rates of recurrence and decreased survival in patients with high-grade soft-tissue sarcomas of the extremities. Journal of Clinical Oncology 1985;3(5):698-709.
40. You D, Yoo YK, Choi HJ, Kim DG. Blood Transfusion as an Independent Risk Factor for Recurrence after Hepatocellular Carcinoma Resection. Transplantation 2018;102:S906.
41. Linder BJ, Frank I, Cheville JC, Tollefson MK, Thompson RH, Tarrell RF, et al. The Impact of Perioperative Blood Transfusion on Cancer Recurrence and Survival Following Radical Cystectomy. European Urology 2013 2013/05/01/;63(5):839-45.
42. Kietpeerakool C, Supoken A, Laopaiboon M, Lumbiganon P. Effectiveness of tranexamic acid in reducing blood loss during cytoreductive surgery for advanced ovarian cancer. Cochrane Database of Systematic Reviews 2016(1).
43. Lundin ES, Johansson T, Zachrisson H, Leandersson U, Bäckman F, Falknäs L, et al. Single-dose tranexamic acid in advanced ovarian cancer surgery reduces blood loss and transfusions: double-blind placebo-controlled randomized multicenter study. Acta obstetricia et gynecologica Scandinavica 2014;93(4):335-44.
44. Wallace SK, Halverson JW, Jankowski CJ, DeJong SR, Weaver AL, Weinhold MR, et al. Optimizing blood transfusion practices through bundled intervention implementation in patients with gynecologic cancer undergoing laparotomy. Obstetrics & Gynecology 2018;131(5):891-98.
45. Hoover KW, Tao G, Kent CK. Trends in the diagnosis and treatment of ectopic pregnancy in the United States. Obstetrics and gynecology 2010 Mar;115(3):495-502.
46. Van Den Eeden SK, Shan J, Bruce C, Glasser M. Ectopic pregnancy rate and treatment utilization in a large managed care organization. Obstetrics and gynecology 2005 May;105(5 Pt 1):1052-7.
47. Hendrix NW, Chauhan SP, Mobley J, Devoe LD, Smith RP. Risk factors associated with blood transfusion in ectopic pregnancy. The Journal of reproductive medicine 1999 May;44(5):433-40.
48. Takeda A, Manabe S, Mitsui T, Nakamura H. Management of patients with ectopic pregnancy with massive hemoperitoneum by laparoscopic surgery with intraoperative autologous blood transfusion. Journal of minimally invasive gynecology 2006;13(1):43-48.
49. Yamada T, Okamoto Y, Kasamatsu H, Mori H. Intraoperative autologous blood transfusion for hemoperitoneum resulting from ectopic pregnancy or ovarian bleeding during laparoscopic surgery. JSLS: Journal of the Society of Laparoendoscopic Surgeons 2003;7(2):97.
50. Murphy NC, Hayes NE, Ainle FBN, Flood KM. Jehovah's Witness patients presenting with ruptured ectopic pregnancies: two case reports. Journal of medical case reports 2014;8(1):312.
51. Arowojolu A, Ogunbode O. Cervical ectopic pregnancy managed with methotrexate and tranexamic acid: A case report. African journal of medicine and medical sciences 2014;43(4):361-64.
52. Zambrano N, Reilly J, Moretti M, Lakhi N. Double balloon cervical ripening catheter for control of massive hemorrhage in a cervical ectopic pregnancy. Case reports in obstetrics and gynecology 2017;2017.
53. Bianchi P, Salvatori MM, Torcia F, Cozza G, Mossa B. Cervical pregnancy. Fertility and sterility 2011;95(6):2123. e3-23. e4.
54. Ergun B, Bastu E, Ozsurmeli M, Celik C. Tranexamic acid: a potential adjunct to resectoscopic endometrial ablation. International surgery 2013;97(4):310-14.
55. Mousa SA, Yassen AM, Alhadary HS, Sadek EES, Abdel-Hady E-S. Hematological profile and transfusion requirement during hysteroscopic myomectomy: a comparative study between oxytocin and tranexamic acid infusion. Egyptian Journal of Anaesthesia 2012;28(2):125-32.

