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Diosmin for Treatment of Menorrhagia in Women Using Copper IUD

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ABSTRACT
Background: Many ladies deal with the difficulty of menorrhagia. Among women aged 30 to 49 years, one in twenty suffers from menorrhagia, with 30% claiming their IUD is to blame for 10% to 15% of their bleeding.
Objectives: This study aimed to determine if diosmin is effective in lowering menstrual blood loss in IUCD-afflicted women who have menorrhagia. **Patients and methods:** One hundred ladies were enrolled in this clinical trial investigation. They were selected among the women who went to the Family Planning Clinic, Ain Shams University's School of Medicine. They were complaining of heavy periods after switching to a copper IUCD. The study was conducted during the period from October 2015 to August 2016.
Results: However, there was statistical significant difference between bleeding before therapy and after the first cycle of treatment in both groups, but no difference in bleeding during the first, second, or third cycles of treatment. However, there were notable differences in the groups' mean bleeding days before and after therapy. **Conclusion:** Diosmin is a drug that is beneficial in reducing the increased menstrual blood loss in women who are using copper IUDs, according to the study's findings.
Keywords: Diosmin; Menorrhagia; Copper IUD.

INTRODUCTION

Numerous ladies suffer from menorrhagia. One from twenty women between the ages of 30 and 49 years suffers from menorrhagia, and roughly 30% of these women attribute 10% to 15% of their bleeding to their IUD [(1)]. IUDs have the lowest failure rate of all forms of birth control, at less than 1% [(1)]. This gadget is used by over 100 million women worldwide [(2)]. IUD-related side effects including cramping and heavier periods are rather prevalent [(3)]. In addition, there is a risk that the bleeding will be severe enough to cause iron deficiency anaemia [(4)]. The cumulative net chance of removal of a Copper T380A IUD for bleeding after 12 years of usage was 36 per 100 women in a big study funded by the World Health Organization [(5)].

Oral tablets containing the flavonoid glycoside diosmin (Daflon ®500, Servier Egypt, 6th October, Egypt) were utilised in the current investigation. Diosmin preserves the microcirculation by preventing the process that damages the microcirculation. It fights venous inflammation by reducing leukocyte activation and, as a result, by suppressing the production of inflammatory mediators, primarily free radicals and prostaglandins. For this reason, diosmin restores normal capillary permeability and fortifies capillary resistance [(6)].

Prostaglandin E_2 and prostaglandin F_2 levels in the endometrium are higher in women who have heavy menstruation. When cyclooxygenase is suppressed, as it is by NSAIDs, prostaglandin levels decrease. Mefenamic acid, naproxen, ibuprofen, flurbiprofen, meclofenamic acid, diclofenac, indomethacin, and acetylsalicylic acid were discovered to be more efficient than placebo at reducing menstrual blood loss in women with regular menstrual cycles, but less effective than tranexamic acid, according to a Cochrane review published in 2013 [(7)].

PATIENTS AND METHODS

One hundred females, through the period from October 2015 to August 2016, participated in this investigation. They were chosen among the ladies who presented to Ain Shams University Family Planning Clinic with complaints of heavy menstrual bleeding caused by the copper IUCDs they were now using. All women underwent the same processes, which included a thorough clinical history that took into account factors such as age, parity, IUCD usage length, menorrhagia duration, and prior use of alternative contraceptive methods.

The following factors should be included in all of the instances in this study: The data from this research were entered onto ClinicalTrials.gov with the identifier NCT02616731.

Inclusion Criteria: Those included in the study were between the ages of 20 and 40 years, had no history of systemic causes of abnormal uterine bleeding (such as hypertension or hemorrhagic blood diseases), had no other local causes of abnormal uterine bleeding (such as fibroid, adenomyosis, or polyps), did not take any drugs that decreased blood coagulation, and had a properly fitted and non-misplaced IUD as determined by ultrasound.

Exclusion criteria: Factors that increase the likelihood of abnormal uterine bleeding include being between the ages of 20 and 40, having irregular menstrual cycles, having a history of hemorrhagic blood diseases or hypertension, having a uterine fibroid, adenomyosis, or polyps, or using blood-thinning medications or having a missing intrauterine device (IUD).

The patients were divided into two equal groups: ***1st group*****:** used placebo as control group and ***2nd group*** that received 500 mg t.d.s. of diosmin oral tablets

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(Daflon®) starting on the first day of the menstrual cycle until the bleeding stopped.

Participants were asked about their menstrual histories before enrolling in the research. This included the frequency and length of their cycles, any symptoms they had during their periods, and whether or not they experienced any bleeding in between periods. Medical conditions, drug use, and blood abnormalities were also taken into account.

The transvaginal ultrasound was performed to rule out potential local reasons of irregular uterine bleeding, such as a misplaced IUD. All participants had a complete blood count (CBC) taken before the trial began to rule out the possibility of anaemia. The potential for adverse effects and the recommended ingestion technique were both discussed with both groups. Patients in each group were instructed to stick to their group's treatment plan for the next three cycles. A third CBC was taken after the third cycle.

