

Original Article

EFFICACY OF TRANEXAMIC ACID IN MENORRHAGIA IN COMPARISON TO NORETHISTERON

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Objective: To compare the efficacy of tranexamic acid with norethisterone in the management of menorrhagia.

Material & Methods: Total 66 patients were included in this study (33 patients randomly allocated to Group A and B).

Results: In group A and group B mean age was 33.12 ± 4.98 and 31.42 ± 5.47 years respectively. After management, number of towels used/day were reduced in group A and B and were 3.21 ± 0.65 , 2.85 ± 0.62 , 2.33 ± 0.54 , 2.21 ± 0.60 and 3.30 ± 0.88 , 3.15 ± 0.87 , 2.94 ± 1.03 , 2.85 ± 1.06 at one, two, three and six months follow-up respectively with significant difference between two groups ($p=0.002$). Passage of blood clots in group A and B at one, two, three and six months were reduced in patients 19 (57.5%), 19 (57.5%), 20 (60.6%), 23 (69.6%) and 10 (30.4%), 13 (39.4%), 12 (36.4%), 12 (36.4%) respectively ($p=0.0035$). Haemoglobin level in group A was 9.633 ± 0.946 g/dl at six months while in group B it was 9.385 ± 1.061 g/dl with insignificant result in both groups ($p=0.159$).

Conclusion: Tranexamic acid is more safe, effective and tolerable treatment than norethisterone for patients with ovulatory menorrhagia with avoidance of possibly unnecessary surgery.

Key Words: Menorrhagia, Tranexamic acid and Norethisterone.

Introduction

Menorrhagia (heavy periods) is defined as a blood loss of greater than 80 ml per period. It affects 30% of women in reproductive age. It results in 12% referrals to gynaecology clinics in whom 60% undergo hysterectomy.¹

Menorrhagia can be caused by fibroids, adenomyosis, intra-uterine contraception device usage and pelvic infections. Menorrhagia having no obvious pathology is defined as dysfunctional uterine bleeding (DUB).¹

Medical treatment, with avoidance of possibly unnecessary surgery, is an attractive treatment option.⁴ First line management of menorrhagia includes prostaglandin inhibitors (NSAIDs), anti-fibrinolytics (Tranexamic acid), oral contraceptive pills, high dose progestogens and progesterone intra-uterine system.²

Norethisterone (2nd generation progestogen) exerts its clinical effect by preventing endometrial proliferation. Its side effects (abdominal bloating, weight gain, breast tenderness), prolonged use and poor compliance as compared to tranexamic acid limit its use. Patients should be counseled so that compliance for medical therapy is enhanced.

Tranexamic acid (synthetic lysine derivative) controls menorrhagia by its anti-fibrinolytic effect and causes significant reduction of menstrual bleeding by 45-54%. Tranexamic acid is one of the

most effective agent in reducing menstrual bleeding as compared to norethisterone (17%).³ Although menorrhagia is very common problem but local evidence regarding its management is very scarce and requires extensive research to achieve valid figures.

This study was conducted to build up confidence over tranexamic acid by adding to data as it is cost effective, safe (having less side effects) and ideal for those who do not require contraception in comparison with norethisterone.

Material & Methods

After taking ethical committee's approval, patients were selected from outpatient department according to inclusion criteria and each patient was evaluated by detailed history (gynecological, medical and family) and examination (GPE, abdominal and pelvic). All patients in outpatient department fulfilling following criteria were included: age 25-30 years, having regular and heavy menstrual bleeding. Exclusion criteria were as follows: age above 40 years, having fibroids, endometrial polyps (on history, examination & ultrasound), intrauterine contraception device (history and examination), coagulation disorders (history and clinical record).

Informed written consent was taken. Benefits (cost effectiveness, acceptability) & side effects (nausea,

vomiting, weight gain) of drugs were explained. Patients were randomly divided into groups A and B by lottery method. 33 patients were included in group A and were advised to take oral tranexamic acid 500 mg three times a day from the 1st menstrual day to 5th day cyclically. Another 33 patients were included in group B and were advised to take oral norethisterone 5 mg three times a day starting from 5th menstrual day to 26th day cyclically. Each patient was counseled to take drugs regularly and advised to come in outpatient department every month. For proper follow up, the address and telephone numbers of patients were collected. Follow up was made monthly for first three months during therapy and then after three months. Observations regarding effectiveness in each group in terms of reduction in menstrual bleeding by decrease in number of towels / tampons used per day and decreased passage of clots from baseline were recorded. Haemoglobin estimation was done at the beginning and improvement at the end of therapy was observed.

