Original Article

To Study the Efficacy and Safety of Diosmin with Tranexamic Acid and Mefenamic Acid Versus only Tranexamic Acid and Mefenamic Acid in Medical Management of Abnormal Uterine Bleeding: A Randomized Controlled Trial

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ABSTRACT

Background: Abnormal uterine bleeding (AUB) is a common problem in reproductive age group and perimenopausal age group being responsible for many outpatient visits. Traditional management of AUB consists of giving mefenamic acid, tranexamic acid, or their combination with progestogens or hormonal intrauterine deviced levonorgestrel intrauterine system (LNG-IUS) for severe or nonresponsive cases. The objective of the current study was to study the efficacy and safety of adding diosmin along with tranexamic acid and mefenamic acid in reducing menstrual blood loss in AUB patients. **Materials and Methods:** It was a prospective double-blind randomized controlled trial in which 900 mg of diosmin was given once daily along with 500 mg tranexamic acid and 250 mg mefenamic acid during menstruation (Group I-92 patients), or only tranexamic acid and mefenamic acid during menstruation (Group II-92 patients). **Results:** Mean age, parity, body mass index, and socioeconomic status were similar in the two groups. It was 35.68 years versus 36.78 years, 2.2 versus 2.3, 23.68 kg/m^2 versus 24.62 kg/m^2 respectively. Mean days of bleeding before this treatment were 6.8 versus 6.6 (P = 0.33) and were 3.5 versus 5.2 (P = 0.02) after treatment. There was a significant reduction in both groups as compared to before treatment (P = 0.021 in Group I, 0.027 in Group II) but the reduction was greater in Group I (P = 0.02). The amount of blood loss was 385 ml versus 390 ml (P = 0.7) before treatment which was significantly reduced in both groups to 68 ml versus 112 ml (P = 0.02 in Group I, 0.03 in Group II) with more decrease in Group I than in Group II (P = 0.01). Mean hemoglobin at beginning of the study was 8.4 versus 8.5 g/dl in Group I and Group II (P = 0.02) and significantly increased in both groups posttreatment to 10.9 and 9.8 g/dl in Group I and Group II (P = 0.012 in Group I, 0.011 in Group II) with increase being more in Group I than Group II (P = 0.03). Pictorial blood assessment chart score was 398 versus 406 (P = 0.35) before treatment and decreased significantly to 86.5 and 110.5 (P = 0.001 in Group I, 0.001 in Group II) with more decrease being in Group I than II (P = 0.01). There was significant decrease in dysmenorrhea with

Submitted: 26-Dec-2022
Revised: 06-Feb-2023
Accepted: 07-Mar-2023
Published: 18-Sep-2023

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Access this article online

Quick Response Code:

Website: https://journals.lww.com/jomh

DOI: 10.4103/jmh.jmh_253_22

How to cite this article: Sharma JB, Kumari R, Kumari S, Jain S, Dharmendra S. To study the efficacy and safety of diosmin with tranexamic acid and mefenamic acid versus only tranexamic acid and mefenamic acid in medical management of abnormal uterine bleeding: A randomized controlled trial. J Mid-life Health 2023;14:87-93.

both treatments with no difference in the two groups. Various adverse effects such as nausea, vomiting, abdominal pain, diarrhea, constipation, and headache were equal in the two groups. **Conclusion:** Both the group's diosmin with tranexamic acid and mefenamic acid (Group I) and tranexamic acid and mefenamic acid (Group II) were efficacious in reducing menstrual blood loss, number of menstrual days and dysmenorrhea with effect being more by addition of diosmin. Adverse effects were equal in both the two groups.

