



Department of Vermont Health Access Therapeutic Class Review

Hemostatic Agents

Overview/Summary

Aminocaproic acid (Amicar[®]) and tranexamic acid (Lysteda[®]) are two hemostatic agents that are Food and Drug Administration (FDA)-approved for the treatment of bleeding disorders.^{1,2} Both products are available as oral and injectable formulations, and aminocaproic acid is available generically.¹⁻⁵ Specifically, aminocaproic acid is approved for the treatment of acute bleeding syndromes including surgical and non-surgical hematuria, and hemorrhage due to increased fibrinolysis.^{1,3} Tranexamic acid tablets are FDA-approved for the treatment of cyclic heavy menstrual bleeding.⁴ The injectable form of tranexamic acid (Cyklokapron[®]) is approved for short-term use (two to eight days) in hemophiliacs to reduce or prevent hemorrhage and to reduce the need for replacement therapy during and following tooth extraction.⁵ This review will focus primarily on the use of the oral formulations of the hemostatic agents. Aminocaproic acid and tranexamic acid are synthetic lysine analogs that act primarily by occupying the lysine binding sites on plasminogen, which inhibits the conversion of plasminogen to plasmin, and therefore fibrinolysis.¹⁻⁴ The *in vitro* antifibrinolytic potency of aminocaproic acid is reported to be approximately one-fifth to one-tenth that of tranexamic acid, and also has a shorter half-life which results in more frequent dosing.²

Aminocaproic acid is useful in the treatment of acute bleeding syndromes resulting from systemic hyperfibrinolysis and urinary fibrinolysis.^{1,3} Aminocaproic acid has been used in systemic hyperfibrinolysis associated with placenta abruption, cardiac surgery, hematologic disorders, hepatic cirrhosis, neoplastic disorders (e.g., carcinoma of the cervix, lung, prostate, and stomach), and portacaval shunt. It has also been used in urinary fibrinolysis associated with surgical and nonsurgical hematuria. Due to the limited number of well-designed, published clinical trials, it is not clear if these FDA-approved indications were based on the results of studies with the intravenous or oral formulations of aminocaproic acid.

Despite only being approved by the FDA for heavy menstrual bleeding since 2009, an oral formulation of tranexamic acid has been available in Europe for many years for this indication. Tranexamic acid has been shown to be useful in reducing blood loss by 29 to 58% when used for up to five days during menstruation in women with heavy menstrual bleeding.⁶ Clinical studies have reported that tranexamic acid was more effective than nonsteroidal anti-inflammatory drugs (NSAIDs) and luteal phase progestins in reducing heavy menstrual bleeding, but less effective than the levonorgestrel intrauterine device.^{7,8} The levonorgestrel intrauterine device is recommended as first-line treatment for heavy menstrual bleeding if hormonal treatment is acceptable and long-term use is anticipated. Tranexamic acid, NSAIDs or combination oral contraceptives are recommended as second-line therapy. If hormonal therapy is not acceptable, tranexamic acid and NSAIDs are considered first-line treatment options.^{6,9}

Oral aminocaproic acid and tranexamic acid are generally well tolerated.¹⁻⁴ Diarrhea, dizziness, headache, and nausea are the most frequently reported adverse effects with aminocaproic acid.³ Abdominal pain, back pain, headache, and nasal and sinus symptoms are the most frequently reported adverse effects with tranexamic acid.⁴ Due to their antifibrinolytic activity, both aminocaproic acid and tranexamic acid have the potential to cause thromboembolic events. Neither hemostatic agent is approved by the FDA for use in children.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade Name)	Medication Class	Generic Availability
Aminocaproic acid (Amicar [®] *)	Hemostatic agent	✓
Tranexamic acid (Lysteda [®])	Hemostatic agent	-

*Available generically in one dosage form or strength.

Indications

Table 2. Food and Drug Administration (FDA) Approved Indications¹⁻⁴

Indication	Aminocaproic Acid	Tranexamic Acid
Treatment of acute bleeding syndromes to enhance hemostasis when fibrinolysis contributes to bleeding*	✓	
Treatment of cyclic heavy menstrual bleeding		✓

*Causes may include abruptio placentae, cardiac surgery, hematologic disorders, hepatic cirrhosis, neoplastic disorders (e.g., carcinoma of the cervix, lung, prostate, and stomach), portacaval shunt, and urinary fibrinolysis associated with surgical or nonsurgical hematuria.

In addition to their Food and Drug Administration-approved indications, when administered by the oral route, these agents have the potential to be used off-label for the following conditions:^{2,3}

- Acute promyelocytic leukemia (aminocaproic acid)
- Angioedema (aminocaproic acid and tranexamic acid)
- Dental procedures in hemophiliacs (aminocaproic acid and tranexamic acid)
- Gastrointestinal hemorrhage (tranexamic acid)
- Intraocular hemorrhage (e.g., hyphema) (aminocaproic acid and tranexamic acid)
- Operation on cervix (tranexamic acid)
- Subarachnoid hemorrhage (aminocaproic acid and tranexamic acid)

Pharmacokinetics

Table 3. Pharmacokinetics¹⁻⁴

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Aminocaproic acid	100	65 (unchanged)	Adipic acid*	1 to 5
Tranexamic acid	45	95 (unchanged)	None	11

*Primary metabolite but activity not reported.

Clinical Trials

Published clinical trials evaluating the safety and efficacy of the oral hemostatic agents for the management of various coagulation disorders are outlined in Table 4.

Despite the fact that aminocaproic acid has been used to control various bleeding disorders over the past 30 years, there is limited published data evaluating the efficacy and safety of oral aminocaproic acid for its approved indications. Clinical studies and case reports have reported successes with the use of oral aminocaproic acid in patients with amegakaryocytic thrombocytopenia (especially in decreasing the need for platelet transfusions), hyperfibrinolysis and cirrhosis, hematuria and menorrhagia.^{10-13,20} In an open-label study of 52 patients with cirrhosis, 37 patients (71%) received aminocaproic acid because they had experienced at least one bleeding episode, of which 34 patients (92%) had improvement or resolution of their bleeding after treatment (*P* values not reported, no comparative arm).¹¹

In a small double-blind, crossover study (N=37), Nilsson and colleagues evaluated oral aminocaproic acid in women with suspected menorrhagia. Women who were enrolled in the study received either aminocaproic acid 18 g daily or placebo on a tapered schedule over eight days during two consecutive menstrual cycles. After two cycles of treatment, women receiving aminocaproic acid experienced

significantly less menstrual blood loss when compared to women who received placebo (52 vs 127 mL, respectively; $P < 0.001$).¹³ Kasonde et al evaluated the effect of oral aminocaproic acid 12 g daily in 91 women with menorrhagia after placement of an intrauterine device. Menstrual blood loss was significantly reduced in women who received oral aminocaproic acid during their menstrual period compared to women in the control group (54.1 vs 81.6 mL; $P < 0.001$).²⁰