Results

During observation, it was found that in both groups A and B, the mean age of women having menorrhagia was 32.27 ± 5.26 years (**Table-1**). In group A, mean age was 33.12 ± 4.98 while in group B,

it was 31.42 ± 5.47 years. Parity distribution revealed that most of the women in both groups were in the range of 4.24 ± 1.40 (**Table-1**). In group A, mean parity was 4.06 ± 1.39 and in group B, it was 4.42 ± 1.41 . While studying the distribution of cases by weight it was observed that in women having menorrhagia in both groups the mean weight was 64.33 ± 8.46 kg (**Table-1**). In group A, mean weight was 66.55 ± 8.00 while in group B, it was 62.12 ± 8.44 kg. As regards menstrual blood loss it was observed that mean number of pads used/day were 4.18 ± 0.85 in group A while in group B mean number of pads used/day were 3.82 ± 1.10 . The difference between two groups was insignificant ($p=0.069$) (**Table-2**).

After management, the number of pads used/day were reduced in group A from the baseline and were 3.21 ± 0.65 , 2.85 ± 0.62 , 2.33 ± 0.54 and 2.21 ± 0.60 at one, two, three and six months follow-ups respectively (**Table-3**).

In group B number of pads used/day were 3.30 ± 0.88 , 3.15 ± 0.87 , 2.94 ± 1.03 and 2.85 ± 1.06 at one, two, three and six months follow-up respectively. The difference between two groups at six months was significant ($p=0.002$). Passage of blood clots (menstrual history) was present in 25 patients (75.7%) in group A and 24 patients (72.7%) in group B. The difference between two groups was insignificant

Table-1: Age distribution of patients in both groups

Variables	Minium	Maximum	Mean	Std. Deviation
Age (years)	25	40	32.27	5.26
Parity	01	06	4.24	1.40
Weight (kg)	51	81	64.33	8.46

Table-2: Number of pads used per day.

Number of towels used/day	Group-A (Tranexamic acid)	Group-B (Norethisterone)	P-Value (1-sided)
Before Treatment	4.18 ± 0.85	3.82 ± 1.10	0.069
After one month	3.21 ± 0.65	3.30 ± 0.88	0.318
After two months	2.85 ± 0.62	3.1 ± 0.87	0.054
After three month	2.33 ± 0.54	2.94 ± 1.03	0.002
After six months	2.21 ± 0.60	2.85 ± 1.06	0.002

Table-3: Passage of blood clots before treatment.

Passage of blood clots	Group-A (Tranexamic acid)		Group-B (Norethisterone)	
Yes	25	75.7	24	72.7
No	08	24.3	09	27.3
Total	33	100.0	33	100.0

Table-4: Passage of blood clots after three months of treatment.

Passage of blood clots	Group-A (Tranexamic acid)		Group-B (Norethisterone)	
Yes	13	39.4	21	63.6
No	20	60.63	12	36.4
Total	33	100.0	33	100.0

Chi Square=3.882, df=1, p-value= 0.024

Table-5: Haemoglobin estimation.

Haemoglobin Estimation	Group-A (Tranexamic acid)	Group-B (Norethisterone)	P-Value (1-Sided)
Before Treatment	2.509±1.199	8.6±1.018	0.37
After Six Month	9.633±0.946	9.385±1.061	0.159

(P=0.389) (**Table-4**).

Passage of blood clots in group A at one, two, three and six months follow-up were decreased in patients 19 (57.5%) , 19 (57.5%) 20 (60.6%) and 23 (69.6%) respectively. While in group B passage of blood clots at one, two, three and six months follow-up were decreased in patients 10 (30.4%), 13 (39.4%), 12 (36.4%) and 12 (36.4%) (**Table-4**) respectively. The difference between two groups at six months was significant (p=0.0035). Haemoglobin level recorded at the start of treatment revealed that in group A level was 8.509±1.199 mg/dl while in group B level was 8.6±1.018 mg/dl. The difference between two groups was insignificant (p=0.37) (**Table-5**).

Haemoglobin level found in group A was 9.633±0.946 at six months while in group B it was 9.385±1.061mg/dl. The difference between two groups was found to be insignificant (p=0.159) (**Table-5**).

Discussion

During observation, this study confirmed that tranexamic acid is a safe and effective therapy in women with menorrhagia and is highly likely to decrease blood loss as compared to norethisterone.¹ Progestogens in form of oral norethisterone offer no advantage over other medical therapies such as danazol, tranexamic acid, non-steroidal anti-inflammatory drugs (NSAIDs) and the IUS in the treatment of ovulatory menorrhagia.

Excessively heavy menstrual bleeding (HMB) or menorrhagia is an important cause of ill health in women in developed world. Menorrhagia is socially embarrassing, physically incapacitating condition and has great financial burden. It is not a direct cause of death but it is the commonest cause of deterioration of women's health.² DUB is defined as excessive or prolonged and regular or irregular

bleeding, in the absence of any organic uterine pathology, endocrine or haematological disorder. Women's greatest attributes are rhythm, periodicity and pattern in her life, so are menstruation, conception and motherhood. In healthy woman, menstruation starts in approximately between the age of 12-14 yrs and persists throughout reproductive life.³ Excessive menstrual bleeding is one of the commonest complaint seen by family doctors and gynaecologists. It affects 10-30% of menstruating women at any one time yet nearly a third of all women consider their menstruation to be excessive. Menorrhagia accounts for 15% of gynaecological referrals and half of the 90,000 hysterectomies performed every year in the United Kingdom.⁴ It is estimated that the United Kingdom spends 800 million per year to treat females with menorrhagia and in a Swedish study 10% of working females were absent from duty because of excessive bleeding. The mechanisms controlling menstrual bleeding are poorly understood. Previous studies have shown increased endometrial fibrinolysis and change in prostaglandin balance.^{4,5}

