**INTRODUCTION**

Menorrhagia (excessively heavy menstrual bleeding ie more than 80mls blood loss per menstrual cycle) can cause social embarrassment and may result in chronic anemia. While menorrhagia may be due to the use of IUDs or to systemic and local disorders, most cases of this condition are not associated with any abnormality. It is in these instances when certain drugs may prove useful. In treating menorrhagia, the primary aim should be to improve quality of life. Women are willing to undergo quite invasive treatment in order to achieve this. Drug therapy is the initial treatment of choice and the only option for those who wish to preserve their reproductive function.

Despite the availability of a number of drugs, there is a general lack of an evidence-based approach, marked variation in practice and continuing uncertainty regarding the most appropriate therapy. Adverse effects and problems with compliance also undermine the success of medical treatment.

**PHARMACOLOGICAL AGENTS USED FOR THE TREATMENT OF MENORRHAGIA**

Despite being used extensively in the past, oral luteal phase norethisterone is probably one of the least effective agents. Women requiring contraception have a choice of the combined oral contraceptive pill, levonorgestrel-releasing intrauterine system (LNG-IUS) or long-acting progestogens.

Danazol, gestrinone and gonadotropin-releasing hormone analogues are all effective in terms of reducing menstrual blood loss but adverse effects and costs limit their long-term use. They have a role as second-line drugs for a short period of time in women awaiting surgery. While current evidence suggests that the LNG-IUS is an effective treatment, further evaluation, including long-term follow up, is awaited.

Tranexamic acid and mefenamic acid are among the most effective first-line drugs used to treat menorrhagia. Meanwhile, the quest continues for the ideal form of medical treatment for menorrhagia—one that is effective, affordable and acceptable.

**TRANEXAMIC ACID IN THE MANAGEMENT OF MENORRHAGIA**

Tranexamic acid is a synthetic lysine derivative that exerts its antifibrinolytic effect by reversibly blocking lysine binding sites on plasminogen and thus preventing fibrin degradation. In a number of small clinical studies in women with idiopathic menorrhagia, tranexamic acid 2-4.5 g/day for 4-7 days reduced menstrual blood loss by 34-59% over 2-3 cycles, significantly more so than placebo, mefenamic acid, flurbiprofen, ethamsylate and oral luteal phase norethisterone at clinically relevant dosages.

Tranexamic acid 1.5 g three times daily for 5 days also significantly reduced menstrual blood loss in women with intrauterine contraceptive device-associated menorrhagia compared with diclofenac sodium (150 mg in three divided doses on day 1 followed by 25 mg three times daily on days 2-5) or placebo. Tranexamic acid, mefenamic acid, ethamsylate, flurbiprofen or diclofenac sodium had no effect on the duration of menses in the studies that reported such data.

In a large noncomparative, non blind, quality-of-life study, 81% of women were satisfied with tranexamic acid 3-6 g/day for 3-4 days/cycle for three cycles, and 94% judged their menstrual blood loss to be ‘decreased’ or ‘strongly decreased’ compared with
untreated menstruations.

In conclusion, the oral antifibrinolytic drug tranexamic acid is an effective and well tolerated treatment for idiopathic menorrhagia. In clinical trials, tranexamic acid was more effective at reducing menstrual blood loss than mefenamic acid, flurbiprofen, ethamsylate and oral luteal phase norethisterone. Comparative studies of tranexamic acid with epsilon - amino caproic acid, danazol and combined oral contraceptives, as well as long-term tolerability studies, would help to further define the place of the drug in the treatment of menorrhagia. Nevertheless, tranexamic acid may be considered as a first-line treatment for the initial management of idiopathic menorrhagia, especially for patients in whom hormonal treatment is either not recommended or not wanted.2

**TRANEXAMIC ACID IN SURGERY AND OTHER INDICATIONS**

Tranexamic acid is a synthetic derivative of the amino acid lysine that exerts its antifibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen molecules.

Intravenously administered tranexamic acid (most commonly 10 mg/kg followed by infusion of 1 mg/kg/hour) caused reduction in relative postoperative blood losses in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB), with statistically significant reduction in transfusion requirements in some studies. Tranexamic acid had similar efficacy to aprotinin 2 x 10(6) kallikrein inhibitory units (KIU) and was superior to dipyridamole in the reduction of postoperative blood losses. Transfusion requirements were reduced significantly by 43% with tranexamic acid and by 60% with aprotinin in 1 study.

