JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH

How to cite this article:

NAJAM R, AGARWAL D, TYAGI R, SINGH S. COMPARISON OF TRANEXIMIC ACID WITH A COMBINATION OF TRANEXIMIC ACID AND MEFENAMIC ACID IN REDUCING MENSTRUAL BLOOD LOSS IN OVULATORY DYSFUNCTIONAL UTERINE BLEEDING (DUB). Journal of Clinical and Diagnostic Research [serial online] 2010 October [cited: 2010 October 14]; 4: 3020-3025.

Available from
http://www.jcdr.in/article_fulltext.asp?issn=0973-709x&year=2010&volume=&issue=&page=&issn=0973-709x&id=882

ORIGINAL ARTICLE

Comparison of Traneximic Acid with a Combination of Traneximic Acid and Mefenamic Acid in Reducing Menstrual Blood Loss in Ovulatory Dysfunctional Uterine Bleeding (DUB)

NAJAM R*, AGARWAL D**, TYAGI R***, SINGH S****

ABSTRACT

Objective: To compare the efficacy of traneximic acid (Txa), with a combination of traneximic acid (Txa) and mefenamic acid (Mfa) in reducing menstrual blood loss in patients of ovulatory DUB. **Design:** Prospective, randomised trial performed in 110 patients of ovulatory dysfunctional uterine bleeding. **Intervention:** Patients diagnosed with ovuatory DUB based on the history of regular heavy cyclical bleeding, with normal transvaginal sonography (n= 110 patients), were included in the study. The patients were grouped into two, group T receiving tablets of 500mg Txa, three times a day from day 1 to 5 of the menstrual cycle, and group TM receiving tablets of 500mg Txa +250mg Mfa, three times a day from day 1 to 5 of the menstrual cycle, for 3 cycles i.e. 3 months. The efficacy of the treatment in both the groups was evaluated by recording the reduction in menstrual blood loss (measured by calculating pictorial blood assessment chart scores) and the improvement in post-treatment haemoglobin concentrations at 3 and 6 months follow up. **Results:** Of the 110 patients who were followed up for a period of 6 months, 38.1% (n=42) were in the age group of 30-39 years. 54.5% of the patients (n=60) presented with moderate anaemia at the first outpatient visit. In the T group, the mean pre-treatment haemoglobin concentration was 9.5 g/dl and the mean PBAC score was 250. At 6 months of follow up, the mean haemoglobin concentration was 12.0 g/dl, which showed an improvement by 26.3% and the mean PBAC score was 125, which showed an improvement by 50%. In group TM, the mean pre-treatment haemoglobin concentration and the PBAC score were 8.6 g/dl and 246, respectively, while at 6 months of follow up, the mean haemoglobin concentration was 12.3g/dl, which showed an improvement of 38.9% and the PBAC score was 100, with a decline of 59.3%. **Conclusion:** Both traneximic acid and a combination of traneximic acid and mefenamic acid are effective in decreasing PBAC scores and reducing menstrual blood loss in DUB, though a combination of traneximic acid and mefenamic acid showed better long term results.

Key Words: Dysfunctional uterine bleeding (DUB), traneximic acid (Txa), mefenamic acid (Mfa), haemoglobin concentration, pictorial blood assessment chart (PBAC), menstrual blood loss (MBL).

*Assistant professor, Department of Obstetrics and Gynecology, **Associate professor, Department of Pathology, *** Resident, Department of Obstetrics and Gynecology, ****Resident, Department of Obstetrics and Gynecology, Teerthanker Mahaveer Medical College, Moradabad,U.P. (India)

Corresponding Author:
Dr. Rehana Najam ,Assistant Prpfessor
Department of Obstetrics and Gynecology
Teerthanker Mahaveer Medical College, Bagarpur, Delhi Road, Moradabad, U.P. (India)
E mail: najamnajam@rediffmail.com

