

Uterine Artery Doppler Study for Evaluation of the Efficacy of Mefenamic Acid and Tranexamic Acid in Treatment of Menorrhagia Induced by Copper IUCD

Aziza H. Nassef¹, Asmaa Fathelbab², Maisara Abdallah³

¹Lecturer of Obstetrics and Gynecology, Faculty of Medicine (for Girls), Al-Azhar University, Egypt.

²Professor of Obstetrics and Gynecology, Faculty of Medicine (for Girls), Al-Azhar University, Egypt.

³ Resident in Obstetrics and Gynecology department. Faculty of Medicine (for Girls), Al-Azhar University, Egypt.

aziza.nassef@gmail.com, maisaratantawy@gmail.com, drasmaafathelbab@gmail.com

Abstract: Background: An intrauterine device is one form of long-acting reversible contraception, which is the most effective type of reversible contraceptive. Failure rate with the copper IUD is about 0.8%, with the greatest satisfaction among users of contraception. As of 2007, IUDs are the most widely used form of reversible contraception, with more than 180 million users worldwide. **Objectives:** to evaluate and compare the efficacy of mefenamic acid and tranexamic acid in controlling menorrhagia induced by Copper T-380A intrauterine contraceptive device (IUCD) by clinical assessment and study of uterine artery Doppler. **Materials and methods:** 60 women, aged (18-40) years old who had menorrhagia with copper IUD insertion were recruited from outpatient clinic of Alzhraa university hospital between August 2018 to April 2019. The women were randomly divided into 2 group: **Group 1**, women who received tranexamic acid 500 mg three times daily for 3-5 days for three consecutive menstrual cycles). And **Group 2**, women who received mefenamic acid 500 mg three times daily for 3-5 days for three consecutive menstrual cycles. The method of blood loss volume calculation was instructed to all participants during the first visit. **Results:** both drugs, tranexamic acid and mefenamic acid had the same clinical effects on Copper T-380A IUD-induced menorrhagia. As regarding uterine artery Doppler, it shows that there was a significant difference between the two groups regarding the percent changes in uterine artery Doppler between group1 and Group II. **Conclusion:** Both drugs, tranexamic acid and mefenamic acid had the same clinical effect on Copper T-380A IUD-induced menorrhagia but the effect of mefenamic acid on uterine artery dopler study was more significant than the effect of tranexamic acid.

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Keywords: Uterine Artery Doppler, Mefenamic Acid, Tranexamic Acid, Menorrhagia Induced, Copper IUCD.

1. Introduction

An intrauterine device is one form of long-acting reversible contraception, which is the most effective type of reversible contraceptive. Failure rate with the copper IUD is about 0.8%, with the greatest satisfaction among users of contraception. As of 2007, IUDs are the most widely used form of reversible contraception, with more than 180 million users worldwide¹.

The most common complication of using IUD includes excessive amount of bleeding and cramps. Also, the bleeding may be severe that leads to iron deficiency anemia².

Menorrhagia is an abnormal uterine bleeding that is characterized by heavy and/ or prolonged menstrual bleeding. Menorrhagia is a well-known side effect of using a non-hormonal intrauterine device for contraception³.

Many factors have been suggested to illustrate IUD related bleeding, including increased vascularity of the endometrium, decreased platelet aggregation, increased fibrinolytic activity and excess prostaglandin

release in the endometrial cavity. Menorrhagia is a heavy cyclical menstrual blood loss (more than 80ml per menstrual cycle) over a minimum of three consecutive cycle⁴. Menorrhagia can be caused by abnormal blood clotting, disruption of normal hormonal regulation of periods, or disorders of the endometrial lining of the uterus. Abnormal uterine bleeding including menorrhagia and intermenstrual bleeding, is one of the most frequent side effects of intrauterine device (IUD) use, and the most common medical reasons for premature discontinuation of the IUD. Among women 30-49 years of age⁵.

Treatment of menorrhagia should be tailored to each case. There are many factors that should be taken into consideration when choosing the appropriate medical treatment include the age of each case, associating medical diseases, family history, and desire for fertility. The treatment of IUD related menorrhagia can be by means of oral anti-fibrinolytic agent (Tranexamic acid) and NSAID (Mefenamic acid).