Keywords: *Abnormal uterine bleeding, diosmin, medical treatment, mefenamic acid, PALM-COEIN classification, tranexamic acid*

Introduction

Abnormal uterine bleeding (AUB) is a common presenting complaint in outpatient department. AUB is defined as excessively heavy, prolonged or frequent bleeding of uterine origin, not due to pregnancy, pelvic, or generalized medical disease.[1-3] AUB is therefore a diagnosis of exclusion. The term AUB, denotes heavy menstrual bleeding and/or intermenstrual bleeding. This condition can be caused by structural and nonstructural etiologies, with specific types of AUB categorized by the PALM-COEIN classification system. This classification was introduced in 2011 by the International Federation of Gynaecology and Obstetrics. Each letter of the PALM-COEIN system represents a distinct cause of AUB, which were subdivided into either structural (PALM) or nonstructural (COEIN) causes. Of the 9 categories in the classification system (PALM-COEIN), the first 4 are defined as visually objective structural criteria (PALM: Polyp, adenomyosis, leiomyoma, and malignancy and hyperplasia). The second 4 are unrelated to structural abnormalities (COEI: Coagulopathy, ovulatory dysfunction, endometrial, and iatrogenic), and the final category is for entities that are not yet classified (N).[4-9]

AUB can be classified into anovulatory and ovulatory AUB. In anovulatory AUB, the graafian follicle does not rupture, ovulation does not occur and corpus luteum is not formed.[5] Thus, the production of estrogen is sustained or fluctuant being unopposed by the secretion of progesterone. In peri-menopausal women, the dynamics of estrogen secretion are disturbed leading to fluctuating plasma levels, due to defect in hypothalamic–pituitary axis and intra-ovarian mechanism.[10] In adolescent, there is a defect in the hypothalamic feedback response to estrogen, due to immaturation of hypothalamic control.[5] Daily plasma measurement of luteinizing hormone, follicle-stimulating hormone, estrogen, and progesterone levels in these women have shown that the cycles are indistinguishable from normal, on the basis of the levels of these hormones.

It is often thought that hormonal imbalance is a cause of AUB, but in patients of ovulatory AUB, the hormonal levels have been found to be normal. Even the secretory endometrium is indistinguishable from normal. Then, it becomes very clear that some local functional abnormality exists within the uterus or some unidentified circulating substance exacerbates menstrual bleeding, thus causing AUB.[5-9]

Therapies are instituted depending on the severity, pattern, duration of bleeding, and the age of patients. The treatment could be nonhormonal and hormonal. Nonhormonal therapy includes prostaglandin synthase inhibitors, nonsteroidal anti-inflammatory drug (NSAIDs) such as mefenamic acid, anti-fibrinolytics (tranexamic acid), ethamsylate, diosmin, ormeloxifene, and mifepristone.[11-15] The hormonal therapy includes hormonal progestogens, combined estrogen and progesterone (OCP), danazol, GnRH analogs, and testosterone.[5]

Mefenamic acid, an NSAID and anthranilic acid derivative, is also known to reduce menstrual blood loss by 20%, in a dose of 1 g three times per day. Diosmin, chemically, is a flavone derivative which occurs naturally as a glycoside. For over more than 40 years, it is widely used as a phlebotonic and vascular protecting agent. The pharmacological characteristics of diosmin are determined by diosmetin. The activity of diosmetin depends on the sugar moiety and its stereo specific binding. Diosmin is synthesized by extracting hesperidin from citrus rinds and converting the hesperidin to diosmin. It has various pharmacological actions such as phlebotonic action, anti-edema, vasoprotective, anti-inflammatory action, and free radical scavenging.[13-15] Diosmin is considered as a vascular protecting agent and with its multimodal action, it is used to treat AUB.[11,12]

Previous studies have evaluated the efficacy of various treatment modalities (NSAIDS, hormones, and antifibrinolytics) and have proven their role in AUB. Tranexamic acid was studied in combination therapy with mefenamic acid.

The present study aimed to establish, evaluate, and strengthen the evidence of the beneficial effects of micronized 100% diosmin and its efficacy and reduction of bleedings for AUB. There are many studies which have been conducted before, and have thrown light

on the efficacy of diosmin in uterine bleeding and menorrhagia.