Introduction

DUB is defined as excessive, heavy, prolonged or frequent bleeding of uterine origin that is not due to pregnancy, or any recognisable pelvic or systemic disease. The diagnosis of DUB is that of exclusion, where all pelvic and systemic causes of excessive menstruation have been ruled out. DUB is of two types, ovulatory and anovulatory. Ovulatory DUB accounts for 80% of the cases and is seen in women of the reproductive age group, while anovulatory DUB is seen at menarchae and during perimenopause. Nearly 28% of the female population consider their menstruation as excessive and plan their social activities according to their menstrual cycles, while nearly 10% of the employed women take time off work because of excessive menstrual loss. [1]. About 35-40% of the females with excessive uterine bleeding are referred to hospitals and 60% will have a hysterectomy done in the next five years [2]. DUB is diagnosed in 40-60% of the women with excessive menstrual bleeding, which is defined as blood loss greater than 80ml. The management of DUB includes general measures, including maintaining a menstrual calendar, correction of anaemia, medical treatment and finally, surgical treatment. The medical management of DUB includes NSAIDs, traneximic acid, progestogens, combined OCPs, danazol and levonorgestrel releasing intra uterine device. Morana B *et al* reported that the medical treatment of DUB results in patient satisfaction and a fall in the number of hysterectomies [3]. It has been proved that fibrinolytic activity is increased in the menstrual fluid in menorrhagia and synthetic antifibrinolytics reduce menstrual bood loss [4]. Traneximic acid, a synthetic derivative of the amino acid lysine, exerts its antifibrinolytic activity through the reversible blockade of lysine binding sites on plasminogen molecules. It is 6-10 times more potent than other synthetic antifibrinolytic agents and reduces menstrual blood loss by 45-60%. The side effects of tranaxemic acid therapy include nausea and leg cramps and rarely, deep vein thrombosis. NSAIDs or anti-prostaglandins act by reducing the elevated levels of prostaglandins which are seen in patients of excessive menstrual bleeding. Mefenamic acid, an NSAID and an anthranilic acid derivative, is also known to reduce menstrual blood loss by 20% [3],[4],[5].

Previous studies have evaluated the efficacy of various medical modalities (NSAIDS, hormones, antifibrinolytics, etc) and have established their role, but none has compared an anti-fibrinolytic with a combination of anti-fibrinolytics and NSAIDs in reducing menstrual blood loss in patients of DUB. This study was designed to compare the clinical efficacy of traneximic acid alone and in combination with mefenamic acid in reducing blood loss in patients with ovulatory DUB.

The improvement in the clinical parameters which are associated with dysfunctional uterine bleeding, such as degree of anaemia and reduction in menstrual blood loss, were also evaluated as appropriate responses to therapy.

Materials and Methods

This prospective trial was conducted in the Department of Obstetrics and Gynecology of our institute from October 2008 to September 2009 (12 months), after approval from the institutional ethical committee. Out of the 670 patients of abnormal uterine bleeding, 110 cases having heavy regular cycles (ovulatory DUB) were included in the study after taking written/ informed consent. The inclusion criteria were:

- Patients between 12-45 years.
- In married females, transvaginal sonography (TVS) evaluation on either the 4^{th}, 5^{th} or 6^{th} day of their menstrual cycle, revealing an endometrial thickness of less than 5mm.
- Normal Pap test, thyroid function test, renal function tests, liver function tests, coagulation profile.
- Endometrium sampling for the secretory phase, only in cases of the perimenopausal age group.
- The exclusion criteria included patients with a history of recent IUCD or hormonal therapy, anovulatory or irregular cycles, absence of pregnancy or any pelvic pathology, coagulation

disturbances, polycystic ovarian disease and thyroid, liver or renal dysfunction.

Abdominal ultrasound was performed in unmarried females to evaluate any pelvic pathology. All these cases were assessed with detailed history and meticulous physical examination, including per vaginal and per abdominal assessment. The pre-treatment haemoglobin concentration was measured and recorded in each patient.

The menstrual blood loss was assessed by the pictorial blood assessment chart (PBAC) scores. This was a subjective method of assessing menstrual blood loss (MBL), whereby the patient was asked to examine her pad/tampon/towel for the amount of staining on it and a score was given. In our study, all patients were advised to use sanitary pads of a particular brand (Johnson and Johnson, India Ltd.) to standardize the assessment of blood loss. We decided to use the PBAC because it was simpler, less time consuming and cost effective and did not require a collection of sanitary products. A PBAC score of ≥ 100 shows a diagnosis of menorrhagia and signifies that the MBL is more than 80ml. PBAC had showed a sensitivity of 86% and a specificity of 89% in previous studies [6]. The patients who were enrolled in the study were randomly distributed to the T or the TM group by using computer generated numbers. In the T group, patients received tablets of 500 mg traneximic acid, thrice daily, from day 1 to 5 of the menstrual cycle. In the TM group, patients were given tablets of 500mg traneximic acid and 250mg mefenamic acid, thrice daily, from day 1-5 of the cycle, till 3 cycles. The medication was supplied in an individual pack for each subject.