Meta-analysis of 60 trials showed tranexamic acid and aprotinin, unlike epsilon-amino caproic acid (EACA) and desmopressin, to reduce significantly the number of patients requiring allogeneic blood transfusions after cardiac surgery with CPB. Tranexamic acid was associated with reduction relative to placebo in mortality of 5 to 54% in patients with upper gastrointestinal bleeding. Meta-analysis indicated a reduction of 40%. Reduction of 34 to 57.9% versus placebo or control in mean menstrual blood loss occurred during tranexamic acid therapy in women with menorrhagia; the drug has also been used to good effect in placental bleeding, postpartum hemorrhage and amniotic fluid embolism.

Tranexamic acid significantly reduced mean blood losses after oral surgery in patients with hemophilia and was effective as a mouthwash in dental patients receiving oral anticoagulants. Reduction in blood loss were also obtained with the use of the drug in patients undergoing orthotopic liver transplantation or trans urethral prostatic surgery, and rates of re bleeding were reduced in patients with traumatic haemorrhage. Clinical benefit has also been reported with tranexamic acid in patients with hereditary angioneurotic oedema.3

**TRANEXAMIC ACID FOR HEAVY MENSTRUAL BLEEDING: COCHRANE DATABASE OF SYSTEMATIC REVIEWS**

Plasminogen activators are a group of enzymes that cause fibrinolysis (the dissolution of clots). An increase in the levels of plasminogen activators has been found in the endometrium of women with heavy menstrual bleeding compared to those with normal menstrual loss.

Plasminogen activator inhibitors (antifibrinolytic agents) have therefore been promoted as a treatment for heavy menstrual bleeding. Medical therapy, with the avoidance of possibly unnecessary surgery, is an attractive treatment option. Antifibrinolytic therapy compared to placebo showed a significant reduction in mean blood loss (weighted mean difference (WMD) -94.0, 95% confidence interval (CI) -151.4 to -36.5) and significant change in mean reduction of blood loss (WMD -110.2, 95% CI -146.5 to -73.8). This objective improvement was not mirrored by a patient perceived improvement in monthly menstrual blood loss (relative risk (RR) 2.5, 95% CI 0.9 to 7.3) in the one study which recorded this outcome (Edlund 1995).

Antifibrinolytic agents were compared to only three other medical (non-surgical) therapies: mefenamic acid, norethisterone administered in the luteal phase and ethamsylate. In all instances, there was a significant reduction in mean blood loss (WMD -73.0, 95% CI -123.4 to -22.6; WMD -111.0, 95% CI -178.5 to -43.5; and WMD -100, 95% CI -143.9 to -56.1 respectively) and a strong, although non-significant trend in favour of tranexamic acid in the participants’ perception of an improvement in menstrual blood loss. The review of trials found that tranexamic acid, the most commonly used antifibrinolytic agent helps reduce heavy menstrual bleeding.

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 with NSAIDs and ethamsylate when these treatments were used for heavy menstrual bleeding. Change in the quality of life measures, flooding and leakage and sex life, were significantly improved in the tranexamic acid group when compared to the oral progestagen group. These findings are based in most cases on only one trial.4

**ETHAMSYLATE PLUS TRANEXAMIC ACID VS MEFENAMIC ACID IN MENORRHAGIA**

To compare the efficacy and acceptability of ethamsylate, mefenamic acid, and tranexamic acid for treating menorrhagia a randomized controlled trial was set up at a university department of obstetrics and gynecology.

76 women with dysfunctional uterine bleeding were treated for five days from day 1 of menses during three consecutive menstrual periods. 27 patients were randomized to take ethamsylate 500 mg six hourly, 23 patients to take mefenamic acid 500 mg eight hourly, and 26 patients to take tranexamic acid 1 g six hourly.

Ethamsylate did not reduce mean menstrual blood loss whereas mefenamic acid reduced blood loss by 20% (mean blood loss 186 ml before treatment, 148 ml during treatment) and tranexamic acid reduced blood loss by 54% (mean blood loss 164 ml before treatment, 75 ml during treatment). Sanitary towel usage was significantly reduced in patients treated with mefenamic acid and tranexamic acid.

Tranexamic acid given during menstruation is a safe and highly effective treatment for excessive bleeding. Patients with dysfunctional uterine bleeding should be offered medical treatment with tranexamic acid before a decision is made about surgery.5

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<th>Drug</th>
<th>Composition</th>
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<tr>
<td>BLOC T</td>
<td>Ethamsylate B.P. 250 mg, Tranexamic Acid 250 mg</td>
<td>10 Tablets</td>
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NSAIDs ARE LESS EFFECTIVE THAN TRANEXAMIC ACID FOR MENSTRUAL BLEEDING: COCHRANE REVIEW

Non-steroidal anti-inflammatory drugs (NSAIDs) reduce prostaglandin levels which are elevated in women with excessive menstrual bleeding and also may have a beneficial effect on dysmenorrhea. Seventeen RCTs were identified that fulfilled the inclusion criteria for this review and data were extracted independently.