Noninferiority was seen between 2 arms of therapy, one where tranexamic acid was given along with mefenamic acid and the other group where micronized diosmin is given in place of placebo. In this study, Venusmin (100% micronized diosmin) and placebo were given to the respective groups from 5 days before the expected onset of menstruation and up to the end of bleeding for three consecutive cycles.

Materials and Methods

It was a prospective randomized controlled trial over 2 years (April 2019–March 2021), in 184 women of AUB from gynecology outpatient department of AIIMS, New Delhi, a Tertiary Referral Centre in one unit. Detailed history of menstrual abnormalities, duration and prior treatment, complaints, obstetric, medical, and surgical history was taken for all patients. General and systemic physical examination was performed on all women as per CONSORT Statement [Appendix 1]. Abdominal and gynecological examination was carried out in all women. Participants between 18 and 45 years with heavy menstrual bleeding and who were willing to participate and without any structural causes were included in the present study. A written informed consent was obtained from all the study participants.

The exclusion criteria were structural causes of AUB, pregnancy or pelvic pathology, history of intrauterine device or hormonal therapy, coagulation disorder, thyroid, liver, or renal abnormalities and those not willing to participate. The pretreatment pictorial blood assessment chart (PBAC) score was estimated in all cases and women who were suitable and willing to participate were divided into two equal groups by computer-generated randomized controlled numbers:

Group I:- They received 500 mg tranexamic acid with 250 mg mefenamic acid daily from day 1 to 5 of cycle along with tablet diosmin 900 mg starting 5 days before expected date of menstruation and during 1–5 days of menstruation. The treatment was given for 3 consecutive months.

Group II:- These women of AUB were given 500 mg tranexamic acid and 250 mg mefenamic acid thrice daily from day 1 to 5 of menstrual cycle which placebo starting from 5 days before menses and during menses for 3 consecutive months.

All patients were followed up after 1 month and 4th month (after completion of 3 months of therapy). Detailed history was again taken for amount of menstrual blood loss, duration of menses, any painful period, effect on physical activity. Posttreatment hemoglobin (Hb) was again estimated and PBAC score was calculated on 4th month follow-up visit. Limitation of physical activity was also noted. Effect on large blood stains, effect on dysmenorrhea, and other adverse effects were observed in the two groups.

Ethical approval was taken from the Institute Ethics Committee Ref Number: ICE-70/08.01.2016, RP-10/2016. The study was enrolled for randomized controlled trial (CTRI Number: CTRI/2019/11/021844).

PBAC score was calculated as follows:

1. A lightly stained towel: 1 point, moderately strange towel: 5 points, a towel which was fully soaked: 20 points
2. A lightly stained tampon: 1 point, moderately stained tampon: 5 points, a tampon which was fully soaked: 10 points
3. A clot of 5 cent coin: 1 point, quarter 50 cent coin: 5 points, flooding: 5 points.

Thus, (PBAC) score was calculated.

The characteristics of women such as age, parity, body mass index, and socioeconomic status were noted in all cases. The days of bleeding, the amount of blood loss, pretreatment Hb, PBAC score (see below), effect on limitation of physical activity, dysmenorrhea, and large size stains were noted in all the cases. All patients were followed up for any side-effects while taking the medication was noted.

Statistical analysis

Data were computerized into Spreadsheet and data analysis was carried out using software STATA version 12.0 (Texas, USA). Continuous variables were tested for assumption using "Kolmogorov–Smirnov" test. Descriptive measures such as mean, standard deviation, median and range values were computed for all continuous measures. Percentage values were computed for qualitative variables. Changes in blood loss and stress level between pre- and post-evaluation were tested using Student's *t*-paired test. For more than one time, assessment of continuous measures was subjected for repeated measures Analysis of Covariance. Means of all continuous variables between the two groups were tested using Student's *t*-independent test. A two-tailed $P < 0.05$ was considered for statistical significance.