The patients were followed up at 1, 3 and 6 months intervals after their first prescription and were asked to report earlier in case of any problem. Haemoglobin levels and PBAC scores were used to assess the response to treatment at 3 and 6 months. The occurrence of any side effects was recorded in both the groups during the study period.

Statistical Analysis

The power study was calculated by taking an alpha error of 0.05 and a beta error of 0.8% to evaluate a 30% improvement in the haemoglobin concentration post treatment, as mentioned in previous studies. A sample size of 110 patients was required. Therefore, we enrolled this number of patients in our study.

The data were analyzed by using the statistical software, SPSS, version 16.0 (SPSS ltd, Chicago, IL). The categorical data was analyzed by using the x^2 test, while the continuous variables were analyzed by using the Student's t-test. The results are presented as median (range) and number (percentage) for continuous variables. A *P*-value <0.05 was considered as statistically significant and a *P* value <0.001 was considered as highly significant.

Results

The patient characteristics were comparable in both the groups (*P*>0.05) prior to intervention [Table/Fig 1].

[Table/Fig 1]: Patient characteristics of the two groups prior to treatment

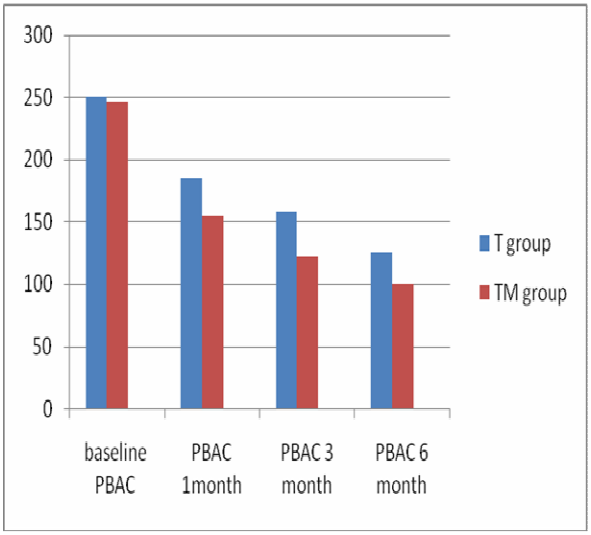
Characteristics	T group (n=55)	TM group (n=55)
Age (yrs)*	37 (13-49)	39 (12-47)
Duration of symptoms (month) *	10.5 (4.5-16)	11.7 (3.6-13.6)
Hb concentration (g/dl) *	9.5 (7.2-11.8)	8.6 (6.5-10-2)
PBAC scores*	250 (221-267)	246 (213-254)
BMI	22	21

*: **Mean with Range**

Of the 110 cases, 40.9% (n=45) were in the age group of 30-39 years, followed by 26.3% (n=29) cases in the perimenopausal age group (40-45 years). In our study, the maximum number of patients were para 3 (n=25). The common bleeding patterns observed were; menorrhagia (n=75; 68%), polymenorrhagia (n=28; 25.4%) and metrorrhagia (n=7; 6.3%). The leuteal phase progesterone study revealed normal results (>5pg/ml) in 15 cases of adolescent females with either nulliparity or unmarried status and having a clinical suspicion of

anovulatory DUB. Endometrial sampling was performed only in 29 cases of the perimenopausal age group and it revealed no hyperpastic or neoplastic changes.

In the TM group, the average pre-intervention PBAC score was 246, at 1 month follow up it was 155 and at the end of 6 months of follow up, it was 100, which was a significant improvement ($P < 0.01$) [Table/Fig 2]. In the T group, the average pre injection PBAC score at the 6th month was 250. At 1 month follow-up, it was 185 and at 6 months of follow up, it was 125, , which depicted an insignificant improvement ($P > 0.05$).



[Table/Fig 2]: Mean PBAC scores in T and TM group at 1, 3 and 6 months follow up.

The haemoglobin levels recorded at the first outpatient visit revealed that moderate anaemia was the commonest presentation (n=60), while 30 cases had mild anaemia and 14 patients had severe anaemia [Table/Fig 3]. We followed the ICMR classification of anaemia in our study. The incidence of anaemia in both the groups was non-significant ($P > 0.05$).

[Table/Fig 3]: Severity of anaemia observed in patients during Ist outpatient visit.

