IJBPAS, February, 2015, 4(2): 267-274

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

COMPARING THE EFFECTS OF MEFENAMIC ACID AND TRANEXAMIC ACID IN TREATING MENORRHAGIA

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ABSTRACT

Menorrhagia as one of the most commonly expressed complaints of women at reproductive age leads to anemia and its complications. This study compares the efficacy and acceptability of Tranexamic acid with Mefenamic acid in treating menorrhagia in order to show the most effective, and at the same time, the most acceptable drug for Iranians.

During 2012-2013,60 patients, aged 15-49, with menorrhagia who referred to Ayatollah Taleghani hospital in Tehran, Iran, were randomly divided into 2 thirty-patient groups. The first group received Mefenamic acid cap and the other received Tranexamic acid cap during the first three days of their period for 2 subsequent cycles; following that, their bleeding changes were evaluated.

Repeated Measures ANOVA analysis pointed out that while the decreasing pattern of bleeding for each drug was statistically significant (P value =0 /001), the difference between the decreasing pattern of bleeding resulted from the use of the two drugs was not significant (p=0/059).Both groups depicted the same level of satisfaction (p=0/079) and no serious complications were reported.

The efficacy of Mefenamic acid and Teranexamic acid in treating menorrhagia was the same for both groups.

ClinicalTrials.gov/IRCT 2013011912190N1

Keywords: Menorrhagia – Mefenamic acid- Tranexamic acid

INTRODUCTION

Menorrhagia is one of the most commonly expressed complaints for which approximately five percent of 30 – 49- year-old women consult the doctors yearly **[1]**. The upper limit of monthly bleeding is 80ml per cycle, which is 2 standard deviation from the mean. (Mean menstrual bleeding per cycle is 36 – 52/7 ml) **[2]**. Menorrhagia happens when there is an increase in menstrual bleeding in multi regular subsequent cycles or the time the bleeding duration rises to more than 7 days **[3]**. Most of the patients who complain of menorrhagia have no known organic diseases and have normal physical examinations, laboratory tests and imaging (sonography) results **[4]**. Menorrhagia, if repeated, causes a decrease in Iron reserve and anemia and Subsequently, anemia causes mental and cardiac complications and dysfunction in other organs. So paying attention to menorrhagia and its treatment can lead to lower morbidity in reproductive aged women. It is worth noticing that most of the iron deficient anemia morbidities are the result of more than 60ml bleeding per cycle **[5]**. The evaluation of the actual bleeding volume is not an easy task because women's evaluation of their own bleeding volume is not reliable. 25 percent of the women who consider their bleeding level as high had menstrual bleeding less than 35ml **[6]**. The estimation of blood loss volume was done based on the number of pads or tampons soaking per day or per cycle. The patient's estimations of the bleeding volumes are not accurate and reliable because they are not well aware of the normal range of bleeding and their evaluations are inexact **[7]**. Although Janssen and colleagues (1995) take low Hb as a good sign of menorrhagia, there might be normal Hb patients with menorrhagia .So it is not an ideal screening test **[8]**. All of the techniques used for menorrhagia research purposes are difficult and clinically impractical. Examples are Alkalin Haematin test and Radio Isotop techniques. So, we need an accurate method of estimating the blood loss which is clinically applicable. In this way treatment without indication is prevented. In this study a pictorial chart for the evaluation of menorrhagia was designed. This chart showed high clinical accuracy and its application was feasible. Worldwide use of hormonal therapy is based on the wrong assumption that menorrhagia happens because of imbalance in hormones and an ovulatory cycles, but the fact is most of the women with abnormal bleeding show no evidence of hormonal imbalance and based on some studies 95 percent have regular ovulatory cycles **[9]**. The

