Role of a non-hormonal oral anti-fibrinolytic hemostatic agent (tranexamic acid) for management of patients with dysfunctional uterine bleeding

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Summary

Objective: Perimenaposal dysfunctional bleeding is a common complaint seen in gynecology clinics. Tranexamic acid is a cheap, over the counter hemostatic agent with antifibrinolytic activity that can be used for management of excessive menstrual bleeding. However, there are few reports analyzing its effectiveness in the management of abnormal menstrual bleeding. This study aimed to evaluate the effectiveness of oral transexamic acid treatment in patients with excessive dysfunctional perimenopausal menorrhagia. *Method:* One hundred and thirty-two consecutive patients with dysfunctional perimenepausal uterine bleeding who were admitted to Cankırı Government Hospital between March 2007 and January 2008 were prospectively enrolled into this one-sided study. All the patients were asked to fill out menstrual diaries and to come to follow-up three months after the initial evaluation. All patients took 500 mg of transexamic acid (Transamine® 3x2) during their menses as the primary treatment and iron preparations if Hb was < 10 g/dl. The paired sample t-test was used for statistical evaluation. *Results:* Mean age of the patients was 42.8 (range 38-46 yrs). Median bleeding time was nine days (range 8-12 days) and median Hb was 10.6 g/dl (range 8.2-11.7) before starting the treatment. During follow-up 45 patients were unresponsive to transamine and needed further treatments (overall response rate was 65.9%). Among responsive patients, after three cycles of transamine usage median bleeding time was five days (range 3-8 days) and median Hb values were 12.1 g/dl. *Conclusion:* Oral tranexamic acid is a reasonable treatment option for patients with excessive dysfunctional perimenopousal bleeding with a 66.0% response rate.

Key words: Transexamic acid; Abnormal uterine bleeding; Abnormal perimenopausal bleeding; Oral antifibrinolytic agent; Homeostasis.

Introduction

One-third of all women experience heavy menstrual bleeding at some point in their life. Menstrual blood loss increases with age. Menorrhagia is usually defined as heavy but regular menstrual bleeding of over 80 ml/cycle [1-8]. Medical therapy, with the avoidance of possibly unnecessary surgery, is an attractive treatment option [8-14]. A wide variety of medications are available to reduce heavy menstrual bleeding but there is considerable variation in practice and uncertainty about the most appropriate therapy [1-14]. The most effective is intrauterine levonorgestrel [4]. Other options are oral progestogens, combined oral contraceptive pills, tranexamic acid, mefenamic acid, danazol and gonadotrophin-releasing hormone (GnRH) analogues [4].

Tranexamic acid is a cheap, over-the-counter homeostatic agent with antifibrinolytic activity that can be used for the management of excessive menstrual bleeding. However, there are few reports analyzing its effectiveness in the management of abnormal menstrual bleeding [1-14]. This study aimed to evaluate the effectiveness of oral transexamic acid treatment in patients with excessive dysfunctional perimenopausal menorrhagia.

Revised manuscript accepted for publication September 22, 2008

Material and Methods

One hundred and thirty-two consecutive patients with dysfunctional perimenopausal uterine bleeding who were admitted to Cankırı Government Hospital between March 2007 and January 2008 were prospectively enrolled in this one-sided study.

All patients complained of menorrhagia. Each patient was evaluated by pelvic examination, transabdominal ultrasonography, cervical smear and Karman endometrial aspiration. Complete blood counts and blood hormonal profiles (FSH, LH, PRL and TSH) were collected for each patient before starting treatment. Women with postmenopausal bleeding, intermenstrual bleeding, iatrogenic or pathological causes of heavy menstrual bleeding were excluded.

All the patients were asked to fill out menstrual diaries and attend follow-up three months after the initial evaluation. All patients took 500 mg of transexamic acid (Transamine® 3x2) during their menses as the primary treatment and iron preparations if Hb was < 10 g/dl. A paired sample t-test was used for statistical evaluation.

Results

Mean age of the patients was 42.8 (range 38-46 yrs). Median bleeding time was nine days (8-12) and median hgb was 10.6 g/dl (8.2-11.7) before starting treatment. During follow-up 45 patients were unresponsive to transamine and needed further treatments (overall response rate was 65.9%). Among responsive patients, after three cycles of transamine usage, median bleeding time was five days (range 3-8) and median hgb values were 12,1 g/dl ($p < 0.01$).

Table 1. — *Pictorial Blood Assessment Chart*.