56. van den Brûle F, Buicu C, Dequesne J, Herman P, Gaspard UJ. Treatment of peroperative hemorrage during operative hysteroscopy using bipolar energy with intrauterine tranexamic acid: a case report. Gynecological Surgery 2004;1(3):205-06.
57. Sayyahmelli M, MOOSAZADEH R, MOSTAFA GP, NAZARI F. Comparison of the Intraoperative Outcomes of Intrauterine Instillation of Epsilon-Aminocaproic Acid and Intravenous Oxytocin in Hysteroscopy Surgeries. 2016.
58. Manizheh S-m, Elaheh O, Simin T, Mehry JS, Parvin MG, Bahareh N, et al. The effect of intrauterine instillation of E-Aminocaproic Acid during hysteroscopic operations in the management of intractable uterine hemorrhage: a randomized clinical trial. Life Sci J 2013;10:1369-74.
59. Ferring-Pharmaceuticals-Inc. Lysteda (tranexamic acid) tablets: highlights of Prescribing Information 2013. 2013 [cited 2019 June 22]; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022430s004lbl.pdf
60. Pfizer-Injectables. Cyklokapron (tranexamic acid injection). 2017 [cited 2019 June 22]; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/019281s041lbl.pdf
61. Pfizer-Canada-Inc. Product Monograph GD-Tranexamic Acid. 2018 [cited 2019 June 22]; Available from: https://www.pfizer.ca/sites/g/files/g10050796/f/201810/GD-Tranexamic_Acid_PM_E_220955_22Oct2018.pdf
62. Prasad R, Patki A, Padhy S, Ramchandran G. Single intravenous bolus versus perioperative continuous infusion of tranexamic acid to reduce blood loss in abdominal oncosurgical procedures: A prospective randomized double-blind clinical study. Journal of anaesthesiology, clinical pharmacology 2018 Oct-Dec;34(4):529-34.
63. Hourlier H, Reina N, Fennema P. Single dose intravenous tranexamic acid as effective as continuous infusion in primary total knee arthroplasty: a randomised clinical trial. Archives of Orthopaedic and Trauma Surgery 2015 April 01;135(4):465-71.
64. Breau RH, Kokolo MB, Punjani N, Cagiannos I, Beck A, Niznick N, et al. The effects of lysine analogs during pelvic surgery: a systematic review and meta-analysis. Transfusion medicine reviews 2014;28(3):145-55.
65. Topsoee MF, Settnes A, Ottesen B, Bergholt T. A systematic review and meta-analysis of the effect of prophylactic tranexamic acid treatment in major benign uterine surgery. International Journal of Gynecology & Obstetrics 2017;136(2):120-27.
66. Kagoma YK, Crowther MA, Douketis J, Bhandari M, Eikelboom J, Lim W. Use of antifibrinolytic therapy to reduce transfusion in patients undergoing orthopedic surgery: a systematic review of randomized trials. Thrombosis research 2009;123(5):687-96.
67. Ma SA, Brindle W, Burton G, Gallacher S, Hong FC, Manelius I, et al. Tranexamic acid is associated with less blood transfusion in off-pump coronary artery bypass graft surgery: a systematic review and meta-analysis. Journal of cardiothoracic and vascular anesthesia 2011;25(1):26-35.
68. Murkin JM, Falter F, Granton J, Young B, Burt C, Chu M. High-dose tranexamic acid is associated with nonischemic clinical seizures in cardiac surgical patients. Anesthesia & Analgesia 2010;110(2):350-53.
69. Lin Z, Xiaoyi Z. Tranexamic acid-associated seizures: a meta-analysis. Seizure 2016;36:70-73.
70. Cravens GT, Brown MJ, Brown DR, Wass CT. Antifibrinolytic therapy use to mitigate blood loss during staged complex major spine surgery: postoperative visual color changes after tranexamic acid administration. Anesthesiology: The Journal of the American Society of Anesthesiologists 2006;105(6):1274-76.
71. Kitamura H, Matsui I, Itoh N, Fujii T, Aizawa M, Yamamoto R, et al. Tranexamic acid-induced visual impairment in a hemodialysis patient. Journal of Clinical and Experimental Nephrology 2003;7(4):311-14.