Tranexamic acid is a synthetic derivative of the amino acid lysine. It's available in many trade names. It exerts its antifibrinolytic effect through the reversible blockade of lysine-binding sites on plasminogen molecules. It inhibits endometrial plasminogen activator and thus prevents fibrinolysis and the breakdown of clot. Its side effects are uncommon, while its prolonged treatment may heighten the risk of an increased thrombotic tendency, such as deep vein thrombosis.

Mefenamic acid is a member of the fenamate group of nonsteroidal anti-inflammatory drugs (NSAIDs). Each capsule contains 500mg of mefenamic acid for oral administration. Mefenamic acid is a competitive inhibitor of COX-1 and COX-2, which are responsible for the first committed step in prostaglandin biosynthesis. Decreasing the activity of these enzymes thus reduces the production of prostaglandins, which are implicated in inflammation and pain processes. Mefenamic acid is recommended to be taken with food to minimize GIT side effects (Lukes *et al.*, 2010)⁶.

2. Materials and Methods:

This is a clinical trial. Where 60 women were recruited from the outpatient clinic of Obstetrics and Gynecology Al-Azhar University Hospitals from August 2018 till April 2019. All cases had history of a normal cycles length (cycle length 24 -35 days), and had either increased duration of menstrual bleeding (more than 7 days) or increased menstrual blood volume of greater than 80 ml per cycle after copper IUD insertion. Cases that had any medical disease (hypertension, diabetes, blood disease, thyroid disease, liver problem, coagulopathy, or cases who received anti-coagulant therapy, etc.) and cases who had any gynecological abnormalities such as (myoma, adenomyosis, cervical polyp.....etc.) were excluded from the study. Cases were randomly divided into 2 groups by quasi randomization: **Group 1**, cases who were attended to outpatient clinics at each Saturday (30 cases) and they subjected to plan A treatment (receive tranexamic acid 500 mg three times daily for 3-5 days of three consecutive menstrual cycles), and **Group 2**, cases who were attended to outpatient clinics at each Tuesday (30 cases) and they subjected to plan B treatment (receive mefenamic acid 500 mg three times daily for 3-5 days of three consecutive menstrual cycles).

The method of blood loss volume calculation was instructed to all participants during the first visit. Pictures of bloody sanitary pads smeary to 10, 20, 30, and 40 mL blood were shown to them. All cases were asked to keep a daily record of the number of sanitary pads used and group them according to the pictures of pads that were lightly (10 mL), mildly (20 mL),

moderately (30 mL), or completely (40 mL) saturated. If the total score was more than 80 mL points per menstrual cycle, it was an indication of a greater than 80 mL blood loss. All cases were subjected to careful history taking, general, gynecological examination, and routine investigation. **Transvaginal** Ultrasound was performed while the case lied in supine position with her legs semi flexed and abducted to allow easy manipulation of the vaginal probe and the woman had an empty bladder, because a full bladder can cause uterine and ovarian displacement and can modify the impedance to flow in the vessels supplying the organs. the vaginal probe was applied by a coupling gel which was introduced into a rubber glove and another layer of coupling gel was applied to the glove. The probe was then introduced into the vagina for routine vaginal scanning. The first part of the duplex scan was a real time image, in which the following were checked: size of the uterus, presence of uterine masses, endometrial thickness, and presence of any pelvic masses. At the level of the internal cervical os, the Doppler beam was adjusted to visualize the uterine artery by manipulating the probe so that the Doppler crossed the axis of the uterine artery. The blood flow indices of the uterine artery were then calculated. The pulsatility index (PI) and resistance index (RI) were obtained three times for each uterine artery (Right and left). The mean PI and RI were then calculated and compared between both groups. Follow up for 3 months to assess the clinical improvement and uterine artery Doppler indices were done to all cases.