mechanisms of controlling menstrual bleeding are poorly understood. In the past decades, studies had shown that the increase in endometrial fibrinolysis and an imbalance in Prostaglandin caused functional uterine bleeding **[10]**. Tranexamic acid (250mg oral capsule) which isa synthetic amino acid was introduced in Sweden as Cyclokapron® in 1969 and has since been used in order to decrease menstrual blood loss. It's anti fibrinolytic effects are achieved by preventing the Plasminogen from binding to fibrin filaments and so it prevents clot dissolution. Mefenamic acid is an NSAID and exerts its anti-prostaglandin effects by inhibiting prostaglandin synthesis, so it balances prostaglandins and decreases menstrual bleeding. Anti fibrinoletic drugs such as Tranexamic acid and anti-prostaglandin drugs such as Mefenamic acid are preferred to hormonal drugs the time the contraception is not a goal, as they are used only during menstrual period. Although several studies have evaluated and compared the effects of Mefenamic acid and Tranexamic acid and compared their effects with each other and on other drugs, so far no specific study has compared the effects of these two drugs on the treatment of menorrhagia in Iranian women to show which one must be preferred as the first choice.

METHODOLOGY

This study was a single-blind clinical trial that was approved by Ethics Committee of Shahid Beheshti University of Medical Science. During 2012-2013, 60 patients, aged 15-49 suffering from menorrhagia that referred to Gynecology clinic of Taleghani Hospital in Tehran, Iran were enrolled. Organic causes of menorrhagia were excluded by gynecological examination, sonography, endometrial biopsy and a cervical smear test and patients with a history of renal or hepatic impairment; previous thromboembolic disease, peptic ulcer and coagulation disorders were not enrolled. The entire patient signed the informed consent form. In order to estimate the volume of blood loss, a pictorial chart was designed in which standard sanitary pads were stained with different amounts of bloodand their photos were printed as a chart. The patients who complained about heavy or long menstrual bleeding periods were observed for one cycle. First they were taught how to mark the pictorial charts (They were needed to mark the type and the number of the pads used during their menstrual bleeding periods), then 60 patients with more than 80ml menstrual bleeding or those who had experienced menstrual duration for more than 7 days were selected and divided into two groups (A & B) randomly. Group A took 2

Tranexamic acid capsules and group B received 2 Mefenamic acid capsules three times a day during the first three days of menstruation. Patients were asked to mark the charts during menses for 2 treatment cycles and one cycle after discontinuation. Completion of the forms based on the patients' marking of the charts was performed by a person who had no knowledge about the type of the drug used by the patients. Then SPSS software (11th edition) was used for data analysis. Ultimately, Repeated Measure ANOVA and Paired T Test were used for comprehensive analysis.

RESULTS

Before this study, the mean of menstrual bleeding volume in group A patients (who received Tranexamic acid) was 166.35 ml and in Mefenamic acid group (group B) it was 146.52ml. After the first and second cycles of treatment, it reduced to 122.12 and85.77 ml in group A patients and 111.09 and 85 ml in group B patients. So, the reduction of bleeding volume after the two cycles of treatment was 102.88mlfor group A and72.39ml for group B. Although the difference between the two groups was 30ml, T test evaluation showed that it was not statistically meaningful. The bleeding volume in the first cycle following the treatment was 63.46 for group A and 74.13 for group B.

Repeated Measures ANOVA shows that the decline of bleeding volume for each drug was statistically meaningful (p-value= 0/001).Paired T test pointed out that the decreasing pattern of bleeding volume was statistically meaningful for both drugs (**Figure 1**).

Bleeding duration for Tranexamic acid group before and after the treatment was 9.68 and 7.28 days and for Mefenamic acid was 7.87 and 6.65 days respectively. This decline is statistically meaningful (p-value<0/001).The difference between decreased days of bleeding for the two groups was 1/18 days. T-test evaluation pointed out that the difference was not statistically meaningful **(Figure 3)**.

70% of the patients in group A and 43.3% in group B were completely satisfied with the treatment. Although 70% of the patients in group A declared that they would choose the drug if the problem recurs, only 50% of group B patients made such a remark. The difference in the level of satisfaction between the two groups was not significant (chi square=5.081, df=2 and p=0.079). 20 patients belonging to group A and 24 patient from group B reported no complications. In group A, Vertigo was the most common complication which 5 patients suffered and in group B 3 patients had dyspepsia and 2 patients complained about epigastric pain.

