

# Comparing the Effects of Tranexamic Acid and Mefenamic Acid in IUD-induced Menorrhagia: Randomized Controlled Trial

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## ABSTRACT

### Background

Intrauterine device (IUD) is a safe and efficient method for preventing pregnancy favored by many women. Menorrhagia is the most common complication of using copper IUD. We aimed to compare the effect of tranexamic acid and mefenamic acid on the reduction of copper IUD-induced menorrhagia.

### Methods

In this randomized controlled trial, 84 women who were using IUD (TCu-380) with complaints of menorrhagia were randomly divided into two equal groups (mefenamic acid and tranexamic acid). The pictorial blood assessment chart (PBAC) was used to measure their bleeding rate. These groups used the capsules in two consecutive cycles and PBAC chart was completed for the samples in three consecutive cycles. The results were analyzed using statistical tests and SPSS software.

### Results

Tranexamic acid significantly reduced the amount of bleeding compared with mefenamic acid in the first cycle ( $P<0.05$ ). A significant difference was seen in mean bleeding days in the two groups before and after treatment during the first month ( $P<0.05$ ). In the second cycle, both drug treatments were equally influential on the reduction of bleeding days and decreased the bleeding period. In both groups, a significant difference was observed between the first and second cycles of treatment ( $P<0.05$ ).

### Conclusion

Treating IUD-induced menorrhagia (TCU380) using tranexamic acid was more effective than mefenamic acid in emergency setting for reducing bleeding days and amount of bleeding. Also, it had faster treatment effects in decreasing the amount and number of bleeding days.

**Trial Registration Number:** IRCT201205092515N8

**KEYWORDS:** IUD; Menorrhagia; Mefenamic Acid; Tranexamic Acid

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## INTRODUCTION

Rapid population growth in the recent century has become a threat for human life. In today's modern society, voluntary control of fertility is very important.<sup>1</sup> Implementing family planning programs in countries with rapid population growth has reduced deaths of mothers and children by 32% and almost 10%, respectively.<sup>2</sup> Among the contraceptive methods, IUD is a safe one with failure rate of below 1%,<sup>3</sup> which is approximately equal to tubal sterilization.<sup>1</sup> More than 100 million women around the world use this device.<sup>4</sup> The most common complication of using IUD includes increased bleeding and cramps.<sup>5</sup> Also, bleeding may be to the extent that leads to iron deficiency anemia.<sup>6</sup> Therefore, increased amounts of bleeding have a great impact on the lives of many women.<sup>7</sup>

Menorrhagia is a debilitating problem that involves a large group of women and their doctors. Among women 30-49 years of age, 1 out of every 20 women refers with menorrhagia and about 30% of the women report that 10-15% of their menorrhagia was caused by IUDs.<sup>1</sup> To treat menorrhagia, nonsteroidal anti-inflammatory drugs, progesterone, danazol, GnRH agonists and antifibrinolytic drugs can be used.<sup>8</sup> Non-hormonal Hemostatic medicines are divided into two groups of non-steroidal anti-inflammatory and antifibrinolytic ones. In the non-steroidal anti-inflammatory group, mefenamic acid is widely applied.<sup>9</sup> Also, it is used in treating the bleeding and cramps after planting IUD (TCu-380).<sup>10</sup> In treating such bleedings, antifibrinolytic agents are more influential.<sup>11</sup> Tranexamic acid is the best option for those who suffer from irregular uterine bleeding and plan to become pregnant in the near future.<sup>12</sup>

Considering that no similar studies have been done in Iran, we aimed to compare the effects of tranexamic acid and mefenamic acid in preventing menorrhagia and present a suitable solution for IUD (TCu-380) users in order to increase its durability and maximize its benefits.

## MATERIALS AND METHODS

This study was a randomized controlled trial conducted during 2012 at health clinics of Bandar Abbas, southern Iran. The studied samples included 84 women using IUD (TCu-380) with complaints of severe menstrual bleeding. After obtaining the approval of the Research Deputy of Shiraz University of Medical Sciences and receiving the ethics code from the Ethics Committee, the research objectives and methods were explained to the women who were qualified to enter the study and their written consents were obtained, as well.

