Available online at http://www.ijims.com
ISSN: 2348 – 0343

Comparison of Tranexamic acid with a combination of Traneximic acid and Mefenamic acid in reducing menstrual blood loss in ovulatory Dysfunctional uterine bleeding (DUB)

Radha Rani [1*], Meena BS [2], Sukhwinder Singh [3], Ahilya Patel [4], Rajoria Lata [2]

1. Senior Resident , Dept. of Obstetrics and Gynaecology, PGIMS, Rohtak
2. Professor ,Dept. of Obstetrics and Gynaecology,S.M.S. Medical College, Jaipur
3. PG Resident, Dept. of Paediatrics, PGIMS ,Rohtak
4. IIIrd year PG Resident, PGIMS, Rohtak
*Corresponding author: Radha Rani

Abstract

This study was undertaken to compare the efficacy of Tranexamic acid (TXA) with a combination of Traneximic acid and Mefenamic acid (MFA) in reducing menstrual blood loss in ovulatory Dysfunctional uterine bleeding. This study is a prospective, Interventional study performed in 150 patients of ovulatory DUB. Patients diagnosed with ovulatory DUB, with normal transvaginalsonography (n=150 patients), were included in the study. The patients were grouped into two, group T receiving tablets of 500 mg txa , three times a day from day 1 to 5 of the menstrual cycle, and group TM receiving tablets of 500 mg txa + 250 mg 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 group 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. 150 patients who were followed up for a period of 6 months. Out of 150 cases, 41.3% (n=62) were in the age group of 36-40 years, followed by 36% (n=54) cases in 31-35 yrs. Age group.in our study maximum number of patients were para 4 or more(n=58). Majority of cases were in category of moderate anaemia (Hb=7.1-10.0) and duration of menorrhagia was 4-6 months. Improvement in Mean Hb concentration was 27.3% gm/dl in T-GROUP.While in TM-GROUP, improvement in Mean haemoglobin concentration was 37.3% gm/dl. Which was significantly higher than T-Group (p<.01).In T-GROUP, improvement in Mean PCV was 16.16% in T-group.While in TM-GROUP, improvement in Mean PCV was 17.5% in TM-GROUP which was significantly higher than T-Group (P<.01).Improvement inMean PBAC Score was 45.06% in T-GROUP after 6 months.While in TM-Group improvement in Mean PBAC Score was 55.41% in which was significantly higher than T-group (P< .01).Out of 75 cases in T-GROUP, Only 10 (13.33%) cases were relieved from dysmenorrhea after treatment .While in TM-GROUP, 29 (38.66%) of cases were relieved from dysmenorrhea in TM-GROUP which was significantly higher.It was concluded that both Tranexamic acid alone or in combination with mefenamic acid, is effective in reducing menstrual blood loss, though the efficacy of combination therapy is more superior in Ovulatory DUB.

Key words: dysfunctional uterine bleeding(DUB), tranexamic acid (TXA), mefenamic acid (MFA), hemoglobin concentration, packed cell volume (PCV), pictorial blood assessment chart(PBAC),menstrual blood loss(MBL).

Introduction

DUB is defined as a state of abnormal uterine bleeding without any clinically detectable organic, systemic and iatrogenic cause (pelvic pathology ex. Tumor, inflammation or pregnancy excluded.) Prevalence varies widely

but DUB has an incidence of 5% among new patients attending the outpatient department. It is the most common menstrual disorder that can affect any women from menarche to menopause.[1]Dub is of two types, Ovulatory DUB (20%) and Anovulatory DUB (80%)[2]. Ovulatory DUB accounts for 20% of the cases and is seen in women of the reproductive age group, while anovulatory DUB is seen at menarche 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[3]. A large proportion of cases will subsequently undergo hysterectomy which is the definitive care for menorrhagia, but hospitalization and anesthesia are required with its associated risk of morbidity and mortality and the procedure is not suitable for women who wish to preserve their fertility or for women nearing menopause.[1]A good medical treatment will reduce hysterectomies and associated morbidity and mortality. Although conservative surgery (endometrial ablation) is an alternative to hysterectomy, its cost is a limiting factor in developing countries. Thus drug therapy should be the first line treatment before recourse tosurgery. Many drugs for DUB are available. Oral drugs used are NSAIDs, Antifibrinolytics ,Progestins , OCP , Danazol and GnRH Analogue. It has been proved that fibrinolytic activity is increased in the menstrual fluid in menorrhagia and synthetic anti-fibrinolytics reduce menstrualblood loss[4] .Tranexamic acid, a synthetic derivative of the amino acid lysine , exerts its fibrinolytic activity through the reversible blockade of lysine binding sites on plasminogen molecules. It reduces menstrual blood loss by 45-60%. The side effects of TxA 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%.

