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Original Research Article

Diosmin versus tranexamic acid in heavy menstrual bleeding: a randomized controlled trial

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ABSTRACT

Background: Heavy menstrual bleeding (HMB) is defined as cyclical bleeding at regular intervals but excessive in amount which affect the physical, social and mental aspects of life of a woman. The prevalence is 10-30% in reproductive age women and 50% in perimenopausal women. HMB is not just a clinical burden but also a huge social and economic burden. The aims and objective of my study is to compare the efficacy of diosmin and tranexamic acid in acute HMB in terms of average duration of menstrual cycle, PBAC/PABC score, endometrial thickness, hemoglobin concentration and finally need for other modes of treatment.

Methods: The study was a randomized control trial in which the patients (sample size-72) were divided into two groups-group D (n=36) and group T (n=36). Group D was treated with tab diosmin 500 mg thrice daily from day 1 to day 5 of menstrual cycle. Similarly group T was treated with tab tranexamic acid 500 mg thrice daily from day 1 to day 5 of menstrual cycle. The PBAC score was taken at the end of three months along with endometrial thickness and hemoglobin concentration. The results were compared with values obtained before initiating treatment.

Results: In this study after 3 months of treatment; the patients in group D had an initial PBAC score of 423.52 and at the end of treatment it was decreased to 149.89 ($p<0.0001$). Reduction was 60.5%. Group T patients had an initial PBAC score of 441 which was reduced to 177.94 ($p<0.0001$) after treatment. The reduction in this group was 59.6%.

Conclusions: In this study it was found that both tranexamic acid and diosmin were effective in reduction of HMB, in terms of PBAC score, average duration of menstrual cycle and endometrial thickness. But the in reduction in PBAC score was similar in both the groups. The failure rates were also similar in both the groups, but improvements in hemoglobin concentration were only marginal

Keywords: Diosmin, Tranexamic acid, HMB, Menorrhagia

INTRODUCTION

The term "Menorrhagia" is defined as cyclical bleeding occurring in regular intervals but excessive in amount and/or duration which affects the physical, mental, and social aspects of life a woman. It is described as abnormally long or heavy menses, lasting >7 days or involving blood loss >80 ml.¹ This term is recently replaced by the phrase "heavy menstrual bleeding" (HMB). These, terms are often used interchangeably. AUB is reported to occur in 9 to 14% women between menarche and menopause. The prevalence is 10-30% of reproductive

age women and 50% in perimenopausal women. In a study conducted by Liu et al it was estimated that the conservatively estimated annual direct and indirect economic costs of AUB were approximately \$1 billion and \$12 billion, respectively.² Thus, HMB is not just a clinical burden, but also a huge social and even an economic burden. Excessive menstrual bleeding may add up to the severity of anemia because of nutritional deficiency and parasitic infections in a country like India. Currently, available options for treating HMB may be broadly divided into medical and surgical modalities. The options for medical management include non-steroidal anti-

inflammatory agents, tranexamic acid, micronized flavonoids (diosmin) combined hormonal contraceptives, cyclic progestins, danazol, and levonorgestrel-releasing intrauterine system (LNG-US) while the surgical treatment options are endometrial ablation/ resection or hysterectomy. In this study we are comparing the efficacy of diosmin and tranexamic acid in acute HMB. Menorrhagia during the reproductive years may be caused by an imbalance in the metabolism of local endometrial prostaglandins.³ A micronized purified flavonoid fraction containing 90% of diosmin and 10% of flavonoids expressed as hesperidin has been shown to suppress prostaglandins E₂, F_{2a}, thromboxane A₂, and prostacycline; reduce capillary hyperfragility; and increase lymphatic drainage.⁴ Tranexamic acid is a synthetic lysine derivative that exerts its antifibrinolytic effect by reversibly blocking lysine binding sites on plasminogen and thus preventing fibrin degradation.⁵

The aims and objectives of my study is to compare the efficacy of diosmin and tranexamic acid in acute HMB in terms of average duration of menstrual cycle, PBAC/PABC score, Endometrial thickness, hemoglobin concentration and finally need for other modes of treatment.