Despite aggressive medical management, most women with menorrhagia unrelated to pregnancy and malignancy will eventually need surgery as it is the definite treatment. However, there continues to be a need for effective medical therapies for menorrhagia. The medical therapy includes non-hormonal therapy (anti-fibrinolytics, anti-prostaglandins & ethamsylate) and hormonal therapy (estrogens, progesterone & its derivatives, combined estrogen and progestogens).⁶ Surgical options include endometrial ablation of the first and second generation and hysterectomy.^{6,5} Concerns about the invasiveness of hysterectomy have lead to the development of minimal access surgery including endometrial resection/ablation. Due to less practice this technique is not considered

in our set up.⁷

Medical therapy, with avoidance of possibly unnecessary surgery, is an attractive alternative. However, there is continuous debate for effective medical therapy for menorrhagia.

The objective of this study was to compare the efficacy of tranexamic acid with norethisterone in the management of menorrhagia. During observation, it was found that most of the women with excessive bleeding were having mean age of 32.27 ± 5.26 years and mean parity was 4.24 ± 1.40 which is comparable to a study carried out by Neelam et al showing mean age and parity of 34.22 ± 8.82 years and 2.52 ± 1.31 .

Regarding weight distribution, it was found that mean weight in women having menorrhagia was 64.33 ± 8.46 kg. In a number of clinical studies carried out all over the world, it was observed that tranexamic acid reduced menstrual blood by 66.0%, 60.3% and 34-59% over 2-3 cycles which is comparable to 69.6% in this study.⁸

In our study, norethisterone was also advised and it reduced menstrual blood loss by 36.4% which is comparable to study results (17-20%) carried out in Beijing, China and Addenbrooke's hospital, Cambridge.¹¹

Gultekin et al¹² observed tranexamic acid reduced menstrual blood loss by 66%. This figure is very much close to our results i-e 69.6%.

Norethisterone reduced menstrual blood loss by 36.4% in our study which as compared to patients of Preston JT et al is a high figure. This low figure in patients of Preston might be due to difference in dose and duration of norethisterone intake. In this study norethisterone was taken 5 mg TDS from 5-26 days of menstrual cycle.

Bonnar J et al confirmed that tranexamic acid reduced blood loss by 54% in terms of significant reduction in the number of towels used/day and reduction of passage of clots after three cycles and remarkably after six cycles which is also comparable to our results (69.6%).¹¹

Reduction of menstrual bleeding was not observed by haemoglobin estimation after six months of treatment in both groups. Mean haemoglobin pre-treatment was 8.509 ± 1.99 gm/dl in group A while 8.6 ± 1.018 gm/dl in group B. After six months, haemoglobin level in group A was 9.633 ± 0.946 gm/dl and 9.385 ± 1.061 gm/dl in group B. The difference between two groups was insignificant ($p=0.159$).

Gultekin M et al, in their study, reported the role of tranexamic acid in the management of DUB and

observed that it reduced the menstrual blood loss by 66%.¹² The baseline haemoglobin in their study was 10.6 g/dl which increased to 12.1g/dl after three cycles of treatment with tranexamic acid. Similar improvements in mean haemoglobin levels after treatment with tranexamic acid have been observed by other researchers in their studies.¹³ This insignificant result in our study might be due to poverty, poor dietary habits, poor intake of iron supplementation and laboratory error. So this comparative study of tranexamic acid with norethisterone is in agreement with results of previous studies, quoted above. Although it was not as effective as intrauterine administration of levonorgestrel but the comparative studies, would help to further define the place of the drug in the treatment of menorrhagia. So it is considered first line treatment in patients with menorrhagia in whom hormonal treatment is contraindicated. Surgery remains the definite treatment option. Patients should be educated that hysterectomy has major socioeconomic costs & is not without complications; thereby compliance for medical therapy can be enhanced.

Conclusion

Over 90% of menstrual blood loss occurs during the first three days of menstruation both in normal menstruation and in menorrhagia. Treatment to reduce menstrual blood loss will have maximal effect if given during these days. Tranexamic acid is more safe, effective and tolerable treatment as compared to norethisterone for patients with ovulatory menorrhagia.

Norethisterone at this dose offers no advantage over the tranexamic acid. Patients should be offered effective drug treatment with tranexamic acid before deciding on surgical treatment.

In present study, there are certain limitations such as small number of patients, age limit 25-40 yrs; so further studies are needed to determine the most effective drug treatment for menorrhagia.

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