Results

It was a study done on 184 women with AUB divided equally into Group I (92 women) who received diosmin, tranexamic acid, and mefenamic acid during menses and Group II (92 women) who received only tranexamic acid and mefenamic acid.

The characteristics of women into groups are shown in Table 1. The mean age, parity, and body mass index in the two groups were 35.68 ± 4.73 years versus 36.78 ± 4.56 years, 2.2 versus 2.3 and 23.68 ± 3.71 kg/m^2 versus 24.62 ± 4.12 kg/m^2, respectively, and were similar (P = 0.24, 0.341, 0.426, respectively). The socioeconomic status was also similar with most patients being in lower and middle class (P = 0.38). Table 2 shows days of bleeding in the two groups following the effect of two types of treatments. The mean days of bleeding in Group I were 6.8 ± 1.5 days and in Group II were 6.6 ± 1.6 days which was similar (P = 0.35). Posttreatment, there was significant reduction in days of bleeding in both the groups (3.5 ± 0.98 days in Group I versus 5.2 ± 1.2 days in Group II) as compared to pretreatment (P = 0.021 in Group I, 0.028 in Group II) being more in Group I than in Group II (P = 0.02). The amount of blood loss and effect of treatment is shown in Table 3. The mean amount of blood loss is similar (385 ± 78 ml) in Group I and (390 ± 80 ml) in Group II (P = 0.72). Posttreatment, there was significant reduction in amount of mean blood loss in both groups (68 ± 27 ml in Group I), 112 ± 48 ml in Group II (P = 0.02 in Group I, 0.03 in Group II being more in Group I than in Group II (P = 0.01).

Pretreatment and posttreatment Hb into two groups is shown in Table 4. Before treatment, the Hb was (8.4 ± 1.63 g/dl) in Group I and (8.5 ± 1.58 g/dL) in Group II and was similar (P = 0.287). Posttreatment, Hb increased significantly in both the groups being 10.9 ± 1.8 g/dl in Group I (P = 0.012) and 9.8 ± 1.75 g/dl in Group II (P = 0.011) with improvement being more in Group I (P = 0.03). PBAC score before and after treatment is shown in Table 5 with mean score being (398 ± 168) in Group I and (406 ± 178) in Group II (P = 0.35). Posttreatment, PBAC score decreased significantly in both the groups with mean being (86.5 ± 32) in Group I (P = 0.001) and (110.5 ± 48.6) in Group II (P = 0.001) with decrease being more in Group I than in Group II (P = 0.01).

Influence of two treatments on physical activity is shown in Table 6. Pretreatment 22 (23.9%) and 23 (25%) participants in Group I and II had quite a bit limited activity (P = 0.42) while 24 (26.08%) and 24 (26.08%) had extreme limitation (P = 0.38). Posttreatment only 7 (7.6%) women in Group I and 13 (14.13%) women in Group II had quite a bit limitation and 2 (2.17%) and 4 (4.34%) women had severe limitation in the two groups with better outcome in Group I.

Table 7 shows effect of two treatment groups on reduction in large stains. Before treatment, 48 (52.17%) in Group I and 50 (54.34%) in Group II had large stains. Posttreatment, it significantly to 4 (4.34%) in Group I and 6 (6.52%) in Group II (P = 0.01) with no significant difference in the two groups (P = 0.07).

