Original Article

Comparison of Tranexamic Acid and Norethisterone in the Treatment of Dysfunctional Uterine Bleeding with Menorrhagia

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Abstract

Objective: **Comparison of Efficacy of Tranexamic acid with Norethisterone in decreasing amount of menstrual blood loss and the frequency of side effects in the treatment of dysfunctional uterine bleeding with menorrhagia.**

Study design: **Randomized Controlled trial.**

Setting: **Obstetrics/Gynae Unit II, Holy Family Hospital. Rawalpindi.**

Duration of study: **15th May 2006 to 15th Nov 2006.**

Methodology: **Sixty patients were included in the study, who were selected by consecutive sampling and were divided into group A and B (random allocation) with 30 patients in each group receiving Norethisterone and Tranexamic acid respectively.**

Results: **The results showed that menstrual blood loss during the treatment cycles in terms of number of days of bleeding and number of pads used, were significantly reduced as compared to the cycles before treatment, in both Norethisterone (10.57±3.2 days before treatment to 8.0±1.84days after treatment) and Tranexamic acid groups (10.64±2.6days to 7.6±1.8days) with (p-value <0.01). However haemoglobin concentration assessed at the end of the treatment cycles had no statistically significant change as compared to haemoglobin at the start of the treatment. Frequency of side effects was more in Norethisterone group but it was not statistically significant.**

Conclusion: **In conclusion although both Tranexamic acid and Norethisterone are effective and safe drugs to be used in the treatment of patients having dysfunctional uterine bleeding with menorrhagia but the trend is more towards Tranexamic acid.**

Keywords: **dysfunctional uterine bleeding, menorrhagia, Tranexamic acid, Norethisterone.**

Introduction

Abnormal uterine bleeding is one of the most frequent gynaecological problems. Eighty percent of cases are due to hormonal disorders, called dysfunctional uterine bleeding (DUB).[1] Menorrhagia is the most common presentation of DUB.[2]

Menorrhagia due to DUB can be treated medically or surgically.[3] Medical treatment includes non steroidal anti inflammatory drugs, antifibrinolytics, oral contraceptive pills, progestogens, danazol (a synthetic androgen) and GnRH analogs.[4]

According to an article which reviews the available literature to compare the efficacy and tolerability of different medical treatments for menorrhagia, Tranexamic acid and Mefenamic acid are among the most effective first line drugs used to treat menorrhagia.[5]

Progestogens and oestrogens & progestogens in combination are already widely used in the management of irregular or excessive bleeding due to DUB but the regimen, dose and type of progestogens used varies widely with little consensus about the optimum treatment approach.[6]

Medical treatments are generally well tolerated, yet many patients complaining of heavy periods are treated surgically often without knowing the true magnitude of blood loss and sometimes without the trial of medical therapy.[7] Even if the medical therapy is chosen there is good evidence that many doctors do not necessarily prescribe the most effective treatments.[8] Despite the availability of a number of drugs, there is a lack of an evidence based approach, marked variations in practice and continuing uncertainty regarding the most appropriate therapy. Adverse effects and problems with compliance are also undermining the success of medical treatment.[5] As advanced medical and surgical options for DUB like progestogen containing intrauterine device MIRENA and endometrial ablation are not preferred options in our setup probably due to their high cost, most patients with DUB are either provided with inappropriate oral medical therapies or major surgical procedure i.e. hysterectomy, with its well defined morbidity and mortality.

Hence there is need for studies to evaluate different medical therapies, non-hormonal and hormonal, available in our setup, so that there is increased use of effective treatments which will provide an alternative to surgery.

Aim of this study is to evaluate the comparative efficacy of Tranexamic acid and Norethisterone in order to provide the patients with most appropriate /effective therapy and avoid inappropriate surgical interventions.

Methodology

Sample size: There were a total of 60 patients included in the study. This sample was divided into two groups with 30 patients in each group (random allocation by lottery method). Group A was called Norethisterone group in which patients had received Norethisterone orally and Group B was called Tranexamic acid group in which patients had received Tranexamic acid orally.

Sampling technique: Non probability consecutive sampling was done in this study.

The study was conducted in Obstetrics/Gynae Unit II, Holy Family Hospital, Rawalpindi.

The age of the patients included in this study ranged from 40 to 50 years, who had regular cycles, normal pelvic examination, had no hormonal therapy within the previous three months, no contraindication to the trial drugs and normal endometrium or showing simple hyperplasia or non specific endometritis as determined on histopathology.

The patients excluded from the study were taking oral contraceptives or anticoagulants, fitted with an intrauterine device, having known hepatic impairment, inflammatory bowel disease, endocrine disorder and all other causes of anaemia except iron deficiency anaemia, having irregular cycles, complex or atypical hyperplasia or carcinoma endometrium.