In November 2009 an oral formulation of tranexamic acid was Food and Drug Administration approved for the treatment of heavy menstrual bleeding.⁴ The approval of tranexamic acid for heavy menstrual bleeding was based on two randomized, placebo-controlled trials over three and six menstrual cycles each. In the study by Lukes et al, the only study which has been published, 196 women aged 18 to 49 were randomized to receive either tranexamic acid 3,900 mg/day (1,300 mg three times daily) or placebo for six consecutive menstrual cycles. To meet the pre-specified three-component primary endpoint, women treated with tranexamic acid needed to have a greater reduction in blood loss compared to women treated with placebo, a reduction in blood loss > 50 mL and a greater reduction in blood loss than the pre-determined meaningful threshold (a reduction in blood loss ≥ 36 mL). After six cycles of treatment, women treated with oral tranexamic acid had greater reductions in menstrual blood loss when compared to women treated with placebo (-69.6 [-40.4%] vs -12.6 mL [-8.2%]; $P < 0.001$).¹⁵

Tranexamic acid has been used in other countries since 1966 for the treatment of menorrhagia.²² A meta-analysis of four clinical trials (N=193) reported that tranexamic acid (4,000 mg/day during the first five days of the menstrual cycle) produced a greater reduction in objective measurements of heavy menstrual bleeding when compared to placebo, flurbiprofen, mefenamic acid and oral luteal phase progestogens.¹⁴ Tranexamic acid was not associated with an increased risk of side effects compared to placebo or the other medical therapies. No trial included in the meta-analyses evaluated thromboembolic events as an outcome. In a case-control study utilizing a database of European women with menorrhagia, tranexamic acid was associated with an increased risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) although the risk estimate did not reach statistical significance.²² Increased risks of venous thromboembolism and a diagnosis of anemia were also associated with mefenamic acid and norethindrone treatment.

In a small randomized controlled trial with a crossover design (N=15) by Andersch et al, a significant reduction in menstrual blood loss was reported during treatment with both tranexamic acid (-140 mL [-53%]; $P < 0.01$) and flurbiprofen (-72 mL [-24%]; $P < 0.01$).⁷ A second small trial by Milson et al compared three different medical treatments for women with idiopathic menorrhagia. The levonorgestrel-releasing intrauterine device was the most effective treatment for reducing blood loss with reductions of 82 to 96% over three to 12 months compared to 44% for tranexamic acid and 21% for flurbiprofen.⁸ Another randomized controlled trial comparing tranexamic acid to medroxyprogesterone in women with dysfunctional uterine bleeding found that after three months of therapy, the mean reduction in menstrual blood loss was 60.3% with tranexamic acid and 57.7% with medroxyprogesterone ($P < 0.005$).¹⁹ In other small studies, tranexamic acid was found to be more effective than diclofenac and intranasal desmopressin in reducing menstrual blood loss; however, more side effects were reported for tranexamic acid than diclofenac.^{17,18}