After receiving their medical history and before entering the study, the samples were evaluated by PT, PTT and CBC tests to reject possibilities of coagulation disorders and severe anemia. They were also evaluated by sonography to reject having intrauterine organic lesions. The patients with liver and renal disorders, moderate and severe anemia, Chlamydia infection, endometrial abscission, thromboembolic and coagulation problems were not included in the study. Women who had used other methods of contraception, tranexamic acid or mefenamic acid were excluded. Women who used IUD (TCu-380) and had confirmed menorrhagia were enrolled in our study.

To recognize IUD-induced menorrhagia, the women were given standard pads with the same size and shape and asked to use them in their next bleeding cycle. In order to measure their bleeding rate we used the pictorial blood assessment chart (PBAC). PBAC is an objective and suitable criterion for measuring the amount of bleeding.<sup>13</sup> This method showed good association for percentage change in blood (Intraclass Correlation Coefficient [ICC] of 0.86, 95% CI, 0.80-0.91) with a sensitivity and specificity of 96 and 92%, respectively.<sup>14</sup> However, Sometimes there were some inadequacies and inaccuracies in the assessment of large volume loss and extraneous blood loss.<sup>15</sup> The researcher tried to solve the problem by showing PBAC to the women. Then, the women were asked about the pads which were

used during their 7 day bleeding cycle. Based on the PBAC chart, the pads were described as “a little wet”, “semi-wet” and “completely wet” and shown to the women. The pads’ degrees of wetness were scored as follows: less than half=1, half or more=5, and completely wet=20 (table 1). Those who scored higher than 100 in the 7-day cycle were determined to have menorrhagia without organic causes.

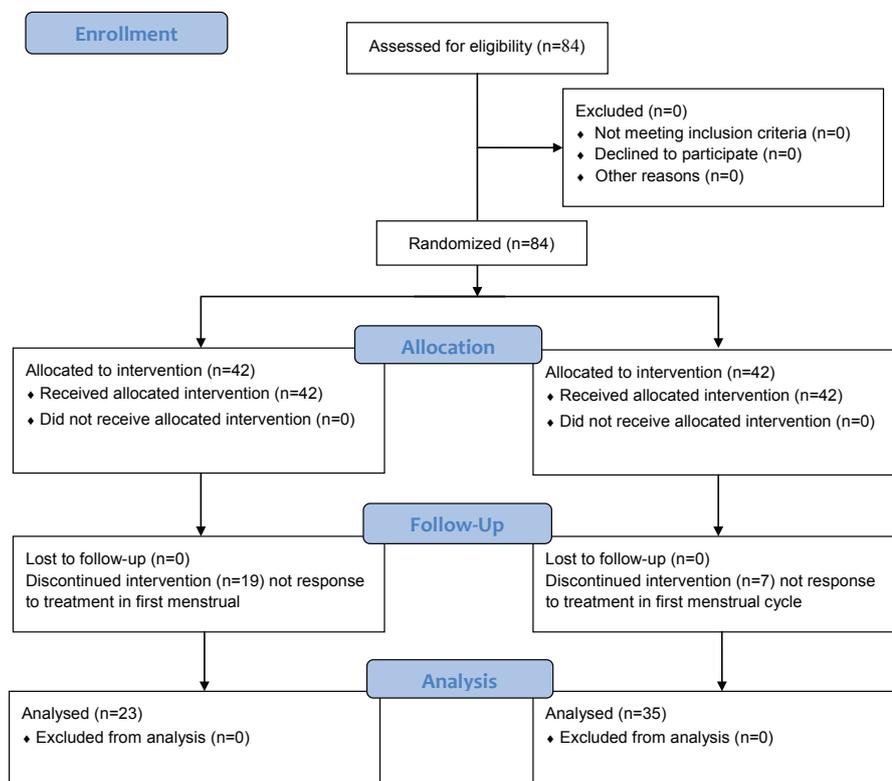
Women with menorrhagia were randomly divided into two experimental groups; 42