After an informed and written consent, patients were recruited from out-patients department after taking detailed history and a clinical examination. Data was recorded on a specially designed Proforma. Previous record of number of days of bleeding and the number of pads used by the patients was noted. Their haematological status was determined by assessing the haemoglobin concentration in gm/dl. Patients were treated in two groups on alternate basis either with Tranexamic acid or with Norethisterone.

Treatment Protocol: Norethisterone acetate, 5mg tablets were given orally three times a day continuously for 21 days, after that the patients had an interval of 7 days for withdrawal bleeding and then repeated the same regimen for the next two cycles. Tranexamic acid capsules of 500 mg were given orally three times a day only during the days of bleeding in each cycle. (Maximum dose of 4gms per day was used).

The patients of both groups were asked to maintain a menstrual calendar showing the days of bleeding, and they were also asked to count the pads used each month. The number of days of vaginal bleeding and the number of pads used were documented. Patients were asked to report back to hospital in case of heavy or continuous bleeding or any intolerable side effect in which case treatment could be abandoned. Frequency of side effects like breakthrough bleeding, headache, nausea, vomiting and itching was noted in each group. After three months treatment the haematological status of the patients was assessed again and recorded. According to the results of the treatment, patients were offered either to continue the same treatment or to shift over to another treatment for menorrhagia.

Data Analysis: Mean and standard deviation were calculated for age, number of days of bleeding, number of pads used by the patients and haemoglobin concentration. These parameters before and after the treatment cycles were compared in both the groups separately each month and then collectively after three months by using paired t-test. These parameters of either group were also compared with each other in all the three months separately as well as collectively by using independent t-test. Frequency of side effects was calculated and compared using chi-square test between group-A and group-B. The significant level had been assigned to p-value <0.05. All data was analyzed by using SPSS version 10.0.

Results

Mean age of women in both the groups was 43 years. Two patients in Tranexamic acid group and two in Norethisterone group were lost to follow up.

Number of days of bleeding after using Tranexamic

Table I. Number of days of bleeding (Mean ± SD)

Groups	Before treatment	During 1st month of treatment	During 2nd month of treatment	During 3rd month of treatment
Norethisterone group (group-A)	10.57±3.2	7.82±1.8	8.53±2.3	7.85±1.7
Tranexamic acid group (group-B)	10.64±2.6	7.96±1.7	7.5±2.2	7.2±2.1

Table II. Number of pads used by the patient (Mean ± SD)

Groups	Before treatment	During 1st month of treatment	During 2nd month of treatment	During 3rd month of treatment
Norethisterone group	5.8±1.3	4.7±1.6	4.5±1.7	4.4±1.9
Tranexamic acid group	5.57±1.4	3.5±1.1	3.11±1.7	2.85±1.4

acid was reduced in a sustained fashion while in case of Norethisterone, decrease in number of days was not sustained (Table I). The reduction in the number of days of bleeding during treatment months when compared to that before the treatment was statistically significant in both the groups ($p<0.05$).

When the amount of bleeding in terms of number of pads used by the patients before and during treatment was compared, both the groups showed significant reduction in the number of pads used ($p<0.05$) (Table II). Although the effect of both drugs was uniform in decreasing the number of pads used, the effect of Tranexamic acid was more abrupt and sustained as compared to Norethisterone.

When the amount of blood loss in terms of haemoglobin concentration at the start and end of treatment was compared in both groups, it showed no statistically significant difference (Table III). Tranexamic acid showed positive effect in raising mean haemoglobin, though this effect did not reach statistical significance, (p-value 0.453). Mean haemoglobin level rather declined in women receiving Norethisterone.

Table III. Haemoglobin concentration (gm/dl)

Groups	At the start of treatment Mean ± SD	At the end of treatment Mean ± SD	P Value
Norethisterone group	10.11±1.2	9.9±1.0	0.124
Tranexamic acid group	10.10±1.4	10.20±0.99	0.453

Considering different side effects observed in the two groups of drugs, the breakthrough bleeding was significantly more ($p<0.05$) in the patients receiving Norethisterone as compared to their counterparts.

Headache was reported by 6.7 % of patients receiving Norethisterone, but no patient receiving Tranexamic acid complained of headache. Nausea was reported by 10 % of patients receiving Tranexamic acid and no patient receiving Norethisterone had noticed this. Vomiting and itching was not reported by any patient in any group.