Clinical Trials

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Bleeding Episodes (Surgical and Non-surgical)				
<p>Gardner et al¹⁰</p> <p>Aminocaproic acid IV and/or PO 2 to 24 g per day for three days to 13 months</p>	<p>Case reports, OL</p> <p>Patients 9 to 76 years of age with amegakaryocytic thrombocytopenia, capillary bleeding (e.g., gastrointestinal, gingival, epistaxis, rectal, hematuria or dental extraction)</p>	<p>N=14</p> <p>3 days to 13 months</p>	<p>Primary: Control of bleeding, safety</p> <p>Secondary: Not reported</p>	<p>Primary: Seven patients received aminocaproic acid for short-term control of bleeding (<1 month), three for an intermediate period (one to four months), and four for long-term control (five to 13 months). Bleeding was controlled in 13 of the 14 patients.</p> <p>Long-term therapy with aminocaproic acid decreased monthly platelet transfusions from six to 40 units per month to zero to four units per month (<i>P</i> value not reported).</p> <p>No significant adverse effects were reported except for orthostatic hypotension, which was ameliorated by a reduction in dosage.</p> <p>Secondary: Not reported</p>
<p>Gunawan et al¹¹</p> <p>Aminocaproic acid 4 to 5 g PO (loading dose for 60% of patients) then 1 g PO QID (maintenance dose for 77% of patients)</p>	<p>OL, RETRO</p> <p>Cirrhotic patients (67% males) with abnormal euglobin lysis times and a mean age of 49 years</p>	<p>N=52</p> <p>13 days (mean duration of treatment)</p>	<p>Primary: Reduction in bleeding episodes, safety</p> <p>Secondary: Not reported</p>	<p>Primary: Of the 52 patients who received aminocaproic acid, 37 patients (71%) received the drug because they had experienced at least one bleeding episode, of which 34 patients (92%) had improvement or resolution of their bleeding (<i>P</i> values not reported, no comparative arm).</p> <p>Fifteen patients received aminocaproic acid because of a very low euglobulin lysis time, decreasing hemoglobin or prior to an operation/invasive procedure, but no overt bleeding. Fourteen patients (94%) continued to do well without a bleeding episode while on aminocaproic acid and one patient (7%) had melena.</p> <p>Only two patients (3%) had aminocaproic acid treatment discontinued because of side effects (rash and lightheadedness). There were no thromboembolic complications of treatment.</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Black et al¹²</p> <p>Aminocaproic acid 6 to 8 g PO per day (in four to six divided doses)</p> <p>Many patients (% not reported) received a loading dose of 5 g (IV or PO).</p>	<p>OL, RETRO (over 12 years)</p> <p>Patients 5 to 88 years of age with sicklemlia and hematuria who were hospitalized</p>	<p>N=40</p> <p>Duration of treatment not reported</p>	<p>Primary: Resolution of hematuria, safety</p> <p>Secondary: Not reported</p>	<p>Primary: There were 44 episodes of sicklemic hematuria that occurred in 40 patients during the 12-year study period. Hematuria subsided spontaneously in 20 episodes.</p> <p>Aminocaproic acid was administered to 22 patients (note: hematuria was usually more severe in patients who received aminocaproic acid). Following administration, hematuria ceased in an average of 2.2 days. Although the course of hematuria tended to be shorter if a loading dose was administered, differences were not determined to be statistically significant. During some of the episodes of hematuria, aminocaproic acid therapy was discontinued one to two days after cessation of the bleeding, and the hematuria was seen to recur. However, after reinitiating aminocaproic acid therapy, the hematuria again subsided. Blood transfusions were required only during three of the 44 bleeding episodes (<i>P</i> values were not reported).</p> <p>Therapy with aminocaproic acid was not associated with an increased incidence of thrombosis in this study.</p> <p>Secondary: Not reported</p>
Menstrual Bleeding				
<p>Nilsson et al¹³</p> <p>Aminocaproic acid 18 g PO per day for four days, then 12 g PO per day for one day, then 9 g PO per day for one day, then 6 g PO per day for one day, then 3 g PO per day for one day</p> <p>vs</p> <p>placebo</p>	<p>DB, XO</p> <p>Women 17 to 50 years of age with suspected menorrhagia</p>	<p>N=37</p> <p>2 menstrual cycles</p>	<p>Primary: Reduction in menstrual blood loss (volume), safety</p> <p>Secondary: Not reported</p>	<p>Primary: The mean blood loss was significantly smaller during periods when aminocaproic acid was administered compared to periods when placebo was administered (52 vs 127 mL, respectively; <i>P</i><0.001). There were no differences in blood loss between women with or without fibroids in respect to either treatment group. In 29 patients who received aminocaproic acid, the reduction in menstrual blood loss was 50 to 90%, for two patients the reduction was <50% and for six patients, there was no change in menstrual blood loss.</p> <p>Thirteen patients had side effects to aminocaproic acid, mainly nausea or "orthostatism". Four patients reported side effects to placebo, and seven patients displayed side effects with both aminocaproic acid and placebo (<i>P</i> values were not reported).</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Lethaby et al¹⁴</p> <p>Tranexamic acid 1 g PO QID on days one to five of menstrual cycle (three trials) or prodrug of tranexamic acid* (one trial)</p> <p>vs</p> <p>placebo (two trials) or other PO medical therapies (ethamsylate*, mefenamic acid, norethisterone; each one trial)</p>	<p>MA</p> <p>RCTs comparing antifibrinolytic therapy vs placebo in women of reproductive age (age not reported) with regular heavy menstrual bleeding (>80 mL blood loss per cycle)</p>	<p>N=193</p> <p>Duration varied (at least 2 menstrual cycles)</p>	<p>Primary: Reduction in menstrual blood loss (volume), change in quality of life</p> <p>Secondary: Not reported</p>	<p>Primary: Compared to placebo, tranexamic acid therapy showed a significant reduction in mean blood loss (WMD, -94.0 mL; 95% CI, -151.4 to -36.5) and a significant change in mean reduction of blood loss (WMD, -110.2 mL; 95% CI, -146.5 to -73.8). However, patients did not perceive the improvement in monthly menstrual blood loss as significant (RR, 2.5; 95% CI, 0.9 to 7.3; <i>P</i> values were not reported).</p> <p>Antifibrinolytic agents were compared to only three other medical (nonsurgical) therapies: mefenamic acid, norethindrone (administered in the luteal phase) and ethamsylate. In all instances, there was a significant reduction in mean blood loss (WMD, -73.0 mL; 95% CI, -123.4 to -22.6; WMD, -111.0 mL; 95% CI, -178.5 to -43.5; and WMD, -100.0 mL; 95% CI, -143.9 to -56.1, respectively) and a strong, although nonsignificant trend in favor of tranexamic acid in the participants' perception of an improvement in menstrual blood loss (<i>P</i> values were not reported).</p> <p>There were no significant differences in the frequency of reported side effects with tranexamic acid when compared to oral luteal phase progestogens (RR, 0.4; 95% CI, 0.1 to 1.2) or withdrawal from treatment because of adverse events when compared to NSAIDs and ethamsylate for the treatment of heavy menstrual bleeding (<i>P</i> values were not reported).</p> <p>Change in the quality of life measures, flooding/leakage and sex life, were significantly improved in the tranexamic acid group when compared to the oral progestogen group.</p> <p>Secondary: Not reported</p>
<p>Lukes et al¹⁵</p> <p>Tranexamic acid 1,300 mg TID for up to five days during menstruation</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Women 18 to 49 years of age with heavy menstrual bleeding, history ≥3 days of heavy bleeding over at</p>	<p>N=196</p> <p>6 cycles</p>	<p>Primary: Three-components: a larger reduction in blood loss compared to placebo, a reduction in blood loss >50</p>	<p>Primary: Women treated with tranexamic acid had statistically significant reductions in mean menstrual blood loss compared to women treated with placebo, (-69.6 [-40.4%] vs -12.6 mL [-8.2%]; <i>P</i><0.001). Furthermore, women treated with tranexamic acid had more menstrual cycles with ≥50 mL reduction in blood loss compared to placebo-treated women (56 vs 19%; <i>P</i><0.001), and more cycles with a reduction in blood loss ≥36 mL (69 vs 29%; <i>P</i><0.001).</p> <p>Secondary:</p>

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	<p>least 4 of their last 6 menstrual periods, and a menstrual blood loss, on average, of ≥ 80 mL over 2 pre-treatment phases</p>		<p>mL and a greater reduction in blood loss than the pre-determined meaningful threshold (a reduction in blood loss ≥ 36 mL)</p> <p>Secondary: Changes from baseline in health-related quality-of-life scores, number of large blood stains, hemoglobin and ferritin concentrations</p>	<p>Women treated with tranexamic acid had significant improvements in health-related quality of life scores compared to women taking placebo. Mean improvement scores for limitations on social or leisure activities were 0.85 for tranexamic acid patients compared to 0.44 for women treated with placebo ($P < 0.001$). Women treated with tranexamic acid also showed increased improvements in scores assessing limitations on physical activities compared to women treated with placebo (0.87 vs 0.40; $P < 0.001$).</p> <p>Moreover, mean scores for limitations in work were significantly improved in tranexamic acid-treated women compared to women taking placebo (0.71 vs 0.16; $P < 0.001$), and for patient perception of treatment-induced changes in menstrual blood loss (-0.47 vs -0.15; $P < 0.001$).</p> <p>The number of women who experienced reductions in the number of large stains was not significantly different between the tranexamic acid and placebo treatment groups (57.4 vs 51.4%; $P = 0.45$).</p> <p>There were no significant changes in hemoglobin for women treated with tranexamic acid, but were significant for the placebo group (0.34 g/dL; $P < 0.001$).</p> <p>Changes in ferritin were not significant for tranexamic acid-treated women compared to placebo-treated women.</p>
<p>Nilsson et al¹⁶</p> <p>Tranexamic acid 1.5 to 6 g PO per day during the first four days of the menstrual cycle</p> <p>vs</p> <p>placebo</p>	<p>DB, RCT, XO</p> <p>Women 15 to 49 years of age (mean 38) with menorrhagia</p>	<p>N=36</p> <p>5 menstrual cycles (2 cycles with no treatment, 2 cycles with tranexamic acid [different doses], and 1 cycle with placebo)</p>	<p>Primary: Reduction in menstrual blood loss (volume), safety</p> <p>Secondary: Not reported</p>	<p>Primary: Women who received tranexamic acid experienced significant reductions in menstrual blood loss compared to the two cycles with no treatment ($P < 0.005$). There was no change in blood loss between treatment and control cycles in women who were treated with placebo ($P > 0.05$).</p> <p>In a sub-analysis (n=19), women receiving tranexamic acid courses of 12 and 24 g experienced a 38 and 51% reduction in menstrual blood loss, respectively (P value not reported). The effect was most pronounced during the first three days of menstruation.</p> <p>Nineteen patients reported side effects with seven patients only reporting side effects with the higher dose of tranexamic acid. The main symptoms were stated to be diarrhea and abdominal pain (P values were not reported).</p>