Statistical analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 20 and the following were done: Qualitative data were presented as number and percentages while quantitative data were presented as mean, standard deviations and ranges. The comparison between two groups with qualitative data were done by using **Chi-square test**. The comparison between two independent groups with quantitative data and parametric distribution was done by using **Independent t-test**. The comparison between two paired groups with quantitative data and parametric distribution were done by using **paired t-test**. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: P > 0.05: Non significant, P < 0.05: Significant, and P < 0.01: Highly significant.

3. Results

Table (1) shows that there was no statistically significant differences between the two groups regarding their demographic data.

Table (2) shows that there was no statistically significant differences between the two groups regarding symptoms but shows statistically highly significant differences between the two groups regarding number of napkins and shows statistically significant differences between the two groups regarding days of bleeding before treatment.

Table (3) shows that there was no statistically significant differences between the two groups regarding symptoms but shows statistically significant differences between the two groups regarding number of napkins per day and shows that there were highly statistically significant differences between the two groups regarding days of bleeding after treatment.

Table (1): Comparison between Two groups regarding Demographic data

Demographic data		Group I	Group II	Test value	P-value	Sig.
		No. = 30	No. = 30			
Age	Mean±SD	32.47 ± 5.64	34.67 ± 3.13	-1.868•	0.067	NS
	Range	22 – 39	29 – 38			
Mode of delivery	SVD	21 (70.0%)	24 (80.0%)	0.800*	0.371	NS
	C.S.	9 (30.0%)	6 (20.0%)			
Parity	Mean±SD	3.40 ± 1.71	3.10 ± 1.37	0.748•	0.457	NS
	Range	1 – 7	1 – 6			
Number of previous Abortion	Mean±SD	0.80 ± 0.96	0.53 ± 1.11	0.997•	0.323	NS
	Range	0 – 3	0 – 4			

NS: Non significant,, S: Significant, HS: highly significant *: Chi-square test; •: Independent t-test

Table (2): Comparison between Two groups before treatment as regarding menorrhgia:

Before ttt		Group I	Group II	Test value	P-value	Sig.
		No. = 30	No. = 30			
Symptoms	No blood clots	4 (13.3%)	4 (13.3%)	0.000*	1.000	NS
	Blood clots	26 (86.7%)	26 (86.7%)			
No of napkin	Mean±SD	4.13 ± 0.51	4.73 ± 0.74	-3.664•	0.001	HS
	Range	3 – 5	4 – 6			
Days of bleeding	Mean±SD	7.67 ± 1.56	6.90 ± 1.06	2.224•	0.030	S
	Range	6 – 10	6 – 10			

NS: Non significant, S: Significant, HS: highly significant *: Chi-square test; •: Independent t-test

Table (3): Comparison between Two groups after treatment as regarding menorrhgia:

After ttt		Group I	Group II	Test value	P-value	Sig.
		No. = 30	No. = 30			
Symptoms	No blood clots	30 (100.0%)	30 (100.0%)	NA	NA	NA
No of napkin	Mean±SD	3.13 ± 0.73	3.47 ± 0.51	-2.053•	0.045	S
	Range	2 – 4	3 – 4			
Days of bleeding	Mean±SD	5.67 ± 0.88	5.13 ± 0.63	2.693•	0.009	HS
	Range	4 – 8	4 – 6			

NS: Non significant, S: Significant, HS: highly significant *: Chi-square test; •: Independent t-test

Table (4) shows that there was non statistically significant differences between the two groups as regarding the percent changes in menorrhgia between group I and Group II after treatment.

Table (5) shows that there was statistically highly significant differences between the two groups regarding pulsatility index of uterine artery Doppler. and shows that there was statistically significant

differences found between the two groups regarding resistive index before treatment.

Table (6) shows that there was statistically highly significant differences between the two groups regarding pulsatility index of uterine artery Doppler after treatment. and shows that there was no statistically significant differences between the two groups regarding resistive index after treatment.