and women were put in the group receiving oral capsules containing 250 mg mefenamic acid (Iran daroo, Iran) and 42 were assigned to the group of oral capsules containing 250 mg tranexamic acid (Iran daroo, Iran). Randomization was done, as follows: the women were asked to choose one number from 1 to 84; the women who selected 42 and less received tranexamic acid capsules and mefenamic acid were given to those with higher than 42 (figure 1).

**Table1:** Pictorial blood assessment chart

| PBAC      |  |
|-----------|--|
| TOWELS    |  |
| 1 point   | For each lightly stained towel                   |
| 5 points  | For each moderately soiled towel                 |
| 20 points | If the towel is completely saturated with blood  |
| TAMPONS   |  |
| 1 point   | For each lightly stained tampon                  |
| 5 points  | For each moderately soiled tampon                |
| 20 points | If the tampon is completely saturated with blood |
| CLOTS     |  |
| 1 point   | For small clot                                   |
| 5 points  | For large clot                                   |

**CONSORT Flow Diagram**



**Figure 1:** Design and protocol of the study.

Both groups were briefed about possible complications and the method of consumption. In the next bleeding cycle, the women were asked to use one capsule every 8 hours on the first 3 days of menstruation and come to the clinic on the final days in order to fill in the PBAC chart for checking the effects of the medication on bleeding. Only women who were treated in first cycle could participate in second cycle. The PBAC chart was completed for them in the second cycle and the women were asked about other possible complications. In the third bleeding cycle, the women who had responded to the treatment in their first cycle were asked to repeat the same dose of medicine in their next cycle. Then, the chart was completed for the third time and number of bleeding days before and after the first and second cycles of treatment were asked.

For every person, personal characteristics, results of examination and tests and treatment type were collected using questionnaires. The obtained data were analyzed using SPSS software, version 16. Descriptive statistics, frequency distribution tables and repeated measurement, paired-sample and independent-sample *t* tests

were used as appropriated.

**RESULTS**

The studied samples included 84 women using IUD (TCu-380). After one month 7 women in the tranexamic acid group and 19 women in the mefenamic acid group who did not response to treatment in first menstrual cycle, were excluded.

The mean±SD age of the women was 27.3±5.14 years and the mean number of children in both groups was more than one. For each group, the mean duration of IUD planting was less than 3 months and the groups did not differ significantly in this regard. In both groups, the women’s mean score in PBAC before treatment was higher than 100. We found a significant difference between the amount of bleeding before treatment and after the first cycle in both treatment groups (P=0.0001, P=0.0003, table 2).

No significant difference was seen between the two experimental groups with respect to the amount of bleeding in the first and second cycles (table 3). However, the mean days of bleeding differed significantly before

**Table 2:** Comparing the amount and mean days of bleeding in Tranexamic acid and Mefenamic acid groups; before treatment and first cycle of treatment

| Drug         | Sample number   | Mean score PBAC and days |                     | P value       |        |
|--------------|-----------------|--------------------------|---------------------|---------------|--------|
|              |                 | Before treatment mean±SD | First cycle mean±SD |               |        |
| *Amount PBAC | Tranexamic acid | 42                       | 155.38±51.61        | 69.31±36.68   | 0.0001 |
|              | Mefenamic acid  | 42                       | 184.62±100.902      | 105.02±78.242 | 0.0003 |
| **mean days  | Tranexamic acid | 42                       | 8.33±1.28           | 6.26±1.17     | 0.0001 |
|              | Mefenamic acid  | 42                       | 8.50±1.25           | 0.92 ±6.30    | 0.0009 |

\*Comparing the amount of bleeding in Tranexamic acid and Mefenamic acid groups before treatment and first cycle of treatment; \*\*comparing the mean days of bleeding in tranexamic acid and mefenamic acid groups; Before treatment and first cycle of treatment