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				Secondary: Not reported
<p>Ylikorkala et al¹⁷</p> <p>Tranexamic acid 1.5 g PO TID for five days for two cycles</p> <p>vs</p> <p>diclofenac 50 mg PO TID on day one followed by 25 mg PO TID for four days for two cycles</p> <p>vs</p> <p>placebo for five days for one cycle</p>	<p>DB, RCT, XO</p> <p>Women with an IUD and excessive menstrual blood loss (age not reported)</p>	<p>N=19</p> <p>5 menstrual cycles</p>	<p>Primary: Reduction in menstrual blood loss (volume), safety, patient assessment of treatment</p> <p>Secondary: Not reported</p>	<p>Primary: The mean blood loss before treatment was 135.1±18.9 mL (range 70 to 294 mL). Tranexamic acid decreased blood loss by 54% to 59.4 mL ($P<0.001$) and diclofenac reduced blood loss by 20% to 102.1 mL ($P<0.01$). The placebo treatment did not change menstrual blood loss (128.3 mL; P value not reported). The reduction in blood loss during treatment with tranexamic acid was significantly greater than the reduction in blood loss observed in the diclofenac treatment group ($P<0.001$).</p> <p>Neither treatment abolished pelvic discomfort during menstruation or shortened its duration.</p> <p>Various side effects were noted by 12 women during 19 tranexamic acid treatments and by five women during six diclofenac treatments. There was no difference in patient hemoglobin levels before or after treatment. Treatment with tranexamic acid was deemed by patients to be significantly better than treatment with placebo ($P<0.05$), but no comparison was made between tranexamic acid and diclofenac.</p> <p>Secondary: Not reported</p>
<p>Kouides et al¹⁸</p> <p>Tranexamic acid 1 g PO QID on days one through five of menstrual cycle for two cycles</p> <p>vs</p> <p>desmopressin 300 µg intranasally QD on days two and three of menstrual cycle for two cycles</p>	<p>MC, RCT, XO</p> <p>Women 18 to 50 years of age with menorrhagia, negative gynecological evaluation and abnormal laboratory hemostasis</p>	<p>N=116</p> <p>4 menstrual cycles</p>	<p>Primary: Reduction in menstrual blood loss (as measured by the mean PBAC score), quality of life, safety</p> <p>Secondary: Not reported</p>	<p>Primary: There was a statistically significant decrease in mean PBAC scores for both treatments (P values not reported). The decrease in PBAC score was significantly greater for tranexamic acid than desmopressin (-105.7 vs -64.1 mL; $P=0.0002$).</p> <p>Use of both tranexamic acid and desmopressin improved quality of life in women with menorrhagia. Specifically, the number of mentally unhealthy days decreased by 3.3 days in women receiving desmopressin ($P=0.003$) and 2.1 days in women receiving tranexamic acid ($P=0.083$).</p> <p>Of the 90 patients who used either study drug for at least one cycle, 14% reported side effects (six patients with tranexamic acid and seven patients with desmopressin). Ten of these patients discontinued participation in the treatment</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>arm because of side effects. The most commonly reported side effect in both study arms was headache. One patient developed symptomatic hyponatremia on desmopressin.</p> <p>Secondary: Not reported</p>
<p>Andersch et al¹⁷</p> <p>Tranexamic acid 1.5 g PO TID per day for three days, then 1 g PO BID for two days for two cycles</p> <p>vs</p> <p>flurbiprofen 100 mg PO BID for five days for two cycles</p> <p>Treatment was started on the first day of menstruation.</p>	<p>OL, RCT, XO</p> <p>Women with idiopathic menorrhagia (mean blood loss >80 mL during 2 periods), mean age of 40.5 years</p>	<p>N=15</p> <p>6 menstrual cycles (2 cycles with no treatment, 2 cycles tranexamic acid, 2 cycles flurbiprofen)</p>	<p>Primary: Reduction in menstrual blood loss (volume), safety</p> <p>Secondary: Not reported</p>	<p>Primary: The mean blood loss during the two control cycles was 295 mL. A significant reduction in menstrual blood loss was reported during treatment with both tranexamic acid (-140 mL [-53%]; $P<0.01$) and flurbiprofen (-72 mL [-24%]; $P<0.01$).</p> <p>Various side effects were recorded by seven of 15 women during treatment with tranexamic acid, and by four of 15 women during treatment with flurbiprofen.</p> <p>Secondary: Not reported</p>
<p>Kriplani et al¹⁹</p> <p>Tranexamic acid 0.5 g PO QID from days one through five of menstrual cycle for three cycles</p> <p>vs</p> <p>medroxyprogesterone 10 mg PO BID from day five to 25 of menstrual cycle for three cycles</p>	<p>RCT</p> <p>Women with heavy menstrual bleeding, mean ages 36 to 37 years of age, with a mean duration of menorrhagia of 24 to 26 months in the treatment arms</p>	<p>N=94</p> <p>6 months</p>	<p>Primary: Reduction in menstrual blood loss (as measured by the mean PBAC score)</p> <p>Secondary: Not reported</p>	<p>Primary: After three months of therapy, the mean reduction in blood loss was 60.3% with tranexamic acid and 57.7% with medroxyprogesterone ($P<0.005$ in both groups). The mean reduction in blood loss after the first and second months was 58.2%, and 61.0% for tranexamic acid and 54.6% and 51.5% for medroxyprogesterone (P values not reported).</p> <p>Lack of response during treatment was seen in 6.1% of patients randomized to tranexamic acid and 28.9% of patients randomized to medroxyprogesterone ($P=0.003$).</p> <p>Recurrence of menorrhagia within three months after stopping therapy was reported in 66.7 and 50.0% of patients in the tranexamic acid and medroxyprogesterone groups, respectively ($P=0.155$).</p>