Table 1: The mean of bleeding volume during and after the administration of Mefenamic acid and Tranexamic acid

Treatment		Mean	Std. Deviation
Mefenamic acid	Bleeding Before	146.52	51.133
	First Visit bleeding	111.09	56.002
	Second Visit bleeding	85.00	32.369
	Bleeding After	74.13	30.993
Tranexamic acid	Bleeding Before	166.35	52.375
	First Visit bleeding	122.12	50.974
	Second Visit bleeding	85.77	48.347
	Bleeding After	63.46	36.763

Table 2: Comparison of mean difference of bleeding & its duration before & after usage of both drugs

			Mean	Std. Deviation	Pvalue
Mefenamic acid	Pair 1	Bleeding Before – bleeding After	72.391	53.553	< 0.001
	Pair 2	Duration Before – during After	1.217	1.953	0.007
Tranexamic acid	Pair 1	Bleeding Before – bleeding After	102.885	56.146	< 0.001
	Pair 2	Duration Before – during After	2.400	3.096	0.001

DISCUSSION

It is worth mentioning that Tranexamic acid is a synthetically derivative of Lysin amino acid which does its anti fibrinolytic effect through reversible block of Lysin-attach sites on plasminogen molecules. So the drug inhibits plasminogen to plasmin change and prevents fibrinolysis and lysis of blood clotting **[11]**. Tranexamic acid, only in the form of 250mg-capsule, is available in the market. It is well tolerated and has few side effects such as mild gastrointestinal complications, as reported by this study. Earlier theoretical concerns about thromboembolism due to anti fibrin lytic action of Tranexamic acid have been refuted by longitudinal studies. For example Rybo (1991) reported that during 1969 to 1987 the rate of thromboembolism in women suffering from menorrhagia was the same as normal individuals. Prostaglandin imbalance plays an important role in menorrhagia; So Mefenamic acid in the form of 250mg-capsule which inhibits prostaglandin synthesis, is used to control menorrhagia. In this study, we observed a good therapeutic effect with Tranexamic acid and Mefenamic acid .It is in favor of meta-analysis of 7 studies **[12]**, which showed more than 45% reduction in menstrual bleeding volume with Tranexamic acid treatment. Sukanya Sirnil and colleagues published an article in 2005. They treated40 menorrhagia women with Tranexamic acid

capsule 1gr every 8 hours in the first five days of period. This led to 49% decrease in bleeding volume with no change in menstrual duration **[13]**. In another study, Tranexamic acid decreased blood loss by 44%.Compared to Mefenamic acid, its effect was more but it was equal to progesterone, especially progesterone IUDs **[14]**. A similar study was conducted at Shahid Sodughi university of Yazd in 2001-2005. 75 women were treated in the first five days of their mens in 3 subsequent cycles.36 patients received Mefenamic acid 500mg every 8 hours and 39 patients took Tranexamic acid 500mg every 6 hours. Mefenamic acid decreased bleeding by 20% and Tranexamic acid by 50% and it was concluded that patients with abnormal bleeding should take Tranexamic acid therapy before surgery **[15]**. Tranexamic acid at a dose higher than the dose routinely used for preventing plasmin formation, inhibits plasmin activity directly **[16]**. It seems that the higher dose, used in some studies, justifies the better effect of Tranexamic acid. This is the effect which was not observed in our study, as both drugs were effective to the same extent. In research studies, the gold standard of measuring menstrual blood loss is the Alkaline Haematin test **[5]** but it is expensive and time consuming. The use of pictorial blood charts designed in this study seems to be a precise and simple method which does not require the collection of bloody pads. Methodological limitation of this study is the small sample size. Randomized double blind control trials with large numbers of patients are needed to compare the two drugs with each other and with other drugs.

ACKNOWLEDGEMENTS

The authors are grateful to all menorrhagic women who came to our center, for their excellent cooperation. We are also very grateful to Shahid Beheshti Gynecology Department for providing the grant of this study.