Table 1: Characteristics of patients in 2 groups (n=184)

	Group I (n=92)	Group II (n=92)	P	Significance
Age				
Range	18–45	19–44	0.24	NS
Mean±SD	35.68±4.73	36.78±4.56		
Parity				
Range	0–5	0–6	0.341	NS
Mean±SD	2.2±0.5	2.3±0.4		
BMI (kg/m^2)				
Range	17–33	18–32	0.426	NS
Mean±SD	23.68±3.71	24.62±4.12		
Socioeconomic status, n (%)				
Lower	45 (48.91)	42 (45.65)	0.38	NS
Middle	44 (47.82)	46 (50)		
Upper	3 (3.26)	4 (4.34)		

NS: Not significant, SD: Standard deviation, BMI: Body mass index

Table 2: Effect of two treatments on days of bleeding (n=184)

	Group 1 (n=92)	Group 2 (n=92)	P	Significance
Days of bleeding				
Range	3–12	4–11	0.35	NS
Mean±SD	6.8±1.5	6.6±1.6		
Posttreatment (4 months)				
Days of bleeding				
Range	2.2–6.7	3–8.2	0.02	Significant
Mean±SD	3.5±0.98	5.2±1.2		
P value (before and after treatment)	0.021	0.028		Significant

NS: Not significant, SD: Standard deviation

Table 3: Effect of two treatment on amount of blood loss (n=184)

	Group I (n=92)	GROUP II (n=92)	P	Significance
Amount of blood loss (mL)				
Range	128–680	130–670	0.72	NS
Mean±SD	385±78	390±80		
Posttreatment amount of blood loss				
Amount of blood loss (mL)				
Range	48–180	65–310	0.01	Significant
Mean±SD	68±27	112±48		
P value (before and after treatment)	0.02	0.03		Significant

NS: Not significant, SD: Standard deviation

Effect on pain relief in two groups is shown in Table 8. A total of 22 women (23.91%) in Group I and 23 women (25%) in Group II were having dysmenorrhea before treatment which was similar (P = 0.58). There was significant reduction in dysmenorrhea rate after the treatment being 6 (6.52%) in Group I (P = 0.01) and 5 (5.43%) in Group II (P = 0.01) with no difference in the two groups (P = 0.71).

Various adverse effects of drugs in two groups are shown in Table 9. Various adverse effects were nausea in 16 (17.39%) versus 17 (18.47%) (P = 1.21), vomiting in 8 (8.69%) versus 8 (8.69%) (P = 1.01), abdominal pain in 5 (5.43%) versus 5 (5.43%) (P = 2.2), diarrhea 3 (3.26%) versus 4 (4.34%) (P = 1.22), constipation 4 (4.3%) versus 5 (5.43%) (P = 1.01), and headache in 2 (2.17%) versus 2 (2.17%) (P = 1.11) in Groups I and II, respectively, with no significant difference in the two groups.

Table 4: Pre-and post-treatment hemoglobin in 2 groups (n=184)

	Group I (n=92)	Group II (n=92)	P	Significance
Haemoglobin (g%)				
Range	6–10.8	7–11	0.287	NS
Mean±SD	8.4±1.63	8.5±1.58		
Posttreatment (4 months) hemoglobin in 2 groups (n=184)				
	Group I (n=92)	**Group II (n=92)**	**P**	**Significance**
Hemoglobin (g%)				
Range	8.1–13.1	7.9–12.5	0.03	Significant
Mean±SD	10.9±1.86	9.8±1.75		
P value (before and after treatment)	0.012	0.011		Significant

NS: Not significant, SD: Standard deviation

Table 5: Pictorial blood assessment chart score before and after treatment

	Group I (n=92)	Group II (n=92)	P	Significance
PBAC score				
Range	140–620	130–610	0.35	NS
Mean±SD	398±168.21	406±178.52		
PBAC score after treatment (n=184)				
	Group I (n=92)	**Group II (n=92)**	**P**	**Significant**
PBAC score				
Range	68–134	82–168	0.01	Significant
Mean±SD	86.5±32.5	110.5±48.6		
P value (before and after treatment)	0.001	0.001		Significant

PBAC: Pictorial blood assessment chart, NS: Not significant, SD: Standard deviation

Discussion

AUB is a common problem in reproductive and perimenopausal age group. It can be due to structural causes (such as polyps, adenomyosis, leiomyoma, hyperplasia or malignancy) or nonstructural causes (coagulopathy, ovulatory dysfunction, endometrial, iatrogenic and not yet classified causes).[4,5] The traditional management of AUB with nonsteroidal anti-inflammatory agents such as mefenamic acid, tranexamic acid and progestogens like norethisterone or LNG intrauterine system with surgery being used after failure of medical management.[11-20]