Patients were warned that the medicine might cause adverse responses including: nausea, vomiting, diarrhoea, itchy skin, anaphylactic shock, and anaphylactoid reactions. Adverse effects on patients' quality of life, including thromboembolic events (such as abdominal distress, nausea, diarrhoea, headache, weird or unpleasant sensations in the tongue, vomiting, and lack of appetite).

Ethical Approval:

Informed written permissions were obtained from all participants after the research was reviewed and approved by Ain Shams University Ethics Board (IRB00009898). Work on people has been done in line with the principles in the Declaration of Helsinki from the World Medical Association.

Statistical analysis: SPSS, the Statistical Package for the Social Sciences, version 20.0, was used for the data analysis. The quantitative data were summarised using mean and standard deviation (SD). Indicators of frequency and percentage were used to present qualitative information. The two means were compared using a t-test for independence. To analyse the relationship between two qualitative factors, we used the Chi-square (X2) test of significance. $P \leq 0.05$ was considered significant.

RESULTS

Table (1) showed that mean age of the studied Diosmin group ,it was 28.64 years and 62% of participants were working.

Table (1): Demographic data

		Diosmin (N=50)	
		Mean	**SD**
Age (years)		28.64	5.68
		N	**%**
Occupation	**Working**	31	62.0
	Housewife	19	38.0

Table (2) showed that there was no statistically significant difference between the two groups on the baseline measurement ($p > 0.05$).

Table (2): Baseline measurements

	Group				t*	P value
	Diosmin (N=50)		Control (N=50)			
	Mean	**SD**	**Mean**	**SD**		
Number of bleeding days	9.52	1.57	9.36	1.63	0.50	0.62
Number of napkins/day	6.14	1.25	5.96	1.19	0.74	0.46
Hb level	10.31	0.73	10.46	0.74	1.02	0.31

*Independent samples t test

This study showed significant statistical difference between both groups regarding second cycle after treatment ($p < 0.05$) as shown in table (3).

Table (3): Second cycle after treatment

	Group				t*	P value
	Diosmin (N=50)		Control (N=50)			
	Mean	**SD**	**Mean**	**SD**		
Number of bleeding days	5.46	2.04	6.80	2.09	3.24	**0.002**
Number of napkins/ day	2.78	0.71	3.26	1.08	2.62	**0.01**

*Independent samples t test

Table (4) showed significant statistical difference between both groups regarding third cycle after treatment ($p < 0.05$).

Table (4): Third cycle after treatment

	Group				t*	P value
	Diosmin (N=50)		Control (N=50)			
	Mean	SD	Mean	SD		
Number of bleeding days	5.42	2.04	6.78	2.06	3.31	**0.001**
Number of napkins/day	2.76	0.72	3.26	1.08	2.72	**0.008**

*Independent samples t test

Regarding number of bleeding days, post hoc test showed that there was significant difference between before vs first cycle, before vs second cycle, before vs third cycle). Also, there was significant difference between the two groups regarding change in number of bleeding days over time (Table 5).

Table (5): Comparison between the two groups regarding change in number of bleeding days

Group	time	Mean	Std. Error	95% CI		F* (P value)	F** (P value)	F*** (P value)
				Lower Bound	Upper Bound			
Diosmin	**Before ttt**	9.520	0.226	9.072	9.968	402.62 **(<0.001)**	7.15 **(0.009)**	20.81 **(<0.001)**
	First cycle	5.480	0.289	4.906	6.054			
	Second cycle	5.460	0.292	4.880	6.040			
	Third cycle	5.420	0.290	4.844	5.996			
Control	**Before ttt**	9.360	0.226	8.912	9.808			
	First cycle	6.820	0.289	6.246	7.394			
	Second cycle	6.800	0.292	6.220	7.380			
	Third cycle	6.780	0.290	6.204	7.356			

Repeated measure ANOVA test

Regarding difference between different times points in number of napkins/day, post hoc test showed that there was significant difference between before vs first cycle, before vs second cycle and before vs third cycle. Difference between the two groups regarding mean number of napkins/day over time (**Table 6).**

Table (6): Comparison between two drugs regarding change in number of napkins

Group	time	Mean	Std. Error	95% CI		F* (P value)	F** (P value)	F*** (P value)
				Lower Bound	Upper Bound			
Diosmin	**Before ttt**	6.140	0.173	5.798	6.482	371.48 **(<0.001)**	4.68 **(0.03)**	4.53 **(0.03)**
	First cycle	2.820	0.131	2.560	3.080			
	Second cycle	2.780	0.130	2.523	3.037			
	Third cycle	2.760	0.130	2.502	3.018			
Control	**Before ttt**	5.960	0.173	5.618	6.302			
	First cycle	3.300	0.131	3.040	3.560			
	Second cycle	3.260	0.130	3.003	3.517			
	Third cycle	3.260	0.130	3.002	3.518			

Repeated measure ANOVA test.