Previous studies have evaluated the efficacy of varius medical modalities (NSAIDs, hormones, anti-fibrinolytics, 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 tranexamic acid alone and in combination with mfenamic 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 response to therapy.

Materials and Methods

This Prospective interventional study was a hospital based study conducted at MahilaChikitsalaya, Sanganeri Gate, Dept. of Obs & Gynae, SMS Medical College, Jaipur fromApril 2012 to April 2013. 150 patients having heavy regular cycles (ovulatory DUB) were included in the study after taking written/informed consent.

Inclusion criteria -

- Patient between 20-40 years.
- In married female endometrial thickness should be less than 5mm by transvaginalsonogrphy.
- Thyroid profile, Renal function test & liver function test & coagulation profile.
- Diagnosis of ovulatory cycle by serum Progesterone.

Exclusion criteria-

- History of recent IUCD or hormone therapy, Anovulatory or irregular cycle.
- Pregnancy or any pelvic pathology.
- Coagulation disturbances.

- Thyroid, liver or renal dysfunction.

All these were assessed with detailed history and meticulous physical examination. The pre-treatment hemoglobin, Packed cell volume (PCV) 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 score was given. In our study, all patients were advised to use sanitary pads of a particular brand 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 collection of sanitary products. A PBAC score of >_100 shows a diagnosis of menorrhagia and signifies that the MBL is more than 80 ml. PBAC had showed a sensitivity of 86% and specificity of 89% in previous studies (6). The patients who were randomly distributed to the T and TM group. In the T-group , patients received tablets of 500 mg tranexamic acid, thrice daily, from day 1 to 5 of the menstrual cycle. In the TM-group, patients were given tablets of 500 mg tranexamic acid and 250 mg mefenamic acid , thrice daily, from day 1-5 of the cycle, till 3 cycles.

The patients were followed up at 3 and 6 months interval after their first prescription and were asked to report earlier in case of any problem. Hemoglobin levels, PCV and PBAC scores were used to assess the response to treatment at 3 and 6 months.

Statistical analysis:

1. For comparison of mean blood Hb level before and after treatment – Paired t Test.
2. For comparison of mean PCV Before and after treatment – Paired t test.
3. For comparison of mean PBAC score before and after treatment – Wilcoxon Sign Rank test.

Results

The patients characteristics were comparable in both the groups prior to intervention (Table 1).

Table1 : Patients characteristics of the two groups prior to treatment

Characteristics	T-Group(n=75)	TM-Group (n= 75)
Age (Yrs.)*	34.17	34.76
Hb concentration (g/dl)*	8.64	9.03
PCV (gm%)*	29.26	30.06
PBAC Scores*	237.41	234.56
BMI*	25.27	25.01

*Mean value

Out of 150 cases, 41.3% (n=62) were in the age group of 36-40 years, followed by 36% (n=54) cases in 31-35 yrs. Age group. In our study maximum number of patients were para 4 or more(n=58). Majority of cases were in category of moderate anaemia (Hb=7.1-10.0) and duration of menorrhagia was 4-6 months.

In T-GROUP, Mean Haemoglobin Concentration was 8.64±.94 before intervention. After 3 months of treatment, mean haemoglobin 10.36±.81, after 6 months of follow up it was 11.0±.94. So improvement in Mean Hb concentration was 27.3% gm/dl in T-GROUP.

Table 2- Improvement in mean heamoglobin at 3 and 6 months after treatment in T-Group and TM-Group

TIME DURATION	**T-GROUP (Mean Hb in gm/dl)**	**TM-GROUP (Mean Hb in gm/dl)**
Pre-intervention	8.64 ± .94	9.03 ± .86
At 3 month	10.36 ± .81	11.6 ± .64
After 6 months	11.0±.82	12.4±.62
Improvement	27.3 % gm/dl	37.3 % gm/dl

t- 51.87 df-74 P<.01 for T group t- 71.04 df-74 P<.01 for T M group

While in TM-GROUP, Mean Haemoglobin Concentration was 9.03±.86 before intervention. After 3 months of treatment, mean haemoglobin was 11.6±.64 , after 6 months of follow up it was12.4±.62. So improvement in Mean haemoglobin concentration was 37.3% gm/dl. Which was significantly higher than T-Group (p<.01).So patients in TM-GROUP were showing greater improvement in mean Hb concentration in comparison to T-GROUP.