Table (4): Comparison between the percent changes between group I and Group II after treatment as regarding menorrhagia:

% change		group I No. = 30	Group II No. = 30	Test value ‡	P-value	Sig.
No of napkin	Median (IQR)	-25 (-40 - 0)	-25 (-40 - -20)	-0.287	0.774	NS
	Range	-50 - 0	-50 - 0			
Days of bleeding	Median (IQR)	-25 (-37.5 - -16.67)	-25 (-28.57 - -16.67)	-0.068	0.946	NS
	Range	-42.86 - 0	-40 - -16.67			

NS: Non significant, S: Significant, HS: highly significant ‡: Mann Whitney test

Table (5): Comparison between Two groups before treatment as regarding uterine artery Doppler:

Before ttt		Group I No. = 30	Group II No. = 30	Test value	P-value	Sig.
PI	Mean±SD	4.42 ± 1.94	2.31 ± 1.05	5.212•	0.000	HS
	Range	1.7 - 8.6	0.9 - 5			
RI	Mean±SD	1.34 ± 1.28	0.85 ± 0.17	2.108•	0.039	S
	Range	0.7 - 6	0.5 - 1			

NS: Non significant, S: Significant, HS: highly significant

*: Chi-square test; •: Independent t-test

Table (6): Comparison between Two groups after treatment as regarding uterine artery Doppler:

After ttt		Group I No. = 30	Group II No. = 30	Test value	P-value	Sig.
PI	Mean±SD	4.00 ± 1.50	2.47 ± 0.97	4.689•	0.000	HS
	Range	1.6 - 6.8	1.1 - 5			
RI	Mean±SD	1.13 ± 0.28	1.08 ± 0.23	0.741•	0.461	NS
	Range	0.5 - 1.5	0.6 - 1.5			

NS: Non significant, S: Significant, HS: highly significant

*: Chi-square test; •: Independent t-test

Table (7) shows that there was highly statistically significant differences between the two groups as regarding the percent changes in uterine artery Doppler between group I and Group II after treatment.

Table (7): Comparison between the percent changes between group I and Group II after treatment as regarding uterine artery Doppler:

% change		Group A No. = 30	Group B No. = 30	Test value ‡	P-value	Sig.
PI	Median (IQR)	-4.61 (-13.33 - 4.62)	8.7 (0 - 20)	-3.329	0.001	HS
	Range	-59.3 - 38.89	-20.83 - 66.67			
RI	Median (IQR)	15.38 (0 - 25)	20 (20 - 42.86)	-2.894	0.004	HS
	Range	0 - 42.86	0 - 66.67			

NS: Non significant, S: Significant, HS: highly significant ‡: Mann Whitney test

4. Discussion

Menorrhagia means an excessive cyclic menstrual blood loss (more than 80ml per cycle) over a minimum of three consecutive cycle. A normal menstrual cycle lasts 21–35 days, with an average of 5 days menstrual flow and the total blood loss varies between 25 and 80 mL (soaking a pad or tampon every 2 hours or less)⁷

The current study was designed to evaluate and compare the efficacy of mefenamic acid and tranexamic acid in controlling menorrhagia induced by Copper T-380A intrauterine contraceptive device (IUCD) by clinical assessment and study of uterine artery Doppler. Here, there were no statistically significant differences between both groups regarding demographic data including age, parity, mode of delivery, and the number of previous abortion.

This is in agreement to ⁸ who compare the efficacy of mefenamic acid and tranexamic acid in controlling menorrhagia induced by copper IUDT380-intra uterine device (IUD), they found no significant differences of both groups (group 1 used tranexamic acid, group 2 used mefenamic acid).

In the current study before treatment there were no significant differences between the two groups in symptom ((26) patients in each group complaining of blood clots and (4) patients with no blood clots) and P-value =1.000. while there were highly significant statistically differences between the two groups in the number of napkins per day the range number of napkin per day in group 1 (3 -5) and in group 2 (4 -6) and the P value =0.001. and there were statistically significant difference between two group in the number of days of bleeding the range days of bleeding in group I (6- 10) and in group II (6- 10) and the P-value=0.030.

After treatment there no statistically significant difference between two groups regarding blood clots both groups have no blood clots after treatment. while there were statistically significant difference between two groups as regarding number of napkins per day which decreased to (2-4) in group 1 and decreased to (3-4) in group 2 and the P- value=0.045. while there were highly significant statistically difference between two groups regarding days of bleeding which decreased to (4-8) in group 1 and decreased to (4-6) in group 2.