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				<p>During the six-month study, more hysterectomies were performed for women in the medroxyprogesterone group than in the tranexamic acid group (17.8 vs 4.0%; $P=0.002$).</p> <p>Secondary: Not reported</p>
<p>Milsom et al⁸</p> <p>Tranexamic acid 1.5 g PO TID per day for three days, then 1 g PO BID for two days for two cycles</p> <p>vs</p> <p>flurbiprofen 100 mg PO BID for five days for two cycles</p> <p>vs</p> <p>levonorgestrel IUD releasing 20 µg per day for 12 months</p>	<p>OL, RCT, XO</p> <p>Women with idiopathic menorrhagia (age not reported)</p>	<p>N=31</p> <p>14 months (2 cycles no treatment)</p>	<p>Primary: Reduction in menstrual blood loss (volume)</p> <p>Secondary: Not reported</p>	<p>Primary: Menstrual blood loss was reduced by all active treatments. The reduction in menstrual blood loss compared to the control cycles was as follows: tranexamic acid, 44.4%; flurbiprofen, 20.7%; and levonorgestrel-releasing IUD after three, six and 12 months, 81.6, 88.0, and 95.8% respectively. The reduction in menstrual blood loss was significantly greater for the levonorgestrel-releasing IUD compared to tranexamic acid ($P<0.01$) and flurbiprofen ($P<0.001$); and tranexamic acid provided a significant reduction in menstrual blood loss compared to flurbiprofen ($P<0.05$).</p> <p>The levonorgestrel-releasing IUD was the only form of treatment to reduce mean menstrual blood loss <80 mL per menstruation, which is the upper limit of normal menstrual blood loss.</p> <p>Secondary: Not reported</p>
<p>Kasonde et al²⁰</p> <p>Aminocaproic acid 3 g PO QID for seven days from the date of IUD insertion, then 3 g QID during menstruation for cycles one through four, six and eight vs matched control</p> <p>or</p> <p>aminocaproic acid 3 g PO</p>	<p>OL (2 studies)</p> <p>Women (age not reported) with a newly inserted IUD (n=56) or menorrhagia associated with an IUD (n=35)</p>	<p>N=91</p> <p>6 to 8 menstrual cycles</p>	<p>Primary: Reduction in menstrual blood loss (volume), safety</p> <p>Secondary: Not reported</p>	<p>Primary: After insertion of an IUD, menstrual blood loss was significantly lower in the aminocaproic acid group compared to the placebo group during the menstrual period (54.1 vs 81.6 mL; $P<0.001$). Significantly fewer women who received aminocaproic acid continued to have intermenstrual "spotting" compared to the control group ($P<0.05$).</p> <p>Women with IUD-associated menorrhagia who were given aminocaproic acid experienced a significant decrease in mean menstrual blood loss ($P<0.001$), but returned to baseline upon discontinuation of aminocaproic acid.</p> <p>Mild to moderate side effects were noted in 78% of women taking aminocaproic acid with nausea, headache and dizziness reported as the most common adverse</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
QID during menstruation for cycles two through four (cycles five and six served as controls)				<p>reactions. Three patients were unable to continue the trial because of side effects.</p> <p>Secondary: Not reported</p>
<p>Winkler²¹</p> <p>Tranexamic acid 3 to 6 g PO per day during three to four days of the menstrual cycle</p>	<p>MC, OL</p> <p>Women with heavy menstrual bleeding (no pathological findings reported) with a median age of 36 years</p>	<p>N=849</p> <p>3 menstrual cycles</p>	<p>Primary: Satisfaction with treatment, change in quality of life (based on a questionnaire), safety</p> <p>Secondary: Not reported</p>	<p>Primary: Satisfaction with tranexamic acid increased over the study period with 81% of the women being “satisfied” or “very satisfied” with treatment after the third menstrual cycle. After their first and third treatment cycle, 87% and 94% ($P<0.0001$), respectively, of the women judged their menstrual blood loss to be decreased or strongly decreased.</p> <p>Impairment of social activities and impairment at work were greatly improved with tranexamic acid treatment ($P<0.0001$). Substantial improvements were also recorded with regard to action radius, alertness, cleanliness, productivity, spirits and overall well-being.</p> <p>After the third menstruation cycle, hemoglobin was increased by an average of 1.06 mg/dL in 262 women who had recorded hemoglobin levels at baseline ($P<0.0001$). About 4% of women reported one or more adverse reactions to tranexamic acid with nausea, stomach problems, headache, and dizziness as the most frequently reported side effects. No serious adverse event was reported.</p> <p>Secondary: Not reported</p>
<p>Sundstrom et al²²</p> <p>Tranexamic acid (doses not reported)</p>	<p>Nested case-control study using General Practice Research Database 1992 to 1998</p> <p>Women 15 to 49 years of age with a diagnosis of menorrhagia</p>	<p>N=122,237 (cohort of women with menorrhagia)</p> <p>Duration varied</p>	<p>Primary: Risk of venous thromboembolism (deep vein thrombosis or pulmonary embolism)</p> <p>Secondary: Not reported</p>	<p>Primary: Among the cohort of women with menorrhagia (N=122,237), the investigators identified 134 cases of venous thromboembolism (82 deep vein thrombosis and 52 pulmonary embolism) and 552 matched controls.</p> <p>Recent use of tranexamic acid for the treatment of menorrhagia was scarce, and no statistically significant association with risk of venous thromboembolism was observed (OR, 3.2; 95% CI, 0.65 to 15.78; P value not reported; note: the OR was adjusted for body mass index, smoking and hemoglobin <11.5 g/dL).</p> <p>The investigators reported that the use of mefenamic acid (OR, 5.54; 95% CI, 2.13 to 14.40) and norethisterone (norethindrone) (OR, 2.41; 95% CI, 1.00 to 5.78) were associated with an increased risk of venous thromboembolism (P value not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>reported). Anemia or a hemoglobin <11.5 g/dL (within 14 days before or after a diagnosis of menorrhagia) was also associated with an increased risk of venous thromboembolism (OR, 2.23; 95% CI, 1.02 to 4.86; <i>P</i> values not reported).</p> <p>Secondary: Not reported</p>

*Product not commercially available in the United States.

Drug abbreviations: BID=two times daily, IUD=intrauterine device, IV=intravenous, NSAIDs=nonsteroidal anti-inflammatory drugs, PC=placebo controlled, PG=parallel group, PO=by mouth, QD=once daily, QID=four times daily, TID=three times daily

Study abbreviations: CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-labeled, OR=odds ratio, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, WMD=weighted mean difference, XO=crossover

Miscellaneous abbreviations: PBAC=pictorial blood assessment chart

Special Populations**Table 5. Special Populations**¹⁻⁴

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Aminocaproic acid	No dosage adjustment required in the elderly. Safety and effectiveness in children have not been established.	Administer with caution.	Administer with caution.	C	Unknown
Tranexamic acid	Not approved for use in postmenopausal women. Safety and effectiveness in children (<18 years) have not been established.	Adjust dosage in patients with serum creatinine >1.4 mg/dL.	No dosage adjustment is required.	B	Yes (1%).