In T-GROUP, mean packed cell volume was 29.26±1.88% before intervention. After 3 months of treatment, it was 32.72±1.61%. After 6 months, it was raised up to 33.99±1.64. So improvement in Mean PCV was 16.16% in T-group.

While in TM-GROUP, mean packed cell volume was 30.06+_1.75% before intervention. After 3 months of treatment, it was 35.32±1.40 %. After 6 months it was raised up to 36.67±1.60.So improvement in Mean PCV was 17.5% in TM-GROUP which was significantly higher than T-Group (P<.01).

Table 3: Improvement in mean PCV at 3 and 6 months after treatment in T-Group and TM-Group

TIME DUARTION	**T-GROUP (Mean PCV in gm%)**	**TM-GROUP (Mean PCV in gm%)**
PRE-INTERVENTION	29.26±1.88	30.06±1.75
AFTER 3 MONTHS	32.72±1.61	35.32±1.40
AFTER 6 MONTH	33.99±1.64	36.67±1.60
IMPROVEMENT IN PCV	16.16%	21.98%

t- 53.8 df-74 P<.01 for T group t- 48.81 df-74 P<.01 for T M group

In T-GROUP, Mean PBAC Score was 237.41±11.18 before intervention. After 3 months of treatment, it reduced up to 150.64±10.73 and after 6months It was 130.43±6.34 . So improvement inMean PBAC Score was 45.06% in T-GROUP after 6 months.

While in TM-Group Mean PBAC Score was 234.56±13.25 before intervention. . After 3 months of treatment, it reduced up to 128.28±5.97, and after 6 monthsit was 104.59±8.56. So improvement in Mean PBAC Score was 55.41% in TM-GROUP after 6 months which was significantly higher than T-group (P< .01).

Table 4: Improvement in mean PBAC Score at 3 and 6 months after treatment in T-Group and TM-Group

TIME DURATION	**T-GROUP (Mean PBAC Score)**	**TM-GROUP (Mean PBAC Score)**
PRE-INTERVENTION	237.41±11.18	234.56±13.25
AFTER 3 MONTHS	150.64±10.73	128.28±5.97
AFTER 6 MONTH	130.43±6.34	104.59±8.56
IMPROVEMENT IN PBAC	45.06%	55.41%

t- 98.79 df-74 P<.01 for T group t- 100.4 df-74 P<.01 for T M group

Out of 75 cases in T-GROUP, 37 (49.33%) cases were having dysmenorrhea along with menorrhagia before treatment. Only 10 (13.33%) cases were relieved from dysmenorrhea after treatment in T-GROUP.

While out of 75 cases in TM-GROUP, 35 (46.66%) cases were having dysmenorrhea along with menorrhagia before initiation of treatment. 29 (38.66%) of cases were relieved from dysmenorrhea in TM-GROUP which was significantly higher.

Table 5: Improvement in Dysmenorrhea after treatment in T-Group and TM-Group

NO. OF PATIENTS HAVING DYSMENORRHEA	T-GROUP		TM-GROUP	
	NO.OF CASES	% OF CASES	NO.OF CASES	% OF CASES
BEFORE TREATMENT	37	49.33	35	46.66
AFTER TREATMENT	27	36.00	6	8.00
RELIEF IN DYSMENORRHEA	10	13.33	29	38.66

X^{2-} 22.6 df-1 P<.01 (significantly higher % of relief in TM Group)