72. Shaaban MM, Ahmed MR, Farhan RE, Dardeer HH. Efficacy of tranexamic acid on myomectomy-associated blood loss in patients with multiple myomas: a randomized controlled clinical trial. Reproductive Sciences 2016;23(7):908-12.

Table 1: Comparison of various dosing regimens of tranexamic acid (TXA) for different gynecologic surgeries

| Study | Intervention | Dose | Notes |
|---|---|---|---|
| **Topsoee 2016** | Benign hysterectomy | 1000mg IV x 1 | Immediately pre-operatively |
| **Arthi 2018** | Benign hysterectomy | 15mg/kg IV x 1 | Infusion over 15mins, 20mins prior to skin incision |
| **Ngichabe 2015** | Abdominal myomectomy | 1000g/50mL NS IV at 100mL/hr | Mean operative time 50.1mins |
| **Caglar 2008** | Abdominal myomectomy | 10mg/kg IV x 1, then 1mg/kg/hr IV x 10hrs | Post-operative infusion dissolved in 1L NS |
| **Grundsell 1984** | Cervical conisation | 1000mg IV x 1, then 1000mg PO TID x 14 days | IV infusion intra-operatively |
| **Celebi 2006** | Hysterectomy, cervical cancer | 10mg/kg x 1 | Immediately pre-operatively |
| **Lundin 2014** | Debulking, ovarian cancer | 15mg/kg IV x 1 | Immediately pre-operatively |
| **Wallace 2018** | Laparotomy, gynecologic cancer | 15mg/kg IV x 1 | Immediately pre-operatively |
| **van den Brûle 2004** | Hysteroscopic myomectomy | 1000mg intrauterine | Instilled via transcervical Foley catheter |

Table 2: Evidence for tranexamic acid (TXA) use in gynecological surgery

| Procedure | Study type (number of patients) | Intervention | Main outcome |
|---|---|---|---|
| *Benign Hysterectomy* | | | |
| Topsoee 2016 | RCT (n = 332) | TXA 1000mg IV x 1 | Decrease blood loss, MD -36.4mL, p = 0.006 |
| Arthi 2018 | RCT (n = 100) | TXA 15mg/kg IV x 1 | Decreased blood loss, 360.16mL vs. 540.22mL, p <0.00001<br>Decreased blood transfusion, 12% vs. 42%, p <0.00001 |
| *Myomectomy* | | | |
| Fusca 2018 | SR/MA (2 RCTs, n = 232) | TXA 10-15mg/kg IV x 1, then 1mg/kg/h x 6-10h | Decreased blood loss, MD -213.1mL, 95% CI: -242.4mL, -183.7mL |
| Shady 2018 | RCT (n = 105) | TXA 1000mg IV x 1<br>or<br>TXA 2g topically x 5 mins intra-operatively | Decreased blood loss, 721.71mL vs. 1080.00mL, p = 0.0001<br>Decreased blood transfusion, 17.1% vs. 54.3%, p = 0.001<br>Decreased blood loss, 683.61mL vs 1080.00mL, p = 0.0001<br>Decreased blood transfusion, 20.0% vs. 54.3%, p = 0.003 |
| *Cervical Conisation* | | | |
| Martin-Hirsch 2010 | Cochrane SR/MA (4 RCTs, n = 640) | TXA 1g IV x 1 then 1.5g-4.5g daily x 12 – 14 days | No difference in primary hemorrhage (<24h)<br>Decreased incidence in secondary hemorrhage (>24h)<br>RR 0.23 (95% CI: 0.11 – 0.50) |
| *Cervical Cancer* | | | |
| Celebi 2006 | RCT (n = 105) | TXA 10mg/kg IV x 1 | Decreased blood loss, 270mL vs. 390-405mL, p = 0.005 |
| *Ovarian Cancer* | | | |
| Kietpeerakool 2016 | Cochrane SR (1 RCT, n = 100) | TXA 15mg/kg IV x 1 | Decreased median blood loss, 520mL vs. 730mL, p = 0.03<br>Decreased blood transfusion, OR 0.44, p = 0.02 |

Abbreviations: CI confidence interval, MD mean difference, RCT randomized control trial, RR relative risk, SR/MA systematic review and meta-analysis