Haemoglobin	Group T (%)	Group TM (%)	Significance
Mild anaemia (10-11 gm%)	13 (23.6)	17 (30.9)	NS
Moderate anaemia (7-9.9 gm%)	33 (60)	27 (49)	NS
Severe anaemia (4-6.9 gm%)	8 (7.2)	6 (5.4)	NS
No anaemia (>11 gm%)	2 (1.8)	4 (3.6)	S

NS: Non-Significant; S: Significant

In the TM group, the mean haemoglobin concentration was 10.6g/dl at 1 month, 11.8g/dl at 3 months and 12.3g/dl at 6 months of follow up, which was significantly high (P=0.04; 0.02 and 0.016 respectively) (Table 3). In the T group, it was 10.2g/dl at 1 month ($P > 0.05$), 11.4g/dl at 3 months and 12.0g/dl at 6 months of follow up (P= 0.04) [Table/Fig 4].

[Table/Fig 4]: Mean Hemoglobin concentration in both the groups during treatment period.

Time Duration	T group (gm/ dl)	TM group (gm/ dl)
Pre-intervention	9.5	8.6
1 month	10.2	10.6
3 month	11.4	11.8
6 month	12.0	12.3

In the T group, the mean haemoglobin concentration registered an improvement of 26.3% at 6 months of follow up, with a PBAC score of 50% improvement. In the TM group, the mean haemoglobin concentration improved by 43% and the PBAC score improved by 59.3% at the end of 6 months.

The side effects of the drugs included minor complaints of nausea and GI disturbances in 9 cases and leg cramps in 7 cases in group T, while in the TM group, 8 and 12 cases presented with the above complaints respectively. No major side effects were encountered in any patient of either group.

Discussion

DUB is defined as excessive or prolonged and regular or irregular menstrual bleeding, in the absence of any organic uterine pathology, endocrine or haematological disorder. The diagnostic aids laid down by the RCOG [7] and the ACOG [8] guidelines include meticulous and detailed history, examination and normal TVS findings, with the exclusion of any organic disorder, in patients of the pre-menopausal age. Considering the burden of unnecessary investigations and financial implications, especially in developing countries, the leuteal phase progesterone study is indicated in nulliparous or unmarried females with clinical suspicion of anovulatory DUB [8],[9]. Moreover, endometrial sampling is indicated in patients of the perimenopausal age group, with suspected hyperplastic/ neoplastic changes; bleeding not responding to medical therapy; history of prolonged unopposed oestrogen stimulation secondary to chronic anovulation [8].

In our study, 67% of the cases (n=74) were in the age group of 30-49 yrs, which was similar to the findings observed by Gleeson NC et al [12], where the median age of the cases was 38.3 years, with a range between 28-49 years.

Gultekin M *et al* [13], in their study, reported the role of traneximic acid in the management of DUB and observed that it reduces the menstrual bleeding by 66%. The baseline haemoglobin concentration in their study was 10.6 g/dl, which increased to 12.1 g/dl after three cycles of treatment with traneximic acid. In our study, the mean haemogobin concentration increased in both the groups, but the percentage increase was more in the TM group (43% vs. 26.3%) at 6 months of follow up. Similar improvements in mean haemoglobin levels after treatment with tranaxemic acid, have been reported by other researchers in their studies [14],[15],[16].

Bonnar J *et al* [14] conducted a randomised controlled trial on 76 women to compare the efficacy of traneximic acid, ethamsylate and mefenamic acid in DUB. The results showed that ethamsylate was ineffective in reducing MBL, whereas mefenamic acid effectively reduced blood loss by 20% and traneximic acid by 54%. Kriplani A *et al* [15] found that patients who were treated by traneximic acid for three cycles showed a significant decrease in the PBAC score from 356.9 to 141.6, i.e. a decline of 60.3%. Sukanya S *et al* [16] conducted a study on the role of traneximic acid in idiopathic menorrhagia and found that the PBAC score improved by 46.1% at the end of 3 cycles of treatment. This was comparable to the results of our study, where traneximic acid improved the PBAC score by 50%, while the combination of traneximic acid and mefenamic acid improved the PBAC score by 59.3%. Ylikorkala *et al* [17] compared traneximic acid with NSAIDs in females with IUD induced menorrhagia and reported a 56% reduction in menstrual bleeding with traneximic acid, as compared to 21% with NSAIDs. In a study conducted by Ulrich HW [18] on the effect of traneximic acid in improving the quality of life in women with heavy menstrual bleeding, the mean haemoglobin concentration showed improvement by 10.5% after three cycles of treatment.

The occurrence of side effects such as leg cramps and nausea was transient in 20-25 % of our cases and was comparable with other studies [13],[15],[16].