In the present study of AUB, patients without structural causes were equally divided into tranexamic acid 500 mg and mefenamic acid 250 mg and placebo thrice daily from day 1 to 5 for three cycles (Group II) and addition of diosmin 900 mg 5 days prior to and during

Table 6: Effect of two treatments on limitation of physical activity

Characteristic	Group I (n=92)	Group II (n=92)	P	Significance
Pretreatment (n=184)				
Limitation of physical activity				
Not limited	8 (8.69)	7 (7.60)	0.29	NS
Slightly limited	18 (19.56)	17 (18.47)	0.27	NS
Moderately limited	20 (21.73)	21 (22.82)	0.31	NS
Severely limited	22 (23.91)	23 (25)	0.42	NS
Extremely limited	24 (26.08)	24 (26.08)	0.38	NS
After treatment (n=184)				
Limitation of physical activity				
Not limited	38 (41.30)	21 (22.82)	0.02	Significant
Slightly limited	37 (40.21)	39 (42.39)	0.87	NS
Moderately limited	8 (8.69)	15 (16.30)	0.01	Significant
Severely limited	7 (7.60)	13 (14.13)	0.02	Significant
Extremely limited	2 (2.17)	4 (4.34)	0.52	NS

NS: Not significant

Table 7: Effect of two treatments on reduction in large stains

	Group I (*n*=92), *n* (%)	Group II (*n*=92), *n* (%)	*P*	Significance
Large stains before treatment	48 (52.17)	50 (54.34)	0.38	NS
Large stains after treatment	4 (4.57)	6 (6.52)	0.07	NS
P value (before and after treatment)	0.011	0.01		NS

NS: Not significant

Table 8: Effect on pain relief (dysmenorrhea) *n*=184

	Group I (*n*=92), *n* (%)	Group II (*n*=92), *n* (%)	*P*	Significance
Dysmenorrhea (menstrual pain) before treatment	22 (23.91)	23 (25)	0.58	NS
Dysmenorrhea after treatment	6 (6.52)	5 (5.43)	0.71	NS
P value	0.01	0.01		Significant

NS: Not significant

Table 9: Adverse effects in two groups

Characteristic adverse effects	Group I (*n*=92), *n* (%)	Group II (*n*=92), *n* (%)	*P*	Significance
Nausea	16 (17.39)	17 (18.47)	1.21	NS
Vomiting	8 (8.69)	8 (8.69)	1.01	NS
Abdominal pain	5 (5.43)	5 (5.43)	2.2	NS
Diarrhea	3 (3.26)	4 (4.34)	1.22	NS
Constipation	4 (4.34)	5 (5.43)	1.01	NS
Headache	2 (2.17)	2 (2.17)	1.11	NS

NS: Not significant

menses in Group I. There was significant improvement in symptoms in both the groups in 4th month with decrease in quantity and duration of blood loss, decrease in dysmenorrhea, decrease in large stains and PBAC. PBAC has been used in quantitative assessment of blood loss in AUB and is useful to see the effects of treatment.[21-23] Similarly, there was significant rise in Hb with both treatments but the rise was higher flavonoid diosmin. There was significant improvement in physical activity limitation between the treatments and in large stains with improvement being more in diosmin group. Pain relief was also observed in both the groups with no significant difference between two groups. The adverse effects were minimal or less serious such as nausea, vomiting, abdominal pain, diarrhea, constipation, and headache which were similar in both the two groups.

Hence, the addition flavonoid diosmin starting 5 days before onset of menstruation with traditional tranexamic and mefenamic acid is associated with significant improvement in Hb rise, decrease in PBAC score and significant reduction in amount and duration of menstrual blood loss without any extra adverse effects.