Discussion

According to the results of this study, the amount of bleeding in terms of number of days of bleeding and the number of pads used by the patients was significantly reduced in both the groups. According to a meta analysis there were seven randomized controlled trials on Antifibrinolytics for heavy menstrual bleeding which were reviewed, they have shown that Antifibrinolytics used in heavy menstrual bleeding significantly reduced objectively measured menstrual blood loss when compared to placebo or other medical therapies (NSAIDS, oral luteal phase progestogens and ethamsylate).[9] Other studies have also shown that oral tranexamic acid is a reasonable treatment option for patients with excessive dysfunctional peri-menopausal bleeding.[10,11] Statistically significant reduction in blood loss by using

Tranexamic acid is also reported in another study done by Preston and Cameron in 1995.[7] They used Tranexamic acid 1gm four times daily for 1 to 4 days of menstruation and compared it with luteal phase Norethisterone, and showed 45% decrease in menstrual blood loss in Tranexamic acid group and 20% decrease in blood loss in patients receiving Norethisterone in luteal phase. 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.[12] In 1996 Bonnar and Sheppard [13] used Tranexamic acid in the dosage of 1 gm 4 times a day and compared it with ethamsylate and Mefenamic acid and found that Tranexamic acid reduced the blood loss by 54% (mean blood loss 164 ml before treatment and 75 ml during treatment),sanitary towel usage was significantly reduced in patients treated with Mefenamic acid and Tranexamic acid. In contrast to these studies we used Tranexamic acid in lesser dosages i.e. 500 mg three times a day for the days of bleeding, and achieved statistically significant reduction in blood loss which shows that Tranexamic acid is equally effective in lesser dosages also.

Significant blood reduction was achieved also by Norethisterone treatment in our study. According to Cochrane Database System Rev.2000 regarding Progesterone/Progestogen releasing systems versus either placebo or any other medication for heavy menstrual bleeding showed that there was only one trial[14] using Norethisterone, in a similar dosage and duration as used in our study, and found large reduction of blood loss from the baseline. In another nonrandomized trial in which oral Norethisterone is used as 5mg three times daily from day 5 to 26 of the cycle menstrual blood loss was also reduced to <80 ml in seven women with regular ovulatory cycles.[15] We found no trial which compared Tranexamic acid with long course of Norethisterone i.e. from day 5 to 25 of the cycle. We used Norethisterone for 21 days and achieved results comparable to that of one trial[7] in which norethisterone was used only during luteal phase. According to another study luteal phase Norethisterone is strongly proven to be ineffective in treating menorrhagia.[16]

Although comparison of both the groups in terms of number of days of bleeding has proved no statistically significant difference but in view of convenience by taking tranexamic acid only during menstrual phase and not for 21 days as in norethisterone, the trend is more towards the effectiveness of Tranexamic acid. Also the decrease in the number of days of bleeding is more smooth and sustained in patients treated with Tranexamic acid as compared to Norethisterone, which also goes in favor of Tranexamic acid group.

Kriplani et al. compared Tranexamic acid to medroxyprogesterone acetate in a prospective randomized study using Tranexamic acid in a dosage of 2 gm per day and found significant decrease in blood loss in both the groups but no remarkable difference between the two in reducing blood loss.[17]

Regarding the side effects of these drugs we found that breakthrough bleeding was significantly more in Norethisterone group as this side effect is peculiar to the hormonal therapy only. Among other side effects 6.7% of patients in Norethisterone group experienced headache and nausea while this was seen in 10 % of patients in Tranexamic acid group. No patient complained of itching or vomiting in either group. A study comparing Tranexamic acid with luteal phase Norethisterone showed that headache was experienced by 32% of patients in Tranexamic acid and 48% of patients in Norethisterone groups. Gastrointestinal symptoms were

present in 12% of Tranexamic acid group and 33% of Norethisterone group.[7] Wellington and Wagstaff reviewed the use of Tranexamic acid in menorrhagia and showed that the most commonly reported drug-related adverse events were gastrointestinal in nature.[12] The total incidence of nausea, vomiting, diarrhoea and dyspepsia in a double-blind study was 12% in patients who received Tranexamic acid 1g four times daily for 4 days for two cycles (not significantly different to the incidence in placebo recipients.[11] We used Tranexamic acid in less dosage as compared to these studies and achieved less side effect profile as well. Lethaby et.al in 2002 compared long and short duration cyclical progestogens and found that 21 day progestogens are better in reducing blood loss but less acceptable due to their side effects.[18] The side effects in progesterone group were comparable to Tranexamic acid group in our study probably because of small study size.

Conclusion

Tranexamic acid and Norethisterone both are effective in reducing objectively measured menstrual blood loss when used in appropriate dosage and duration. Although there is no statistically significant difference in the reduction of blood loss between the two drugs but the trend is more in favour of Tranexamic acid in reducing blood loss and that too with the dosages used as well as in the side effect profile. Tranexamic acid is thus equally effective in less dosage. There is paucity of trials comparing these modalities of treatment worldwide and also in our setup. Therefore it is suggested that in our setup where modern conservative surgical options are not widely available, medical therapies should be assessed in randomized controlled trails so that inappropriate radical surgical interventions can be avoided.

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