There is no doubt that traneximic acid is a highly effective haemostatic agent and that it has shown encouraging results in reducing menstrual bleeding in many previous researches [12],[13],[15],[16],[19]. The combination of tranaxemic acid with mefanamic acid showed good evidence in reducing DUB in the Royal College of Obstetrics and Gynecology (RCOG) guidelines [7]. Our study confirms the efficacy of traneximic acid in the treatment of menorrhagia due to DUB (ovulatory) and a more promising response in combination with mefenamic acid.

A few limitations in the present study were, that it was single blinded, which could have added to a bias in the results. Taking a control group and increasing the sample size could have added to more precision in our results.

In future trials, a larger sample size may be undertaken to compare anti-fibrinolytics with

other medical modes of treatment. Further studies can also investigate the role of polytherapy including OCPs, GnRH analogues and antifibrinolytics, with newly introduced agents in the management of DUB.

Conclusion

We conclude that traneximic acid alone or in combination with mefenamic acid, is effective in reducing menstrual blood loss, though the efficacy of combination therapy is more superior. We recommend its use for reducing the severity of blood loss which is associated with ovulatory DUB and for providing symptomatic improvement for the general health of the patients.

References

[1] Edlund M et al. Quality of life: A Swedish survey of 2200 women with DUB. London Royal Society of Medicine Press 1994:36-7.

[2] Coulter A, Bradlow J, Agass M. Outcomes of referral to gynecology outpatient clinics for menstrual problems: An audit of general practice records. Br J Obstet & Gynecol 1991; 98:789-96.

[3] MoranaB, ZarboR, PuglisiF, ZarboG. Dysfunctional uterine bleeding: Medical therapies. Minerva Ginecol 2003; 55:241-5.

[4] Bonnar J , Sheppard BL, Dockeray CJ. The haemostatic system and DUB. Res Clin Forums1983; 5:27-38.

[5] Bonsgers MY, Mol BW, Brolmann HA. Current treatment of DUB. Maturitas 2004;47: 159-74.

[6] Higham JS, O'Brien PMS, Shaw RW. Asessment of menstrual blood loss using a pictorial chart. Br. J. Obstet. Gynaecol.1990;97:734-9.

[7] Royal college of Obstetricians and Gynaecologists. The initial management of menorrhagia. Evidence based clinical guideline no.1.

[8] Guideline ACOG. Management of Anovulatory Bleeding. 2008 Compendium of Selected Publications. 2000;14:1049-56.

[9] Bradley L D. Abnormal Uterine Bleeding. The Nurse Practitioner: The American Journal of Primary Health Care. 30;10:38-49.

[10] Tod C Aeby, LeighAnn C F. Dysfunctional Uterine Bleeding: Differential Diagnoses & Workup. http://emedicine.medscape.com/article/953078-diagnosis.

[11] Mohandas S. Dysfunctional uterine bleeding. Thrissur Gynaecology. http://www. thrissurgynaecology. com/articles-clinician dysfunctional%20uterine%20 bleeding.htm.

[12] Gleeson NC, Buggy F. The effect of traneximic acid on measured menstrual blood loss and endometrial fibrinolytic enzymes in DUB. Acta Obstet Gynecol Scand 1994; 73:274-7.

[13] Gultiken M, Diribas K, Buru E, Gokceoglu MA. Role of non-hormonal oral anti-fibrinilytic hemostatic agent (traneximic acid) for management of patients with dysfunctional uterine bleeding. Clinical and experimental obstetric & gynecology 2009;36(3):163-5.

[14] Bonnar J, Sheppard BL. Treatment of menorrhagia during menstruation: randomized controlled trial of ethamsylate, mefenamic acid and traneximic acid. Br Med J 1996;313:579-82.

[15] Kriplani A,Kulshreshta V,Agarwal N, Diwakar S. Role of traneximic acid in management of dysfunctional uterine bleeding in comparison with medroxyprogesterone acetate. J Obstet Gynaecol.2006;26(7):673-8.

[16] Sukanya S,UnnopJ. Treatment of idiopathic menorrhagia with traneximic acid. J Med Assoc Thai. 2005;88 (suppl)1-6.

[17] Ylikorkala O, ViinikkaL. Comparison between antifibrinolytic and antiprostaglandin treatment in reduction of increased MBL in women with IUCD. Br. J.Obstet. Gynecol. 1983;90:78-83.

[18] Winkler UH. The effect of traneximic acid on the quality of life in women with heavy menstrual bleeding. Eur J Obst Gynecol 2001;99:238-43.

[19] Casablanca Y. Management of dysfunctional uterine bleeding. Obstet Gynecol Clin North Am. Jun 2008;35(2):219-34.