Conclusion

Both tranexamic acid and mefenamic acid group and tranexamic acid with mefenamic acid and diosmin are highly effective in reducing menstrual blood loss, rise in Hb and pain relief with results being more by adding diosmin. Hence, addition of diosmin to tranexamic acid and mefenamic acid has additional benefits without any adverse effects.

Acknowledgement

The authors are thankful to all the faculty and residents of Obstetrics and Gynaecology Department, AIIMS, Delhi, for their help. The authors would like to thank Walter Bushnell Pvt Ltd for funding the study and supplying free samples but had no access to data or any influence on its results.

Financial support and sponsorship

Walter Bushnell Pvt Ltd, India for giving free drugs.

Conflicts of interest

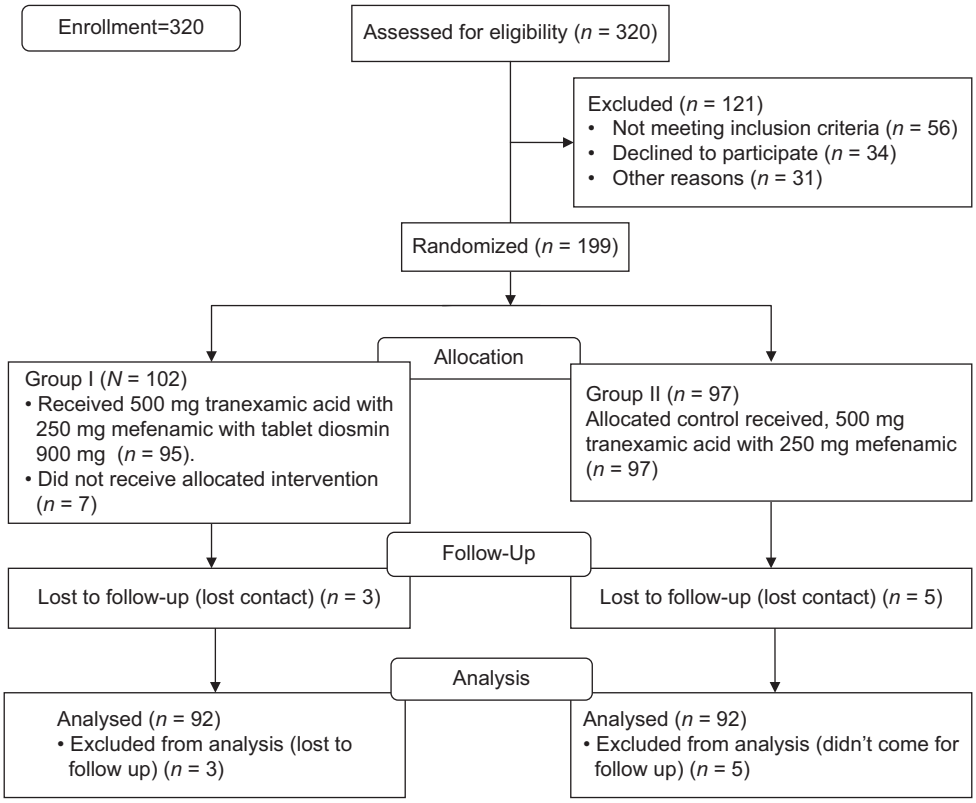
There are no conflicts of interest.