Side-effects of the drugs included minor complaints of nausea, dyspepsia, diarrhoea and GI disturbances and rarely deep vein thrombosis with tranexamic acid. No side effects were encountered in any patient in 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 and ACOG guidelines include meticulous and detailed history, examination and normal TVS finding with the exclusion of any organic disorder.In our study, 41.33% of the cases (n= 62) were in the age group of 36-40 yrs. Which was similar to the finding observed by Glesson NC et al(1994)[5], where the median age of the cases was 38.3 yrs. Najam R & Agrawal D et al (2010)[6]done the comparative study of tranexamic acid with combination of tranexamic acid and mefenamic acid in ovulatory DUB. Baseline Hb was 9.5% in T-Group and 8.6% in TM-Group. After 3 months of treatment, Mean Hb in T-Group was 11.4% and in TM-Group was 11.8%.Glutekein M et al (2009)[7] in their study, reported the role of tranexamic 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 to12.1 g/dl after three cycles of treatment with tranexamic acid. In our study, the mean haemoglobin concentration increased in both the groups, but the percentage increase was more in the TM-group(37.3% vs 27.3%)at 6 months follow up. Kriplani A et al (2006)[8] found that patients who were treated by tranexamic acid for three cycles showed a significant decrease in the PBAC score from 356.9 to 141.6, i.e. decline of 60.3%. SukanyaS et al (2005)[9] conducted a study on the role of tranexamic 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 tranexamic acid improved the PBAC score by 45.06%, while the combination of tranexamic acid and mefenamic acid improved the PBAC score by 55.41% after 6 months of follow up.

Fraser IS, McCarron G et al (1983)[10] studied Thirty-six women with menorrhagia were treated with mefenamic acid during all menstrual periods for more than 1 year. Significant reductions were seen in dysmenorrhea, headache, nausea, diarrhoea, depression, number of sanitary towels used, and number of mefenamic acid capsules taken (P less than .01).Andersch B & Rybo G et al (1988)[11]showed, although Tranexamic acid was generally more effective in reducing menstrual blood loss, Flurbiprofen provides an important therapeutic alternative to antifibrinolytic agents, especially in patients with concomitant dysmenorrhea.

In our study T-GROUP, 10 (13.33%) cases were relieved from dysmenorrhea after treatment while in TM-GROUP, 29 (38.66%) of cases were relieved from dysmenorrhea which was significantly higher in comparison to T- Group.

There is no study done till yet to see the improvement in Packed cell volume .But in our study in T-GROUP, improvement in Mean Packed cell volume concentration was 16.16% after 6 months of treatment, While in TM-GROUP, improvement in Mean Packed Cell volume Concentration was 21.98% which was significantly higher than T-Group (P<.01).

Conclusion

We conclude that Tranexamic acid alone or in combination with mefenamic acid, is effective in reducing menstrual blood loss, though combination therapy is more superior. Both these drugs are safe and increase the quality of life of women with heavy menstrual bleeding. This modality of treatment reduces hazards of hormone therapy as well as requirement of surgical treatment. We recommend this combination for reducing the severity of blood loss and dysmenorrhea which is associated with ovulatory DUB and for providing symptomatic improvement in the general health of the patients.

References

1. Alka Kriplani, Nutan Agrawal **.** Efficacy and safety of Ormeloxifene in management of menorrhagia: A pilot study© 2009 The Authors. Journal compilation © 2009 Japan Society of Obstetrics and Gynecology.
2. Edlund M et al. quality of life: a Sweedish survey of 2200 women with DUB. London Royal Society of Medicine Press 1994: 36-7.
3. Howkins and Bourne et al. Menorrhagia and Dysfunctional uterine bleeding. Shaw's Textbook of Gynecology. 13th edition. Page no.293.
4. BonnarJ , Sheppard BL, Dockeray CJ. The hemostatic system and DUB. Res Clin Forums 1983; 5:27-38.
5. Gleeson NC and Buggy F. The effect of tranexamic acid on measured menstrual blood loss and endometrial fibrinolytic enzymes in DUB. ActaObstetGynecolScand(1994);73:274-7.
6. Najam K, Agarwal LD, 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. 2010 October; (4) : 3020-3025.
7. Kriplani A. Kulshreshtha V, Agrawal N. ,Diwakar S. Role of tranexamic acid in management of dysfunctional uterine bleeding in comparison with medroxyprogesterone acetate. J ObstetGynaecol .2006;26(7):673-8.
8. Sukanya S, UnnopJ. Treatment of idiopathic menorrhagia with tranexamicacid . J Med Assoc Thai. 2005;8.
9. Fraser IS & McCarron G .Long-term treatment of menorrhagia with mefenamic acid.Obstet Gynecol. 1983 Jan;61(1):109-12.
10. Andersch B & Rybo G .Acta Obstet Gynecol Scand. 1988;67(7):645-8. An objective evaluation of flurbiprofen and tranexamic acid in the treatment of idiopathic menorrhagia.Department of Obstetrics and Gynecology, University of Göteborg, Sweden.