	Towels
1 point	For each lightly stained towel
5 points	For each moderately soiled towel
20 points	If the towel was completely saturated with blood
	Tampons
1 point	For each lightly stained tampon
5 points	For each moderately soiled tampon
20 points	If the tampon was completely saturated with blood
	Clots
1 point	For a small clot
5 points	For a large clot

Discussion

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 [10-12]. Plasminogen activator inhibitors (antifibrinolytic agents) have therefore been promoted as a treatment for heavy menstrual bleeding. The effect of tranexamic acid on the fibrinolytic enzymes at the local endometrial level may be responsible for its success in the treatment of menorrhagia [10-12]. 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.

There are few studies evaluating the role of tranexamic acid in abnormal uterine bleeding in the published English literature [1-14]. Some of these studies are related with the usage in postpartum bleeding and some studies have evaluated its effectiveness in the management of uterine bleeding associated with intrauterine device usage [2, 13, 17]. What about its use in dysfunctional uterine bleeding?

Sirinil *et al*. found a 49% decrease (from 350.5 to 178.6) in menstrual blood loss using the pictorial blood loss assessment chart (PBAC, Table 1) in a small number of patients (n = 40) with idiopathic menorrhagia [1]. They used 1 g of tranexamic acid orally three times daily for five days from day 1 of menstruation for two consecutive menstrual periods. They also noted an increase in quality of life by using tranexamic acid in patients with menorrhagia.

In another study by Kriplani et al. the authors compared tranexamic acid (4 g/day) and medroxyprogesterone acetate (MPA, cyclical 10 mg twice-daily) for three cycles in patients with dysfunctional menorrhagia [6]. Mean reduction in PBAC score was 60.3% (from 356.9 to 141.6) in tranexamic acid users and 57.7% in MPA users (from 370.9 to 156.6). Lack of response was seen in 6.1% of patients using tranexamic acid (TXA) and 28.9% of MPA users ($p < 0.005$). In patients who reported three months after stopping the treatment, 66.7% in the TXA group and 50% in the MPA group had recurrence of menorrhagia, ($p = 0.155$). During the six-month study period more hysterectomies were performed in the MPA than in the TXA group (17.8% vs 4%; $p < 0.005$).

Wellington et al. reviewed studies on available medical treatments of dysfunctional uterine bleeding (mefenamic acid, flurbiprofen, etamsylate and oral luteal phase norethisterone and intrauterine administration of levonorgestrel) [8]. They found the greatest reduction (96% after 12 months) in blood loss with the use of intrauterine levonorgestrel. However, 44% of patients treated with levonorgestrel developed amenorrhea. Tranexamic acid 2-4.5 g/day for four to seven days reduced menstrual blood loss by 34-59% over two to three cycles, significantly more so than placebo, mefenamic acid, flurbiprofen, etamsylate and oral luteal phase norethisterone. They nevertheless concluded that TXA might 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 unwanted [8].

Another review meta-analysis was published in the Cochrane Database Systems [10-11]. The authors analyzed four of the 15 available randomized controlled trials with antifibrinolytic agents versus placebo, no treatment or any other medical (non-surgical) therapy for regular heavy menstrual bleeding [10, 11]. They found that antifibrinolytic therapy causes a greater reduction in objective measurements of heavy menstrual bleeding when compared to placebo or other medical therapies (NSAIDS, oral luteal phase progestagens and ethamsylate). This treatment is not associated with an increase in side-effects compared to placebo, NSAIDS, oral luteal phase progestagens or ethamsylate. Flooding and leakage and sex life is significantly improved after TXA therapy when compared with oral luteal progestogens.

The PBAC (Table 1) is one of the best known and most frequent methods to assess the amount of blood lost during menstruation. It is a simple non-laboratory method for semi-objective diagnosis of menorrhagia, using scores recorded by women themselves [15]. It was first described by Higham *et al*. in 1990 [15]. A score of 100 was used to define menorrhagia in its originally described form. However validity of this chart has been debated [16]. The method has been reported to have a sensitivity of 86% and a specificity of 89% [15]. We think that PBAC is one of the best available methods to assess blood loss; however it is still not free of patient subjectivity.