There was difference between the two groups regarding mean Hb level, difference between two groups regarding change in Hb level after treatment. **Table (7)**

Table (7): Comparison between two drugs regarding change in Hb level (Repeated measure ANOVA test)

Group	time	Mean	Std. Error	95% CI		F* (P value)	F** (P value)	F*** (P value)
				Lower Bound	Upper Bound			
Diosmin	**Before ttt**	10.308	0.104	10.101	10.515	48.26 **(<0.001)**	0.33 (0.57)	14.60 **(<0.001)**
	After ttt	10.494	0.105	10.285	10.703			
Control	**Before ttt**	10.458	0.104	10.251	10.665			
	After ttt	10.512	0.105	10.303	10.721			

DISCUSSION

Through a randomised controlled trial with 100 IUD-wearing women, we compared the effectiveness of diosmin vs placebo as a control group for preventing post-implant haemorrhage (TCu-380).

Findings from this research suggest that diosmin is an effective medicine for reducing the increased menstrual blood loss experienced by women who use a copper intrauterine device (IUD). In order to identify IUD-caused menorrhagia, women were given pads of the same size and shape and advised to wear them for the duration of their next menstrual cycle. To gauge how rapidly patients were bleeding, we used a visual blood evaluation chart (patient-based component assessment of change, PBAC).

PBAC is a valid and objective metric for assessing bleeding [(8)]. With a sensitivity of 0.96 and a specificity of 0.92, the percentage change in blood showed a strong relationship with this method (ICC = 0.86, 95% CI = 0.80-0.91) [(9)]. This finding is consistent with that of **EL -Nashar *et al.*** [(10)] and **Zakherah *et al.*** [(11)] who measured their progress before and after therapy using PBAC. It has been shown to be a reliable and easy-to-use instrument for semi-objective evaluation of menstrual blood loss (MBL), and it may be used in clinical settings to help determine whether or not a patient is happy with their therapy and whether or not they should continue

There was statistical insignificant difference between the two groups in the number of abortions or IUCD use.

The average number of napkins used each day, the number of bleeding days, and the haemoglobin level were all the same between groups before treatment (p value > 0.05).

The p-value for the difference in bleeding (days) between the two groups was significantly less than 0.05, indicating a statistically significant difference. The two groups also differed significantly in terms of how long they bled for. Over the course of the study's three cycles, the average length of time that daflon users had menstruation was 6.82 2.07, 6.80 2.09, and 6.78 2.06. These findings are consistent with those reported by **Kriplani *et al.*** [(12)] who used a prospective randomised study of 100 cases to compare the efficacy and safety of 2 g/day TXA in dysfunctional uterine bleeding (DUB) to that of cyclical 10 mg twice-daily medroxyprogesterone acetate (MPA) for 3 cycles. The average PBAC score dropped from 370.9 before treatment to 156.6 after 3 months of MPA (p 0.005 in both groups), and the average percentage of blood loss was reduced by 57.7% with MPA. Patients were followed monthly for 3 months.

Bleeding was significantly different between the two groups before treatment and after the first cycle in both treatment groups, but during the first, second, and third cycles, there was no difference. The average number of days of bleeding before and after therapy varied significantly between the two groups.

This study found a statistically significant difference between the two groups in terms of napkins used per day after treatment (p = 0.05). This difference was most pronounced in the first six days of menstrual bleeding, while it became less noticeable after that because MBL had already decreased in both groups. There was a statistically significant difference in the daily napkin decrease rates between the daflon and control groups. The findings are consistent with those of a randomised controlled study comparing the effectiveness of tranexamic acid, ethamsylate, and mefenamic acid in the treatment of dysfunctional uterine haemorrhage that was done on 76 women and reported by **Bonnar & Sheppard** [(13)]. The findings indicated that although ethamsylate was unsuccessful, both mefenamic acid and tranexamic acid were able to significantly lower MBL by 20% and 54%, respectively. Although **Vermylen *et al.*** [(14)] found no decrease in napkin usage during active therapy with tranexamic acid, other studies have shown that this may be due to a placebo effect.

In this study, the control and daflon groups did not differ significantly in Hb levels after three cycles of treatment (p > 0.5). However, there was a difference between the two groups in terms of the change in Hb levels after treatment.

Anemia was shown to be 74% predictive of menorrhagia when comparing Hb levels to menstrual blood loss (measured using the alkaline haematin technique) in a study by **Barr *et al.*** [(15)]. These side effects may be menstrual symptoms rather than treatment-related side effects, and many women who report them during menorrhagia therapy may not have the condition [(13)].

CONCLUSION

Results from this trial showed that diosmin was beneficial in reducing the increased menstrual blood loss experienced by women using a copper intrauterine device.

DECLARATIONS

Consent for Publication: I confirm that all authors have agreed to submit the manuscript.
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