Comparison between the percent changes there was no statistically significant differences between the two groups as regarding menorrhagia after treatment this mean that both tranexamic acid and mefenamic acid have the same effect on clinical improvement of menorrhagia.

In the tranexamic acid group and in mefenamic acid group the bleeding decreased significantly after 3

months of administration but with no significant differences between both groups.

Agree with ⁸ who found that there were reduction of bleeding in relation to base line bleeding but no differences between mefenamic acid and tranexamic acid group.

Comparison between the percent changes between group1 and Group II after treatment as regarding menorrhagia illustrate that there were no significant differences between both groups as regarding the percent changes in menorrhagia between group1 and Group II after treatment. This means that both tranexamic acid and mefenamic acid have the same clinical effect in treatment of cooper- IUD induced menorrhagia.

Disagree with ⁹study, who found that when the efficacy of NSAIDs and tranexamic acid were compared; the volume of bleeding decreased by 29% and 47%, respectively. The dosage of the drugs in this study was 500 mg for mefenamic acid and 1-24 g for tranexamic acid.

In contrast to ¹⁰study, who compared 3 drugs: mefenamic acid, tranexamic acid, and ethamsylate, and they found that the rate of bleeding reduction were 20% and 54% for the first 2 drugs, respectively, but the third one had no significant effects. The dosage of the drugs in this study was 500 mg for mefenamic acid and 1 g for tranexamic acid, administered four times daily for 5 days during 3 cycles. However, in our study, the dosage was 500 mg three times daily for 3-5 days.

In ¹¹studytranexamic acid was more effective than mefenamic acid for reduction of bleeding days as well as the volume of bleeding. Moreover, tranexamic acid had a quicker effect compared to mefenamic acid.

In ¹²study, the effects of a combination of tranexamic acid and mefenamic acid were compared with the effects of tranexamic acid alone. The combination drug reduced the bleeding by 59.3% and tranexamic acid alone reduced the bleeding by 50%.

In our study, both drugs had the same effect on reducing the days of bleeding as well as the volume of bleeding. The difference between the results of our study compared to the other studies may be due to the difference in the dosage of the administered drugs and the duration of the treatment.

As regarding uterine artery Doppler:

In The current study comparison between the two groups before treatment as regarding uterine artery Doppler it shows that there was statistically highly significant differences between the two groups regarding pulsatility index of uterine artery Doppler, the range of PI in group I (1.7 -8.6) and in Group II (0,9 -5) and P-value = 0.000, and shows that there was

statistically significant differences found between the two groups regarding resistive index before treatment the range of RI in group I (0.7 -6) and in Group II (0,5 -1) and the P-value = 0.039.

After treatment: Comparison between Two groups after treatment as regarding uterine artery Doppler there was statistically highly significant differences between the two groups regarding pulsatility index of uterine artery Doppler after treatment the range of PI in group I decreased to (1.6-6.8) and increased in Group II to (1.1-5) and P –value =0.000 after treatment. and shows that there was no statistically significant differences between the two groups regarding resistive index after treatment.

In our study in Group II pulsatility index PI before treatment range from (0.9 - 5) and increased to (1.1 - 5) after treatment, while resistive index RI before treatment range from (0.5 - 1) and increased to range from (0.6 -1.5).

Comparison between the percent changes between group I and Group II after treatment as regarding uterine artery Doppler: shows that there was highly statistically significant differences between the two groups as regarding the pulsatility index, the PI changed by Median (IQR) = -4.61 (-13.33 - 4.62) in group I and changed by Median (IQR) =8.7 (0 - 20) in Group II after treatment, the RI changed by Median (IQR) =15.38 (0 - 25) in group I and changed by Median (IQR) = 20 (20 - 42.86) Group II after treatment.

This mean that Mefenamic acid (Ponstan®) as a member of the fenamate group of nonsteroidal anti-inflammatory drugs (NSAIDs). Mefenamic acid is a competitive inhibitor of COX-1 and COX-2, which are responsible for the first committed step in prostaglandin biosynthesis. Decreasing the activity of these enzymes thus reduces the production of prostaglandins, which are implicated in inflammation and pain processes affect uterine artery blood flow by increasing both PI and RI so it decrease blood loss.