METHODS

The randomized control trial was conducted in the department of obstetrics and gynaecology, medical college Kolkata, among the patients attending the outpatient department with HMB from March 2019 to February 2020. Sample size was 72 which was divided into two groups, group D (36) treated with diosmin and group T (36) treated with tranexamic acid. Sample size was calculated by sample size calculator (for quantitative data) according to the formula $N=(Za/2)^2/E^2$, where N=required sample size, the critical value would be $Za/2=1.96$ considering 95% confidence interval, E=relative precision, if the incidence estimation falls within 10% of the true proportion with 95% confidence, then $E=0.23$, and the value of the required sample size would be: $N=(1.96)^2/(0.23)^2=72.53=72$. Group D: 36 patients and group T:36 patients. Initially 90 patients were selected. Among them, 6 patients withdrew consent and 8 were excluded on the basis of exclusion criteria. The groups were selected using purposive sampling technique. Women of reproductive age group aged between 18-45 years, with normal pelvic examination, negative cervical cytology with menstrual blood loss ≥ 80 ml or bleeding more than normal cycle or ≥ 8 days or passage of clots more than 1 cm or PABC score of >100 for at least one cycle with or without signs of anemia were included. While women with post-menopausal bleeding PV, fibroids, adenomyosis or endometrial abnormalities, known cases of endometrial and cervical cancer or with hypothyroidism or hyperprolactinemia, pelvic inflammatory disease (PID), with liver or vascular disease or women who are immunocompromised or who had contraindications for diosmin and tranexamic acid use or with haemoglobin

<7 gm% who need additional hematinic or blood transfusion were not included in the study. Two groups formed were compared and then group D were given tablet Diosmin 500 mg thrice daily from day-1 to day-5 of the menstrual cycle. They were asked to take the tablet cyclically for a period of three months. Group T were given tranexamic acid 500 mg thrice daily from day-1 to day-5 of menstrual cycle for a period of three months. The patients in both the groups were asked to come at the end of each month for a total of three months. The PBAC score at the end of the third month were taken for comparison in the study along with endometrial thickness and the hemoglobin concentration. The results were compared with the values present before treatment was initiated. Collected data were analyzed for sensitivity, specificity, positive predictive value, negative predictive value and p value with statistical software GraphPad instat.

RESULTS

A total of 90 patients have been selected initially for our study. Among them 6 people withdrew their consent to be a part of this clinical trial and 8 patients have been excluded based on the exclusion criteria mentioned above and 4 did not show up for follow up. Finally, 72 patients were taken for randomization into two groups of 36 each. There were no refusals after randomization. So, data from 72 patients were available for analysis; group D, group T. Observations were tabulated in excel sheets and analyzed. Continuous data was expressed as mean \pm SD. Statistical tests were considered significant when $p<0.05$. All analyses were conducted using statistical software Instat.exe2003.

Table 1: Distribution of HMB patients according to demographic patterns, Hb%, PBAC score, duration of cycle and symptoms, endometrial thickness.

Parameters (Mean \pm SEM)	Group D (n=36)	Group T (n=36)	P value
Age (Years)	34.82 \pm 1.22	34.14 \pm 1.09	0.46 (NS)
Parity	2.25 \pm 0.2	2.08 \pm 0.17	0.26 (NS)
BMI (Kg/m ²)	24.22 \pm 0.54	24.05 \pm 0.55	0.41 (NS)
Duration of symptoms (Months)	4.83 \pm 0.24	5.98 \pm 0.74	0.07 (NS)
Duration of menstrual cycle (Days)	8.69 \pm 0.34	8.25 \pm 0.26	0.15 (NS)
PBAC score	423.52 \pm 9.88	441 \pm 8.87	0.09 (NS)
Hb%	9.3 \pm 0.16	9.38 \pm 0.16	0.37 (NS)
Endometrial thickness (mm)	11.13 \pm 0.23	11.63 \pm 0.25	0.37 (NS)

Table 1 shows the mean age, BMI, parity, duration of symptoms for group D and that of group T are statistically not significant. The mean PBAC score of group D was calculated to be 423.52 ± 9.88 , and that in group T the mean PBAC score was 441 ± 8.87 . The $p=0.09$ (>0.05) which revealed the difference in data in both the groups was statistically not significant. Moreover, the mean endometrial thickness (mm.) in both groups: group D and T, groups respectively was, 11.13 ± 0.23 and 11.63 ± 0.25 . The $p=0.08$ (>0.05), therefore the difference in data in both

groups were statistically insignificant. Moreover, the mean Hemoglobin concentration (%) for both groups (D, T) respectively are 9.3 ± 0.16 and 9.38 ± 0.16 and the $p=0.37$ (>0.05) which revealed that the difference in data in both groups were statistically insignificant. Furthermore, the average duration of menstrual cycle among group D is 8.69 ± 0.34 and in group T it was 8.25 ± 0.26 . The $p=0.15$ (>0.05), thus there is no statistically significant difference between the two groups.

Table 2: Effect of drugs used in two groups.