Adverse Drug Events**Table 6. Adverse Drug Events (%)**^{1,4}

Adverse Event	Aminocaproic Acid	Tranexamic Acid
Cardiovascular		
Bradycardia	✓	-
Edema	✓	-
Hypotension	✓	-
Peripheral ischemia	✓	-
Syncope	✓	-
Thrombosis	✓	-
Central Nervous System		
Confusion	✓	-
Convulsions	✓	-
Delirium	✓	-
Dizziness	✓	-
Fatigue	-	5
Hallucinations	✓	-
Headache	✓	50
Intracranial hypertension	✓	-
Malaise	✓	-
Migraine	-	6
Stroke	✓	-
Dermatologic		
Pruritus	✓	-
Rash	✓	-
Gastrointestinal		
Abdominal pain	✓	20

Adverse Event	Aminocaproic Acid	Tranexamic Acid
Diarrhea	✓	-
Nausea	✓	-
Vomiting	✓	-
Hematologic		
Agranulocytosis	✓	-
Anemia	-	6
Coagulation disorder	✓	-
Leukopenia	✓	-
Thrombocytopenia	✓	-
Neuromuscular/Skeletal		
Arthralgia	-	7
Back pain	-	21
Increased creatine phosphokinase	✓	-
Muscle cramps and spasms	-	7
Muscle weakness	✓	-
Musculoskeletal pain	-	11
Myalgia	✓	-
Myopathy	✓	-
Myositis	✓	-
Rhabdomyolysis	✓	-
Renal		
Blood urea nitrogen increased	✓	-
Intrarenal obstruction	✓	-
Renal failure	✓	-
Respiratory		
Dyspnea	✓	-
Nasal congestion	✓	-
Nasal and sinus symptoms	-	25
Pulmonary embolism	✓	-
Other		
Allergic reaction	✓	✓
Anaphylactoid reaction	✓	-
Anaphylaxis	✓	✓
Dry ejaculation	✓	-
Tinnitus	✓	-
Vision decreased	✓	-
Watery eyes	✓	-

✓ Frequency (%) not reported.

-Event not reported or incidence <5%.

Contraindications/Precautions

Aminocaproic acid and tranexamic acid are contraindicated in patients with a known hypersensitivity to any component of their formulations.¹⁻⁴

In addition, aminocaproic acid is contraindicated when there is evidence of an active intravascular clotting process and in the presence of disseminated intravascular coagulation without concomitant heparin.³ In situations where the diagnosis is not clear, tests should be performed to confirm whether the cause of bleeding is primary fibrinolysis or disseminated intravascular coagulation before administering aminocaproic acid. The drug should not be administered without a definite diagnosis and/or laboratory finding indicative of hyperfibrinolysis (hyperplasminemia). The use of aminocaproic acid should be accompanied by tests designed to determine the amount of fibrinolysis present. Inhibition of fibrinolysis by aminocaproic acid may theoretically result in clotting or thrombosis. However, there is no definite

evidence that administration of aminocaproic acid has been responsible for the few reported cases of intravascular clotting which followed this treatment. Rather, it appears that such intravascular clotting was most likely due to the patient's preexisting clinical condition (e.g., the presence of disseminated intravascular coagulation).

The manufacturer warns that in patients with upper urinary tract bleeding, aminocaproic acid may cause intrarenal obstruction secondary to glomerular capillary thrombosis or clots in the renal pelvis and ureters.³ For this reason, aminocaproic acid should not be used in hematuria of upper urinary tract origin, unless the possible benefits outweigh the risk. There have been rare reports of skeletal muscle weakness with necrosis of muscle fibers with prolonged administration of aminocaproic acid. Clinical presentation may range from mild myalgias with weakness and fatigue to a severe proximal myopathy with rhabdomyolysis, myoglobinuria, and acute renal failure. Creatine phosphokinase levels should be monitored in patients on long-term therapy and aminocaproic acid should be stopped if a rise in creatine phosphokinase is noted. Resolution follows discontinuation of aminocaproic acid; however, the syndrome may reoccur if therapy is restarted. The possibility of cardiac muscle damage should also be considered when skeletal myopathy occurs.

Reports have appeared in the literature of an increased incidence of certain neurological deficits such as hydrocephalus, cerebral ischemia or cerebral vasospasm associated with the use of antifibrinolytic agents in the treatment of subarachnoid hemorrhage.³ Cerebral edema and cerebral infarction may be caused by use of tranexamic acid in women with subarachnoid hemorrhage.⁴

Tranexamic acid should not be prescribed to women who are known to have the following conditions: active thromboembolic disease (e.g., deep vein thrombosis, pulmonary embolism or cerebral thrombosis); a history of thrombosis or thromboembolism, including retinal vein or artery occlusion; or an intrinsic risk of thrombosis or thromboembolism (e.g., thrombogenic valvular disease, thrombogenic cardiac rhythm disease or hypercoagulopathy).⁴ Retinal venous and arterial occlusion have been reported in patients using tranexamic acid. Patients should be instructed to report visual and ocular symptoms promptly. In the event of such symptoms, patients should be instructed to discontinue tranexamic acid immediately and see an ophthalmologist for a complete ophthalmic evaluation. Ligneous conjunctivitis also has been reported in patients taking tranexamic acid. The conjunctivitis resolved following cessation of the drug.

Drug Interactions

Table 7. Drug Interactions¹⁻⁴

Generic Name	Interacting Medication or Disease	Potential Result
Aminocaproic acid, tranexamic acid	Estrogens, oral contraceptives	Coadministration may produce an increase in clotting factors leading to a hypercoagulable state.
Aminocaproic acid, tranexamic acid	Factor IX complex concentrates, anti-Inhibitor coagulant concentrates	Aminocaproic acid and tranexamic acid should not be administered with these products since the risk of thrombosis may be increased.
Aminocaproic acid, Tranexamic acid	Tretinoin	The procoagulant effect of tretinoin may be exacerbated by concomitant use of tranexamic acid. Use caution when prescribing tranexamic acid to patients with acute promyelocytic leukemia taking tretinoin.
Tranexamic acid	Tissue plasminogen activators	Concomitant therapy may decrease the efficacy of both products.

Dosing and Administration

Table 8. Dosing and Administration¹⁻⁴

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability*
Aminocaproic acid	<p><u>Treatment of acute bleeding syndromes to enhance hemostasis when fibrinolysis contributes to bleeding:</u> Oral: 5,000 mg during the first hour of treatment, followed by 1,000 mg per hour; maximum daily dose, 30 g</p> <p>Note: this method of treatment would ordinarily be continued for about eight hours or until the bleeding situation has been controlled.</p>	Safety and effectiveness in children have not been established.	Syrup: 0.25 g/mL Tablet: 500 mg 1,000 mg [†]
Tranexamic acid	<p><u>Treatment of cyclic heavy menstrual bleeding:</u> Oral: 1,300 mg three times daily for a maximum of five days during monthly menstruation</p>	Safety and effectiveness in children (<18 years) have not been established.	Tablet: 650 mg [†]

* Aminocaproic acid is available as a 250 mg/mL injection and tranexamic acid is available as a 100 mg/mL injection. These formulations are not included in this review.

†Only available as a branded product.

Clinical Guidelines

Only recommendations regarding the use of antifibrinolytic agents are presented in the table below.