As a group, NSAIDs were more effective than placebo at reducing heavy menstrual bleeding but less effective than either tranexamic acid, danazol or the levonorgestrel releasing intrauterine system (LNG IUS). Treatment with danazol caused a shorter duration of menstruation and more adverse events than NSAIDs but this did not appear to affect the acceptability of treatment.

There were no statistically significant differences between NSAIDs and the other treatments (oral luteal progestogen, ethamsylate, an older progesterone releasing intra-uterine system (Progestasert), oral contraceptive pill (OCC)) but most studies were underpowered. There was no evidence of a difference between the individual NSAIDs (naproxen and mefenamic acid) in reducing excessive menstrual bleeding.  

MECHANISM OF ACTION OF ETHAMSYLA TE

Ethamsylate is a synthetic hemostatic drug indicated in cases of capillary bleeding. Ethamsylate acts on the first step of hemostasis by improving platelet adhesiveness and restoring capillary resistance. Recent studies showed that ethamsylate promotes P-selectin-dependent, platelet adhesive mechanisms.

Well-controlled clinical trials clearly show the therapeutic efficacy of ethamsylate in dysfunctional uterine bleeding, with the magnitude of blood-loss reduction being directly proportional to the severity of the menorrhagia. Other well-controlled clinical trials showed therapeutic efficacy of ethamsylate in periventricular hemorrhage in very low birth weight babies and surgical or postsurgical capillary bleeding. It is suggested that the place of ethamsylate as a hemostatic agent is that of a mild but well-tolerated drug, particularly useful in dysfunctional uterine bleeding when contraception is not needed.

ETHAMSYLATE IN THE TREATMENT OF PRIMARY AND IUCD-MENORRAGIA

Twenty-two patients complaining of primary menorrhagia or menorrhagia associated with an intrauterine device (I.U.C.D.) were studied in a double blind trial with crossover of ethamsylate and placebo. Actual menstrual blood-losses were calculated from the iron content of used sanitary material during one pre-trial menstrual period and four trial menstrual periods, during which patients received ethamsylate treatment during two menstrual cycles and placebo during two cycles.

During ethamsylate treatment the mean menstrual blood-loss was reduced by 50% in patients with primary menorrhagia and by 19% in patients with an I.U.C.D. This difference between the two groups is probably accounted for by the differing values of initial blood-loss which was significantly higher in the group with primary menorrhagia.

COMBINATION OF ETHAMSYLATE AND TRANEXAMIC ACID

The combination therapy is a two pronged approach to control bleeding by the antifibrinolytic action of tranexamic acid and achieving hemostasis by improving platelet adhesiveness and restoring capillary resistance by the action of ethamsylate. The combination therapy improves patient compliance as the incidence of adverse effects is reduced and both can be given during the menstrual cycles.

HIGHLIGHTS

- Every year in the United Kingdom around 45,000 hysterectomies and a further 10,000 endometrial ablations are performed for menorrhagia
- The commonest drug prescribed in the British Isles for menorrhagia (norethisterone) has little or no effect in reducing menstrual bleeding
- Tranexamic acid (an antifibrinolytic) 1 g six to eight hourly reduces menstrual blood loss by over half and should be offered to women with dysfunctional bleeding before a decision is made about surgery
- Ethamsylate as a hemostatic agent is a mild but well-tolerated drug, particularly useful in dysfunctional uterine bleeding when contraception is not needed
- Ethamsylate treatment caused the mean menstrual blood-loss to be reduced by 50% in patients with primary menorrhagia and by 19% in patients with an I.U.C.D
- Reductions of 34 to 57.9% versus placebo or control in mean menstrual blood loss occurred during tranexamic acid therapy in women with menorrhagia; the drug has also been used to good effect in placental bleeding, postpartum hemorrhage and caesarian sections of the cervix.

REFERENCES

THE IDEAL HAEMOSTATIC COMBINATION

Etamsylate:
- Pronounced antihaemorrhagic and angioprotective properties
- Restores decreased capillary resistance
- Improves microcirculation and modifies PG synthesis
- Normalises the prolonged bleeding time and increases platelet adhesiveness
- Induces polymerization of hyaluronic acid of blood vessels

Tranexamic Acid:
- Competitive inhibitor of plasminogen activation
- At much higher concentrations, a noncompetitive inhibitor of plasmin
- Tranexamic acid binds more strongly than aminocaproic acid to both the strong and weak receptor sites of the plasminogen molecule
- Prevents binding of activated plasminogen to the fibrin surface

Indicated in:
In patients with hemophilia for short term use to reduce or prevent hemorrhage