This mean that mefenamic acid affect uterine artery Doppler more than tranexamic acid.

Our study agrees with¹³, this is the first demonstration that tranexamic acid has an effect on uterine blood flow. The therapeutic effect of tranexamic acid in women with menorrhagia is thought to result from its antifibrinolytic activity. Surprisingly, our results demonstrated a reduced impedance to blood flow in the uterine arteries. It is likely that this effect is incidental to the action of tranexamic acid in reducing menstrual blood loss.

The results of the study confirmed the clinical efficacy of tranexamic acid in reducing menstrual blood loss. The mechanism by which tranexamic acid may influence vascular resistance is not known. The drug could modulate the activity of vasoactive

peptides, which operate through paracrine mechanisms in the uterine vascular endothelium, or may have direct effects on Ca²⁺ transport. It is unlikely that the effect on decreased menstrual blood loss is related to the changes in uterine artery vascular resistance.

Conclusion

We found that both drugs, tranexamic acid as an anti-fibrinolytic agent, and mefenamic acid as an NSAID, at dosage of 500 mg three times daily for 3-5 days during 3 consecutive months had the same significant effects on Copper T-380A IUD-induced menorrhagia. Their effects are equal on both the volume of blood loss and the duration of menses.

Comparison between both groups after treatment as regarding uterine artery Doppler shows that there were significant differences between the two groups regarding of uterine artery Doppler. This mean that mefenamic acid affect uterine artery Doppler more than tranexamic acid.

References

1. Darney J, Leon S and Philip D (2010): A clinical guidforco Eik-Nes SH, Brubakk A, Ulstein MK (1980): Measurement of human fetal blood Row, Br Med J 280:283-284.
2. Cunningham, Williams Textbook of obstetrics (2010).
3. Zacur HA (2014): Chronic menorrhagia or anovulatory uterine bleeding. <http://www.uptodate.com/home>. Accessed April 6, 2014.
4. Munro MG, Critchley HO, Broder MS, Fraser IS (2011): FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynecol Obstet; 113:3.
5. Berek JS, Novak E. Berek & Novak's gynecology (2012): 15th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012.
6. Lukes AS, Moore KA, Muse KN, et al. (2010): Tranexamic Acid Treatment for Heavy Menstrual Bleeding: A Randomized Controlled Trial. Obstetrics & Gynecology.; 116:865-87.
7. Munro MG, Critchley HO, Broder MS, Fraser IS (2011): FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynecol Obstet; 113:3.
8. Sahakhiz, Farnaz E, Anahita T, Zahra M Masoumeh F (2017): International Journal of Women's Health and Reproduction Sciences; 5(3).

9. Coulter A, Kelland J, Peto V, Reese MC (1995): Treating menorrhagia in primary care: an overview of drug trials and a survey of prescribing practice. *Int J Technol Assess Health Care*; 11(3):456-71.
10. Bonnar J, Sheppard BL (1996): Treatment of menorrhagia during menstruation: randomised controlled trial of ethamsylate, mefenamic acid, and tranexamic acid. *BMJ*; 313(7057):579-82.
11. Kaviani M, Roozbeh N, Azima S, Amoi S (2013): Comparing the effects of tranexamic acid and mefenamic acid in IUD induced menorrhagia: randomized controlled trial. *Int J Community Based Nurs Midwifery*; 1(4):216-223.
12. Najam R, Agarwal D, Tyagi R, Singh S (2010): Comparison of traneximic acid with a combination of traneximic acid and mefenamic acid in reducing menstrual blood loss in ovulatory dysfunctional uterine bleeding (DUB). *J Clin Diagn Res*; 4(5):3020-3025.
13. Bonnar J, Sheppard BL (1996): Treatment of menorrhagia during menstruation: randomised controlled trial of ethamsylate, mefenamic acid, and tranexamic acid. *BMJ*; 313(7057):579-82.

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