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
<p>The French College of Obstetricians & Gynaecologists: Management of Abnormal Uterine Bleeding Before Menopause (2010)⁹</p>	<p><u>Continued fertility is desired</u></p> <ul style="list-style-type: none"> In idiopathic abnormal uterine bleeding, first line treatment is medical, with efficacy ranked as follows: <ul style="list-style-type: none"> Levonorgestrel-releasing intrauterine device (IUD). Tranexamic acid. Oral contraceptives, either estrogens and progestins or synthetic progestins only, 21 days/month. Nonsteroidal anti-inflammatory drugs (NSAIDs). When hormonal treatment is contraindicated, or pregnancy is desired, tranexamic acid is indicated. <p><u>Continued fertility not desired</u></p> <ul style="list-style-type: none"> For women with idiopathic abnormal uterine bleeding who do not wish to become pregnant in the future, the long-term efficacy of conservative surgical treatment is greater than that of oral medical treatment. Placement of a levonorgestrel IUD (or administration of tranexamic acid by default) is recommended for women with idiopathic abnormal uterine bleeding. If this fails, a conservative surgical technique must be proposed; the choices including second-generation endometrial ablation techniques or, if necessary, first-generation techniques. A first line hysterectomy is not recommended in this context. <p><u>Adolescents</u></p> <ul style="list-style-type: none"> Of the medical treatments, the best choices are oral estrogen-progestin contraceptives and non-hormonal treatments.

Clinical Guideline	Recommendations
	<p><u>Patients receiving anticoagulant treatment or with a coagulation disorder</u></p> <ul style="list-style-type: none"> • Multidisciplinary management is recommended. • Treatment is identical to that for patients without coagulation disorders, with priority for medical treatment: the level of evidence for tranexamic acid, combined estrogen-progestins and levonorgestrel IUD is identical to that in the population without coagulation disorders. • Surgical treatment should only be considered if medical treatment fails. • Some treatments are contraindicated, such as tranexamic acid or combined estrogen-progestins. Therefore a levonorgestrel IUD would be preferable. Surgical treatments that should last over time may also be preferred, depending on the patient's age. <p><u>Abnormal uterine bleeding while on contraceptives</u></p> <ul style="list-style-type: none"> • Combined estrogen-progestins: <ul style="list-style-type: none"> ○ Generally, the higher-dose pills cause less bleeding than the lower dose pills, for both estrogens and progestins. ○ The comparison of continuous vs cyclic pills shows less bleeding, in terms of duration and amount, but more breakthrough bleeding and spotting with the continuous pills. ○ Patients should most often be advised to wait two or three months before changing the pill prescription in the case of intermenstrual bleeding without an organic explanation. ○ When the bleeding does not improve, a more estrogenic or more antigonadotropic product should be recommended, if there are reasons to think there is an incomplete anti-gonadotropic effect. ○ After several unsuccessful trials of different products, another mode of contraception should be envisioned. • Progestin-only contraceptives: <ul style="list-style-type: none"> ○ The onset of irregular intermenstrual bleeding/spotting may be improved in part either by administering an estrogen at a replacement dose or by reducing the duration of administration by one day, thus increasing the interruption window. Nonetheless this will not improve the situation for some women, and a different mode of contraception is then indicated. ○ It is usual to recommend changing the type of pill or contraception for women with frequent bleeding on progestin contraceptives. ○ No data justify the recommendation of NSAIDs, antifibrinolytics or added estradiol to diminish bleeding associated with the micro-progestin pills.
<p>National Collaborating Centre for Women's and Children's Health:* Clinical Guideline: Heavy Menstrual Bleeding (2007)⁶</p>	<ul style="list-style-type: none"> • If history and investigations indicate that pharmaceutical treatment is appropriate and either hormonal or nonhormonal treatments are acceptable, treatments should be considered in the following order: <ul style="list-style-type: none"> ○ Levonorgestrel-releasing intrauterine system provided long-term (at least 12 months) use is anticipated. ○ Tranexamic acid or NSAIDs or combination oral contraceptives. ○ Norethisterone (norethindrone) (15 mg) daily from days five to 26 of the menstrual cycle, or injected long-acting progestogens. • If hormonal treatments are not acceptable to the woman, then either tranexamic acid or NSAIDs can be used. • If pharmaceutical treatment is required while investigations and definitive treatment are being organized, either tranexamic acid or NSAIDs should be used.

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> • When heavy menstrual bleeding coexists with dysmenorrhoea, NSAIDs should be preferred over tranexamic acid. • Use of NSAIDs and/or tranexamic acid should be stopped if symptoms do not improve within three menstrual cycles. • When a first pharmaceutical treatment has proved ineffective, a second pharmaceutical treatment can be considered rather than immediate referral to surgery. • Ongoing use of NSAIDs and/or tranexamic acid is recommended for as long as they are found to be beneficial. • Use of a gonadotrophin-releasing hormone analogue could be considered prior to surgery or when all other treatment options for uterine fibroids, including surgery or uterine artery embolization, are contraindicated. If this treatment is to be used for more than six months or if adverse effects are experienced then hormone replacement “addback” therapy is recommended. • Danazol should not be routinely used for the treatment of heavy menstrual bleeding. • Oral progestogens given during the luteal phase only (for seven to 10 days) should not be used for the treatment of heavy menstrual bleeding. • Endometrial ablation may be offered as an initial treatment for heavy menstrual bleeding after full discussion with the woman of the risks and benefits and of other treatment options. • Hysterectomy should not be used as a first-line treatment solely for heavy menstrual bleeding. • Women should be given information on potential unwanted outcomes of the intervention.
<p>American Academy of Family Physicians: Treatment of Menorrhagia (2007)²³</p>	<ul style="list-style-type: none"> • Women who tolerate menstrual bleeding and want to maintain fertility may try medical therapy with continuous oral progestin therapy on days five to 26 of the menstrual cycle. • If future childbearing is desired, an effective long-term option is the levonorgestrel-releasing intrauterine device, which is more effective than continuous progestin in reducing menorrhagia but less effective than endometrial ablation. • A hysterectomy is recommended for women who do not desire further childbearing or menstrual bleeding, but are willing to assume the risk of surgery. Endometrial ablation is a reasonable and effective alternative for women who want to avoid major surgery and do not desire further childbearing. • There is insufficient evidence to make recommendations regarding the effectiveness of danazol, monthly oral contraceptive pills, NSAIDs, or tranexamic acid in reducing menorrhagia.
<p>World Federation of Hemophilia: Guidelines for the Management of Hemophilia (2005)^{24†}</p>	<p><u>Treatment of bleeding</u></p> <ul style="list-style-type: none"> • Due to increased risk for thromboses, antifibrinolytic agents (aminocaproic acid or tranexamic acid), either as primary or adjunctive therapy, are not recommended for treatment of patients with factor IX deficiency already receiving large doses of prothombin complex concentrates. • For gastrointestinal hemorrhage, aminocaproic acid or tranexamic acid may be used as adjunctive therapy for patients with factor VIII deficiency and those with factor IX deficiency who are not being treated with prothrombin complex concentrate. • Do not use antifibrinolytic agents for renal hemorrhage. • Oral hemorrhage may be controlled in patients with factor VIII deficiency