References

1. Côté I, Jacobs P, Cumming DC. Use of health services associated with increased menstrual loss in the United States. Am J Obstet Gynecol 2003;188:343-8.
2. Santer M, Warner P, Wyke S. A Scottish postal survey suggested that the prevailing clinical preoccupation with heavy periods does not reflect the epidemiology of reported symptoms and problems. J Clin Epidemiol 2005;58:1206-10.
3. Shapley M, Jordan K, Croft PR. An epidemiological survey of symptoms of menstrual loss in the community. Br J Gen Pract 2004;54:359-63.
4. Munro MG, Critchley HO, Broder MS, Fraser IS, 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 Gynaecol Obstet 2011;113:3-13.
5. Sharma JB. Textbook of Gynecology. 1st ed. New Delhi: Avichal Publishing Company; 2018.
6. Albers JR, Hull SK, Wesley RM. Abnormal uterine bleeding. Am Fam Physician 2004;69:1915-26.
7. Awwad JT, Toth TL, Schiff I. Abnormal uterine bleeding in the perimenopause. Int J Fertil Menopausal Stud 1993;38:261-9.
8. Munne MG. Abnormal Uterine Blood. 1st ed. Cambridge UK: Cambridge University Press; 2010.
9. Munro MG, Lukes AS, Abnormal Uterine Bleeding and Underlying Hemostatic Disorders Consensus Group. Abnormal

uterine bleeding and underlying hemostatic disorders: Report of a consensus process. Fertil Steril 2005;84:1335-7.
10. Pillai SS. Sonographic and histopathological correlation and evaluation of endometrium in perimenopausal women with abnormal uterine bleeding. Int J Reprod Contracept Obstet Gynecol 2014;3:113-7.
11. Alanwar A, Abbas AM, Hussain SH, Elhawwary G, Mansour DY, Faisal MM, *et al.* Oral micronised flavonoids versus tranexamic acid for treatment of heavy menstrual bleeding secondary to copper IUD use: A randomised double-blind clinical trial. Eur J Contracept Reprod Health Care 2018;23:365-70.
12. Najam R, Agarwal D, Tyagi R, Singh S. Comparison of traneximic acid with a combination of traneximic acid and mefenamic acid in reducing menstrual blood loss in ovulatory Abnormalal uterine bleeding (AUB). J Clin Diagn Res 2010;4:3020-5.
13. Monograph. Diosmin. Altern Med Rev 2004;9:308-11.
14. Boudet C, Peyrin L. Comparative effect of tropolone and diosmin on venous COMT and sympathetic activity in rat. Arch Int Pharmacodyn Ther 1986;283:312-20.
15. Araujo D, Viana F, Osswald W. Diosmin therapy alters the *in vitro* metabolism of noradrenaline by the varicose human saphenous vein. Pharmacol Res 1991;24:253-6.
16. Bofill Rodriguez M, Lethaby A, Farquhar C. Non-steroidal anti-inflammatory drugs for heavy menstrual bleeding. Cochrane Database Syst Rev 2019;9:CD000400.
17. Bryant-Smith AC, Lethaby A, Farquhar C, Hickey M. Antifibrinolytics for heavy menstrual bleeding. Cochrane Database Syst Rev 2018;4:CD000249.
18. Bofill Rodriguez M, Lethaby A, Low C, Cameron IT. Cyclical progestogens for heavy menstrual bleeding. Cochrane Database Syst Rev 2019;8:CD001016.
19. Bofill Rodriguez M, Lethaby A, Jordan V. Progestogen-releasing intrauterine systems for heavy menstrual bleeding. Cochrane Database Syst Rev 2020;6:CD002126.
20. Marjoribanks J, Lethaby A, Farquhar C. Surgery versus medical therapy for heavy menstrual bleeding. Cochrane Database Syst Rev 2016;2016:CD003855.
21. Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. Br J Obstet Gynaecol 1990;97:734-9.
22. Herman MC, Mak N, Geomini PM, Winkens B, Mol BW, Bongers MY, *et al.* Is the Pictorial Blood Loss Assessment Chart (PBAC) score associated with treatment outcome after endometrial ablation for heavy menstrual bleeding? A cohort study. BJOG 2017;124:277-82.
23. Su S, Yang X, Su Q, Zhao Y. Prevalence and knowledge of heavy menstrual bleeding among gynecology outpatients by scanning a WeChat QR Code. PLoS One 2020;15:e0229123.

Appendix



Appendix 1: CONSORT DIAGRAM