**Table 3:** Comparing the bleeding amount and mean days of bleeding between the first and second cycles in both tranexamic acid and mefenamic acid groups

| Drug         | Sample number   | Mean score PBAC and days |                      | P value     |       |
|--------------|-----------------|--------------------------|----------------------|-------------|-------|
|              |                 | First cycle mean±SD      | Second cycle mean±SD |             |       |
| *Amount PBAC | Tranexamic acid | 35                       | 57±23.38             | 68.62±44.90 | 0.63  |
|              | Mefenamic acid  | 23                       | 55.83±23.71          | 60.43±20.38 | 0.60  |
| **Mean days  | Tranexamic acid | 35                       | 6.02±0.78            | 6.42±0.77   | 0.002 |
|              | Mefenamic acid  | 23                       | 5.65±0.71            | 6.47±0.59   | 0.001 |

\*Comparison of bleeding amount between the first and second cycles in both tranexamic acid and mefenamic acid groups; \*\*Comparison of bleeding days in tranexamic acid and mefenamic acid groups at first and second cycle of treatment

and after treatment in both groups ( $P=0.001$ ,  $P=0.002$ , table 3).

Comparing the change trend in the amount of bleeding for those who responded to the first cycle in both groups revealed a significant difference between bleeding amount after using tranexamic acid and mefenamic acid ( $P=0.0001$ , table 4). Also, the amount of bleeding increased in the second cycle relative to the first treatment cycle.

Comparing the change trend in the number of bleeding days for those who responded to the first treatment cycle in both groups revealed a significant difference between the amount of bleeding after using tranexamic acid and mefenamic acid ( $P<0.05$ , table 4). Also, the number of bleeding days increased in the second cycle relative to the first one.

## DISCUSSION

We aimed to compare the effect of using tranexamic acid and mefenamic acid on the bleeding caused by planting IUD (TCu-380). The results showed that tranexamic acid was more effective than mefenamic acid in decreasing bleeding in the first treatment cycle but there was no difference between the two groups in the second cycle. Tranexamic acid has been 88% effective in the treatment of irregular uterine bleedings,<sup>16</sup> which was in line with the results of the present study although the main difference of these two studies was in the hypermenorrhea cause. The amount of bleeding was less in the case of tranexamic acid.<sup>17</sup> Our findings were in line with other studies.

Endometrial fibrinolytic enzymes have an important role in homeostasis of menstrual bleeding. In dysfunctional bleeding, activities

of plasmin and plasminogen activators increase which is seemingly due to fibrinolysis increase.<sup>18</sup> Tranexamic acid applies its antifibrinolytic effects on plasminogen by inverting lysine binding and inhibits plasmin interaction with lysine residuals on fibrin polymers (which destroy fibrin).<sup>19</sup> In a study, the participants were given 500 mg mefenamic acid every 8 hours to one group and 500 mg tranexamic acid every 6 hours to another group from the fifth day of menstruation. The results showed that tranexamic acid and mefenamic acid were effective for the treatment of hypermenorrhea by 50 and 20%, respectively,<sup>20</sup> which is different from our obtained results. These drugs were more effective in treating hypermenorrhea in the mentioned study compared to ours, which might be attributed to the difference between drug dose and its use duration. The maximum plasma concentration was achieved by administering 2 g tranexamic acid per day, 2-3 hours after using tranexamic acid, which could not be affected by consuming food.<sup>21</sup>

In other various studies, tranexamic acid has been reported to be a more influential antifibrinolytic medicine than other types of menorrhagia treatment.<sup>22</sup> Tranexamic acid and medroxyprogesteroneacetate were compared for treating dysfunctional uterine bleeding (DUB) in a study by Kriplani and colleagues. These medicines were given to the patients in 3 cycles and were monitored during these three cycles. The results demonstrated that daily consumption of 2 g tranexamic acid was more influential than hormonal drugs in decreasing the amount of bleeding (60.3% vs. 57.7%). In addition, menorrhagia-induced hysterectomy was lower.<sup>23</sup> Other studies have