Clinical Guideline	Recommendations
	<p>with the use of aminocaproic acid or tranexamic acid alone, or with the use of factor and either antifibrinolytic agent if bleeding is prolonged, significant, or difficult to control. Aminocaproic acid or tranexamic acid may be used in the form of a mouthwash.</p> <p><u>Adjunctive management</u></p> <ul style="list-style-type: none"> • RICE (rest, ice, compression, and elevation) is an important adjunctive management for bleeding in muscles and joints in addition to increasing factor level with clotting factor concentrates or desmopressin in mild hemophilia A. • Antifibrinolytic drugs (e.g., aminocaproic acid, tranexamic acid,) for five to 10 days are effective as adjunctive treatment for mucosal bleeds (e.g., epistaxis, mouth bleed) and are used to decrease the use of coagulation products in dental extractions. Avoid these drugs in renal bleeding as unlysed clots in the renal pelvis and ureter may cause ureteric colic and obstructive nephropathy. Antifibrinolytic drugs should not be given concurrently with nonactivated or activated prothrombin complex concentrates because of potential thrombotic complications. <p><u>Dental care</u></p> <p>For people with mild or moderate hemophilia, nonsurgical dental treatment can be carried out under “antifibrinolytic cover” (aminocaproic acid or tranexamic acid).</p> <ul style="list-style-type: none"> • Local use of fibrin glue and swish-and-swallow rinses of tranexamic acid before and after dental extractions is safe and cost-effective methods to help control bleeding. • Tranexamic acid used topically (10 mL of a 5% solution used as a mouth rinse for two minutes, four times daily for seven days) significantly reduces bleeding. It may be used in combination with oral tranexamic acid tablets for up to five days. • For dental extractions, ensure the patient receives a prior infusion of factor concentrate that raises the level appropriately. Aminocaproic acid or tranexamic acid may be started before factor infusion. The dose of aminocaproic acid, which should be started the night before or morning of the procedure, is 50 to 100 mg/kg orally every four to six hours for five to 10 days (maximum 24 g per 24 hours). The dose of tranexamic acid is 25 to 50 mg/kg orally every six to eight hours for 10 days. A liquid preparation of these drugs may be used as a mouthwash. <p><u>Other pharmacological options</u></p> <ul style="list-style-type: none"> • In addition to conventional coagulation factor concentrates, other agents that may be of great value include aminocaproic acid, desmopressin, and tranexamic acid. • Tranexamic acid is useful as adjunctive therapy in hemophilia and some other bleeding disorders. Tranexamic acid is also useful in dental, gynecologic, or urologic surgery in factor XI-deficient patients and may obviate the need for replacement therapy with concentrates or plasma. • Tranexamic acid alone has no value in prevention of hemoarthroses in hemophilia; however, it is valuable in controlling bleeding from mucosal surfaces (e.g., oral bleeding, epistaxis, menorrhagia) in hemophilia and is particularly valuable in the setting of dental surgery. • Aminocaproic acid is a drug similar to tranexamic acid but is less widely used as it has a shorter plasma half-life, is less potent, and is more toxic.

Clinical Guideline	Recommendations
	Myopathy is a rare adverse reaction specifically reported in association with aminocaproic acid (but not tranexamic acid), typically occurring after administration of high doses for several weeks.

*Commissioned by the National Institute for Health and Clinical Excellence.

†The use of oral aminocaproic acid or tranexamic acid in patients with hemophilia is not approved by the Food and Drug Administration.

Conclusions

The two oral agents in the therapeutic class “Hemostatic Agents” include aminocaproic acid and tranexamic acid. Aminocaproic acid syrup and tablets are Food and Drug Administration (FDA) approved for the treatment of acute surgical and non-surgical bleeding syndromes, and is available generically.^{1,2} The 1,000 mg aminocaproic acid tablet is available only as a branded product under the trade name Amicar[®]. The tranexamic acid tablet is FDA approved for the treatment of cyclic heavy menstrual bleeding.⁴ There are no head-to-head trials comparing these two agents to each other for their FDA-approved indications, although tranexamic acid is thought to be the more potent antifibrinolytic of the two agents, and has a longer half-life.²

Aminocaproic acid is useful in the treatment of acute bleeding syndromes resulting from systemic hyperfibrinolysis and urinary fibrinolysis.¹⁻³ It is approved for use in systemic hyperfibrinolysis associated with abruptio placentae, cardiac surgery, hematologic disorders, hepatic cirrhosis, neoplastic disorders (e.g., carcinoma of the cervix, lung, prostate, and stomach), and portacaval shunt. Aminocaproic acid has also been used in urinary fibrinolysis associated with surgical and nonsurgical hematuria. There appears to be a limited role for oral aminocaproic acid in the management of these conditions in an outpatient setting. Tranexamic acid offers a new treatment option for women with heavy menstrual bleeding and has been shown useful in reducing blood loss by 29 to 58%.⁶ Clinical studies have reported that tranexamic acid was more effective than nonsteroidal anti-inflammatory drugs and luteal phase progestins in reducing heavy menstrual bleeding, but less effective than the levonorgestrel intrauterine device.^{7,8} Current guidelines recommend that hormonal treatment with an oral contraceptive or intrauterine device be considered first-line therapy. When hormonal treatment is contraindicated, or pregnancy is desired, tranexamic acid or nonsteroidal anti-inflammatory agents are indicated.^{6,9} Oral aminocaproic acid and tranexamic acid are generally well tolerated, but both agents have the potential to cause thromboembolic events.¹⁻⁴ Neither hemostatic agent has been approved by the FDA for use in children.

Appendix I: Utilization Within This Drug Class for DVHA: January 1, 2011 to March 31, 2011

Medication	# of Rx's	Market Share (%)	Plan Cost \$	Avg \$/Rx
Amicar [®]	4	57.14%	\$893.41	\$223.35
Lysteda [®]	3	42.86%	\$507.88	\$169.29
Class Total:	7	100%	\$1,401.29	\$200.18

Recommendations

Amicar[®] and its generic equivalent, aminocaproic acid, are not currently managed by the Department of Vermont Health Access. In recognition of the published literature supporting the effectiveness of aminocaproic acid in treating surgical and non-surgical bleeding conditions secondary to increased fibrinolysis, its low utilization and the unlikelihood of inappropriate use, management of this product is not recommended. Tranexamic acid (Lysteda[®]) was recently added to the DVHA preferred drug list as PA required, with the approval criteria outlined below. No changes are recommended.

Lysteda:

- The diagnosis or indication is clinically significant heavy menstrual bleeding
AND
- The patient has been started and stabilized on oral tranexamic acid within the previous 360 days
OR

- The patient does not have a contraindication to therapy with oral tranexamic acid (i.e., active thrombotic disease, history of thrombosis/thromboembolism, or an intrinsic risk of thrombosis/thromboembolism), and if oral tranexamic acid is to be used concomitantly with an estrogen containing hormonal contraceptive product, the risks of combination therapy have been discussed with the patient.

AND

- The patient has had a documented side effect, allergy, contraindication, or an inadequate response with at least one oral contraceptive or progestin containing product despite an adequate trial of at least 90 days, or a rationale for why these products cannot be used (e.g. actively attempting to conceive).

AND

- The patient has had a documented side effect, allergy, contraindication, or an inadequate response with at least one regularly scheduled (not PRN) NSAID or a rationale for why these products cannot be used (e.g. actively attempting to conceive).

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