In this study, unlike others, we did not use the PBAC system but instead, we preferred to use subjective patient complaints about menorraghia by using their menstrual diaries (either decreased blood loss or no response). Moreover, we preferred to use the Hb value of the patients after three cycles of therapy, which is the most objective assessment of the role of tranexamic acid in reducing dysfunctional uterine bleeding. Our results were also in accord with previous studies [5-8]. There was a high response rate to tranexamic acid (65.9%) and the response was also very quick. Among the responders, Hb values and total menstruation duration were significantly improved within three months of treatment. There were no side-effects reported by the patients (neither mild nor moderate-severe side-effects) attributable to TXA during the three months of medication.

As a conclusion, this one-sided descriptive analysis indicates that tranexamic acid is a safe and cheap, over-the-counter non-hormonal medication which can be used for the management of patients with dysfunctional uterine bleeding. Tranexamic acid might 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 unwanted.

References

[1] Srinil S., Jaisamrarn U.: "Treatment of idiopathic menorrhagia with tranexamic acid". *J. Med. Assoc. Thai.,* 2005, *88* (suppl. 2), S1.

[2] Lin X., Gao E.S., Li D., Zhang M., Dou L.X., Yuan W.: "Preventive treatment of intrauterine device-induced menstrual blood loss with tranexamic acid in Chinese women". *Acta Obstet. Gynecol. Scand.,* 2007, *86*, 1126.

[3] Hurskainen R., Grenman S., Komi I., Kujansuu E., Luoto R., Orrainen M. *et al*.: "Diagnosis and treatment of menorrhagia". *Acta Obstet Gynecol Scand.,* 2007, *86*, 749.

[4] Duckitt K.: "Medical management of perimenopausal menorrhagia: an evidence-based approach" (review). *Menopause Int.,* 2007, *13,* 14.

[5] Torjesen I.: "Non-surgical management of heavy menstrual bleeding". *Nurs Times.,* 2007, *103*, 25.

[6] Kriplani A., Kulshrestha V., Agarwal N., Diwakar S.: "Role of tranexamic acid in management of dysfunctional uterine bleeding in comparison with medroxyprogesterone acetate". *J. Obstet. Gynaecol.,* 2006, *26,* 673.

[7] Phupong V., Sophonsritsuk A., Taneepanichskul S.: "The effect of tranexamic acid for treatment of irregular uterine bleeding secondary to Norplant use". *Contraception,* 2006, *73,* 253.

[8] Wellington K., Wagstaff A.J.: "Tranexamic acid: a review of its use in the management of menorrhagia" (review). *Drugs,* 2003, *63,* 1417.

[9] Winkler U.H.: "The effect of tranexamic acid on the quality of life of women with heavy menstrual bleeding". *Eur. J. Obstet. Gynecol. Reprod. Biol.,* 2001, *99,* 238.

[10] Lethaby A., Farquhar C., Cooke I.: "Antifibrinolytics for heavy menstrual bleeding" (review). Cochrane Database Syst Rev. 2000, (4), CD000249.

[11] Cooke I., Lethaby A., Farquhar C.: "Antifibrinolytics for heavy menstrual bleeding" (review). Cochrane Database Syst Rev. 2000; (2), CD000249. Update in: Cochrane Database Syst. Rev. 2000; (4), CD000249.

[12] Gleeson N.C., Buggy F., Sheppard B.L., Bonnar J.: "The effect of tranexamic acid on measured menstrual loss and endometrial fibrinolytic enzymes in dysfunctional uterine bleeding". *Acta Obstet. Gynecol. Scand.*, 1994, *73,* 274.

[13] Milsom I., Andersson K., Andersch B., Rybo G.: "A comparison of flurbiprofen, tranexamic acid, and a levonorgestrel-releasing intrauterine contraceptive device in the treatment of idiopathic menorrhagia". *Am. J. Obstet. Gynecol.*, 1991, *164,* 879.

[14] Andersch B., Milsom I., Rybo G.: "An objective evaluation of flurbiprofen and tranexamic acid in the treatment of idiopathic menorrhagia". *Acta Obstet. Gynecol. Scand.*, 1988, *67*, 645.

[15] Higham J.M., O'Brien P.M., Shaw R.W.: "Assessment of menstrual blood loss using a pictorial chart". *Br. J. Obstet. Gynaecol.*, 1990, *97*, 734.

[16] Reid P.C., Coker A., Coltart R.: "Assessment of menstrual blood loss using a pictorial chart: a validation study". *BJOG,* 2000, *107,* 320.

[17] Gai M.Y., Wu L.F., Su Q.F., Tatsumoto K.: "Clinical observation of blood loss reduced by tranexamic acid during and after caesarian section: a multi-center, randomized trial". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 2004, *112*, 154.

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