**Table 4:** Comparing the change trend in the amount of bleeding (PBAC number) and number of bleeding days in tranexamic acid and mefenamic acid groups

| Drug        | Sample number   | PBAc and day Before treatment mean±SD | PBAc and day first cycle mean±SD | PBAc and day Second cycle mean±SD | P value    |        |
|-------------|-----------------|---------------------------------------|----------------------------------|-----------------------------------|------------|--------|
| Amount PBAC | Tranexamic acid | 35                                    | 160.2±54                         | 57±23.3                           | 68±44      | 0.0001 |
|             | Mefenamic acid  | 23                                    | 199.5±117.3                      | 55.91±24.2                        | 60.72±20.8 | 0.0001 |
| Mean days   | Tranexamic acid | 35                                    | 8.45±1.01                        | 6.02±0.78                         | 6.42±0.77  | 0.0001 |
|             | Mefenamic acid  | 23                                    | 8.81±1.13                        | 5.59±0.66                         | 6.50±0.59  | 0.0001 |

also considered daily consumption of 3 g of tranexamic acid as an effective solution for treating menorrhagia in menstrual cycles along with ovulation.<sup>24</sup> The difference between our study and that of Kriplani and co-workers could be related to the consumption dose of tranexamic acid and the number of treatment cycles. Comparison between tranexamic acid and norethisterone in the treatment of menorrhagia along with ovulation showed that tranexamic acid decreased bleeding by 45% while norethisterone decreased it by 20%.<sup>25</sup>

Some studies agree that alkaline haematin is a difficult method for measuring the amount of bleeding and needs accurate interpretation; on the other hand, PBAC chart is a suitable and practical alternative with sensitivity and specificity of more than 80%.<sup>13</sup> Other researchers who used tranexamic acid in treating menorrhagia in 6 cycles found that menstrual bleeding decreased and the patients' quality of life was enhanced.<sup>26</sup> These results were consistent with those of the present work. In terms of decreasing menstrual bleeding, it seems that tranexamic acid leads to stability of endometrial wall fibrin and consequently reduces bleeding.<sup>19</sup> On the other hand, this medicine does not cause thrombosis. In various studies on use of tranexamic acid for preventing bleeding resulted from mouth and cardiac surgeries and severe bleeding of upper gastrointestinal tract, no thrombosis has been observed.<sup>19,27,28</sup> Moreover, this medicine has not increased risk of thromboembolism in women of the reproductive age with the history of thrombosis.<sup>29,30</sup>

One of the limitations of this study was that intervention was done in two cycles. In the first cycle, both medicines were influential on menorrhagia but this effect was slightly higher for tranexamic acid; however, this difference was not prominent in the second cycle. Planting this copper intrauterine device after the first month caused inflammation in uterus and led to menorrhagia.<sup>31</sup> The second goal of this study was to compare effects of tranexamic acid and mefenamic acid on the days of bleeding. The results showed that mefenamic acid and

tranexamic acid reduced days of bleeding in 78% and 81% of the participants, respectively. However, in the second cycle, the difference was not significant.

Mefenamic acid has not been shown to have any effect on the days of bleeding.<sup>20</sup> In many studies, tranexamic acid showed major effects on bleeding amount but not on bleeding days.<sup>11</sup> However, in the study which compared tranexamic acid with medroxyprogesterone acetate, duration of bleeding significantly decreased in both groups.<sup>23</sup>

## CONCLUSION

Antifibrinolytic agents like tranexamic acid and anti-inflammatory agents like mefenamic acid are used in the treatment of IUD-induced bleeding (TCu-380). Based on this study, it seems that, at times of emergency, tranexamic acid could offer faster treatment effects in decreasing days and amount of bleeding. Conducting various studies on diverse cycles of menstruation should be done considering the medicines' complications.

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**Conflict of interest:** None declared.

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