

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

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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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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 method³⁴ 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 > 80 mL per cycle	MBL (AHM)	Mean MBL change from baseline: TA –53% and FLU –24%; <i>P</i> < 0.01
	2. FLU 100 mg × 2 pd 1–5	15	Regular cycle	Duration of bleeding	No effect on duration of bleeding
	Total	15			Discontinuation: 0%
Bonnar and Sheppard ²⁴	Duration: 2 screening and 2 + 2 treatment cycles				
	Randomized open cross-over study				
	Method of randomization unclear				
	1. ETM 500 mg × 4 pd 1–5	27	Women aged 35–46 years	MBL (AHM)	Mean MBL change from baseline: ETM +3%, TA –54%, ^a and MEF –20%, ^a
	2. TA 1 g × 4 pd 1–5	26	MBL > 80 mL per cycle	Duration of bleeding	<i>P</i> < 0.05 TA compared with MEF,
	3. MEF 500 mg × 3 pd 1–5	23	Normal hysteroscopy, endometrial biopsy, and cervical cytology	Number of sanitary napkins used	<i>P</i> < 0.001 TA compared with ETM
Total	76			No effect on duration of bleeding Reduction in the number of napkins used: <i>P</i> < 0.01 TA compared with baseline Discontinuation: ETM 41%, TA 15%, and MEF 13%	
Callender et al ²⁵	Duration: 3 placebo and 3 treatment cycles				
	Randomization by computer-generated list to one of three groups				
	Blinding unclear				
1. TA 1 g × 4 pd 1–4	20	Women aged 33–48 years	MBL (Total body counter)	Mean MBL change from baseline: TA –36% ^b and placebo –6%, <i>P</i> < 0.05	
2. Placebo pd 1–4	20	Subjectively perceived menorrhagia or iron deficiency anemia	Duration of bleeding	No effect on duration of bleeding	
Total	20		Number of napkins used	Reduction in the number of napkins used: <i>P</i> < 0.01 TA compared with placebo Discontinuation: 20%	
Freeman et al ²⁶	Duration: 3 + 3 treatment cycles				
	Randomized double-blind cross-over study				
	1. TA 650 mg × 3 pd 1–5	115	Women aged 18–49 years	MBL (AHM)	Mean MBL change from baseline: TA low dose –26%, TA high dose –39%, and placebo –2%, <i>P</i> < 0.0001 both TA groups compared with placebo
	2. TA 1.3 g × 3 pd 1–5	112	Average MBL ≥ 80 mL over two cycles	QOL (MIQ)	QOL: improvements in limitations in social/leisure activities, and physical activities in both TA groups compared with placebo (<i>P</i> ≤ 0.0055)
	3. Placebo pd 1–5	67	Regular cycle	Number of large stains	Discontinuation: TA lower dose 9%, TA higher dose 13%, and placebo 9%
Total	294			Mean MBL (PBAC) change from baseline: TA –38% and IN-DDAVP –23%, <i>P</i> = 0.0002	
Kouides et al ²⁷	Duration: 2 screening and 3 treatment cycles				
	Randomized double-blind placebo-controlled study				
	1. TA 1 g × 4 pd 1–5	67	Women aged 18–50 years	MBL (PBAC)	QOL: improved in both groups (significantly on RUTA scale)
2. IN-DDAVP 300 µg × 1 pd 2–3	49	Abnormal laboratory hemostasis	QOL (HRQOL, SF-36, CES-D, and RUTA)	Discontinuation: 43% IN-DDAVP → TA and 33% TA → IN-DDAVP	
Total	116				
Duration: 2 + 2 treatment cycles			PBAC score ≥ 100		
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	49	Women presenting with heavy menstrual bleeding	MBL (PBAC)	Mean MBL (PBAC) change from baseline: TA –60% ^d and MPA –58% ^d
	2. MPA 10 mg × 2 pd 5–25	45	PBAC score > 100	Duration of bleeding	Duration of bleeding decreased in both groups (P < 0.005)
	Total	94		Hemoglobin QOL (VAS)	Hemoglobin increased in both groups (TA, P = 0.003; MPA, P = 0.019) Discontinuation: TA 4% and MPA 27%
Lukes et al ²⁹	1. 1.3 g × 3 pd 1–5	115	Women aged 18–49 years	MBL (AHM)	Mean MBL change from baseline: TA –40% and placebo –8%, P < 0.001
	2. Placebo pd 1–5	72	Average MBL ≥ 80 mL over two cycles	QOL (MIQ)	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)
	Total	187	Regular cycle	Number of large stains	No significant increase in hemoglobin
	Duration: 2 screening and 6 treatment cycles		Uterine fibroids not excluded unless surgical management warranted	Hemoglobin and ferritin	Discontinuation: TA 24% and placebo 26%
	Randomized double-blind placebo-controlled study				Mean MBL change from baseline: 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
Milsom et al ³⁰	1. LNG-IUS (release of 20 µg/day)	16	Women aged 31–49 years	MBL (AHM)	P < 0.001 LNG-IUS compared with FLU, P < 0.01 LNG-IUS compared with TA, P < 0.05 TA compared with FLU
	2. FLU 100 mg × 2 pd 1–5	15	MBL > 80 mL per cycle	Hemoglobin	Hemoglobin increase: LNG-IUS 10%, FLU 0%, and TA 0%
	3. TA 1.5 g × 3 pd 1–3 and 1 g × 2 pd 4–5	15	Regular cycle		
	Total	15			
	LNG-IUS 12 months open-label, then randomization to non-blind treatment (FLU and TA) for 2 + 2 cycles in cross-over fashion				
Nilsson and Rybo ³¹	Method of randomization unclear				
	1. TA 250 mg × 6 pd 1–4 and 500 mg × 6 pd 1–4	36	Women aged 15–49 years	MBL (AHM)	Mean MBL change from baseline: TA –38% (total dose of 12 g per cycle) and –51% (total dose of 24 g per cycle)
	2. TA 500 mg × 6 pd 1–4 and 1 g × 6 hourly pd 1–4		Subjectively perceived menorrhagia		Discontinuation: 0%
	3. Placebo × 6 pd 1–4				
	Total				
Duration: 2 screening and 1 + 1 treatment cycles					
Randomized double-blind cross-over study					
Method of randomization unclear					
Only one cycle of treatment on each dosage					
Preston et al ³²	1. TA 1 g × 4 pd 1–4	25	Age 18 years or more	MBL (AHM)	Mean MBL change from baseline: TA –45% and NOR +20%
	2. NOR 5 mg × 2 pd 19–26	21	Average MBL > 80 mL over	QOL	

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

Notes: * $P < 0.05$; $^{**}P < 0.02$; $^{***}P < 0.01$; $^{****}P < 0.005$; $^{*****}P < 0.001$; $^{*****}P < 0.0001$.
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 Rute 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 al²⁸ 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 al²⁶ ($n = 294$) 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 al²⁹ 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 al²⁶ 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 $\geq 5\%$ 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 al²⁸ ($n = 94$) 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 al⁴⁰ 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 al²⁶ ($n = 294$) 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 Rybo³¹ ($n = 36$) 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 study⁴⁴ 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.

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