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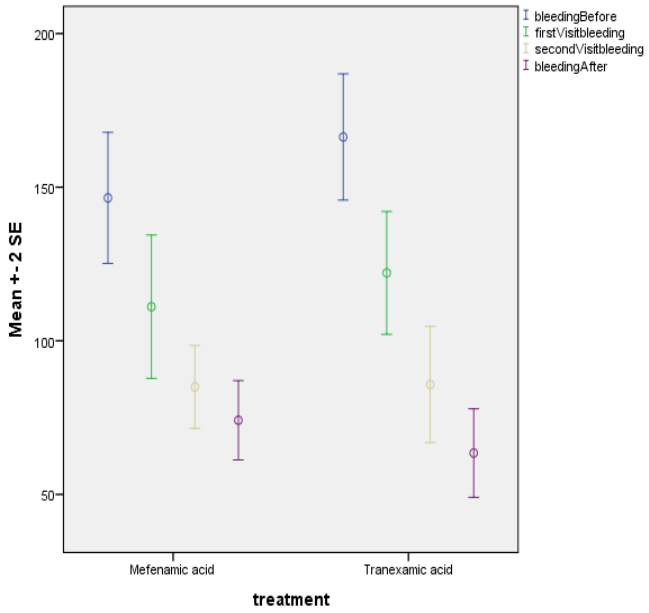

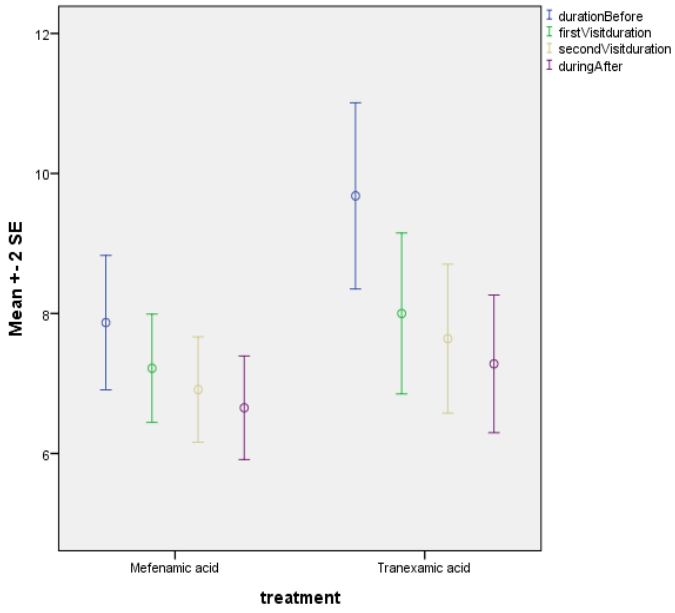

Figure 1 & 2: The standard error of means of bleeding volume during and after the administration of Mefenamic acid and Tranexamic acid

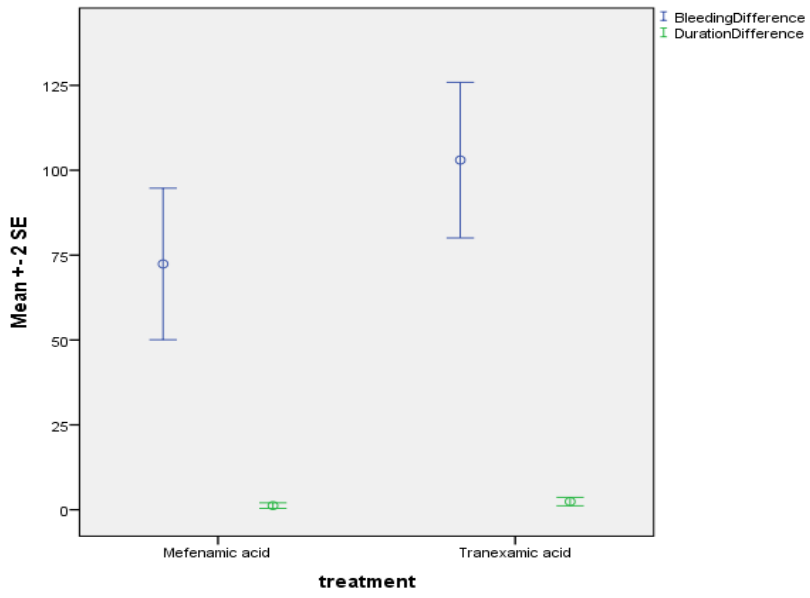

Figure 3: Standard error of means difference of bleeding & duration of it before & after usage of both drugs