Parameters		Before treatment	After treatment	P value	Percentage reduction/improvement after treatment (%)
PBAC score	Group D	423.52 ± 9.88	165.91 ± 22.41	<0.0001 (Significant)	60.5
	Group T	441 ± 8.87	177.94 ± 22.47	<0.0001 (Significant)	59.6
Average duration of menstrual cycle (Days)	Group D	8.69	5.86		32.56
	Group T	8.25	6.11		29.53
Endometrial thickness (mm)	Group D	11.14 ± 0.23	7.2 ± 0.24	<0.0001 (Significant)	35.3
	Group T	11.63 ± 0.25	9.21 ± 0.29	<0.0001 (Significant)	20.8
Hb%	Group D	9.3 ± 0.16	9.44 ± 0.15	0.27 (NS)	1.5
	Group T	9.20 ± 0.13	9.27 ± 0.18	0.30 (NS)	0.76

Table 3: Distribution of failure rates in group D and T.

Variables	Group D	Group T
Number of women who required other treatment	9	9
Percentage of failure rate	25%	25%

DISCUSSION

In our study after 3 months of treatment; the patients in group D had an initial PABC score of 423.52, and at the end of three months it decreased to 149.89. The reduction in the score was 60.5%. The $p<0.0001$. The patients in group T had a PABC score of 441, at the end of three months it decreased to 177.94. The reduction in the score was 59.6%. The $p<0.0001$ both the $p<0.05$; therefore, they are statistically significant. So, it is clearly evident from above figures that the PBAC score decreased in both group D and group T patients, but the reduction was similar in both groups.

These findings were similar to the study conducted by Wellington et al in women with idiopathic menorrhagia in whom tranexamic acid 2-4.5 gm/day for 4-7 days was shown to reduce menstrual blood loss by 34-59% significantly more than placebo, mefenamic acid, fluribiprofen, ethamsylate and oral phase norethisterone at clinically relevant doses.⁶ In a larger trial it was found that 81% women were satisfied by treatment with tranexamic acid. In another study by Leminen et al showed that tranexamic acid reduces menstrual blood loss by 26-60%.⁷

While in another study by Kiseli et al similar results were obtained.⁸ There was a reduction of 60.8% of menstrual blood loss in patients treated with tablet tranexamic acid.

Alanwar et al conducted a randomised double-blind clinical trial: oral micronised flavonoids versus tranexamic acid for treatment of HMB secondary to copper IUD use.⁹ Mean PBAC scores were significantly improved in the tranexamic acid group compared with the micronised flavonoids group (236 ± 48 , 105 ± 26 , 97 ± 16 and 93 ± 15 at the baseline, first, second and third study cycle, respectively, versus 227 ± 52 , 139 ± 29 , 128 ± 25 and 125 ± 24 in the micronised flavonoids group; $p=0.01$). Moreover, the number of bleeding days and number of pads used were significantly reduced in the tranexamic acid group compared with the micronised flavonoids group. But the main cause of bleeding caused by IUD is distortion of endometrial vasculature i.e., direct effect of device on superficial vessels causing abrasions and erosions.^{4,5} This bleeding will be more effectively controlled by tranexamic acid as it has antifibrinolytic actions. While the main cause of HMB during reproductive years is imbalance in local prostaglandins and diosmin acts by suppressing prostaglandins E_2 , $F_{2\alpha}$, TXA_2 and prostacyclins.^{4,19}

A study conducted by Mukherjee et al on treatment of AUB with micronized flavonoids (Diosmin) showed 51.9% reduction in PBAC score which is similar to our study.¹⁰ This study also showed reduction in duration of menstrual cycle from 8.1 days to 5.5 days. This reduction is similar to results obtained in our study. Another study conducted by Bahman et al on effects of quince paste in

HMB.¹¹ Quince paste contains micronized flavonoids. The study showed significant reduction in bleeding score after two months of treatment and also significantly improved the quality-of-life score.

CONCLUSION

In this study it was found that both tranexamic acid and diosmin were effective in reduction of HMB, as evidenced by reduction of PABC score, average duration of menstrual cycle and endometrial thickness. The reduction of menstrual blood loss was equal by tranexamic acid and diosmin. The improvement in haemoglobin percent was only marginal. And the improvement was similar for patients being treated with tablet tranexamic acid and tablet diosmin. The patients, who did not respond adequately to therapy, ultimately had to be shifted to other modes of treatment. It was found that the failure rates were same in both groups. Minor side effects like nausea and dyspepsia were noted in patients in both the groups. None were significant, enough to lead to discontinuation of treatment. Thus, to conclude both tranexamic acid and diosmin are equally effective in treatment of HMB, in terms of PABC score, average duration of menstrual cycle, endometrial thickness, improvement of dysmenorrhea and lesser failure rates.

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