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ORIGINAL ARTICLE

Tranexamic acid versus Depot- Medroxyprogesterone acetate in treatment of perimenopausal irregular uterine bleeding: Randomized clinical trial

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ABSTRACT

Background: Perimenopause is the transitional phase to non-reproductive life in which the ovarian follicular function declines, leading to fluctuating and in the end decreased levels of estrogen and progesterone and high levels of FSH. **Aim and objectives**: compare the effectiveness of DMPA and TXA in treatment of perimenopausal irregular uterine bleeding. **Subjects and methods:** RCT was conducted on Outpatient clinic , Aswan university hospital where 110 consented volunteers who were divided into two groups, 55 each, 1st group received TXA 500 mg 4times daily for 5 days during episode , and in the other received 150mg of DMPA once IM. Follow up for bleeding 3 months later by pictorial blood loss assessment chart (PBAC). **Results**: After one month, (PBAC) was significantly higher in group II compared to group I (0.000). After 3 months, PBAC was significantly higher in group II compared to group I (0.00). There was significant decrease in PBAC after 3 months in comparison with that after 1 month in both group I ($p<0.001$) and group II ($p<0.001$). **Conclusion**: Long-term use of MPA is as effective as TXA in the treatment of perimenopausal irregular uterine bleeding.

INTRODUCTION:

AUB is a symptom and not a disease. It is one of the most frequently encountered complaints in gynecologic practice. It accounts for more than 70% of all gynecological consultations in the peri- and post-menopausal age group.(1)

Tranexamic acid, work by preventing fibrin degradation and is effective treatment for patients with chronic AUB. it has been shown to reduce bleeding in these patients by 30–55%.(2)

Medroxyprogesterone acetate and high-dose oral progestins are used to treat AUB in women who have a contraindication or prefer to avoid estrogen in COCS treatment. Tranexamic acid is an option for women who do not desire or should not use hormonal treatment.(3)

From the above data, our hypothesis is that, depot-Medroxyprogesterone acetate 150 mg as a long acting high dose progestin may play a good role in treatment of AUB and easy monthly used to use compared to other choices as tranexamic acid which used daily.

AIM AND OBJECTIVES: compare the effectiveness of DMPA and TXA in treatment of perimenopausal irregular uterine bleeding.

MATERIALS AND METHODS:

The present study was carried out at the Outpatient gynaecology clinic at Aswan university hospital, A total of 110 women with perimenopausal irregular uterine bleeding divided into two

groups, 55 women will receive tranexamic acid (TXA) 500 mg 4times daily in one group, and in the other, they will receive 150mg of medroxyprogesterone acetate once intramuscular. This number will be large enough to give 95% level of confidence and 80% power of the study,We use Steven K. Thompson equation(4) to calculate the sample size, from the next formule

$$n=\frac{N\times p(1-p)}{\left[\left[N-1\times(d^2\div z^2)\right]+p(1-p)\right]}$$

Where n:sample size (57), N:Population size(66), Z:Confidence level at95%(1.96), d:Error proportion(0.05), P:Probability(50%).

Statistical analysis of the data:

Data will be collected, tabulated, then analyzed using IBM©SPSS© Statistics version 22 (IBM© Corp., Armonk, NY).

Normally distributed numerical data will be presented as mean and SD, and skewed data as median and interquartile range. Qualitative data will be presented as number and percentage.

Comparison of normally distributed numerical data will be done using the unpaired t test. Skewed data will be compared using the Mann-Whitney test. Categorical data will be compared using the Pearson chi-squared test or Fisher's exact test, when appropriate.

RESULTS:

In the present study, there **was no statistically significant between two groups** through baseline data, vital signs and pretreatment laboratory investigations **including u/s.**

During follow up after treatment, we reported after the 1st month, that there was statically significant increasing in hemoglobin levels in (group I) compared to hemoglobin levels in (group II) with (p-value=0.038*) as the mean 12.32 g/dl and 11.87 g/dl in (group I) and (group II) respectively with SD around 1.1 in comparison to the baseline hemoglobin levels

However, there was a highly statically significant increasing in both studied groups based on the base line hemoglobin levels (p-value=0.000).

After the 3rd month, we found that the hemoglobin levels increased with high statically significant levels in both groups compared with the baseline hemoglobin levels and the 1st month hemoglobin levels with (p-value=0.000) as the mean hemoglobin levels in (group I) was 14.15g/dl compared with 11.36 before treatment and 12.32 after the 1st month and Also in (group II), the mean hemoglobin levels after the 3rd month of was 13.13g/dl compared with 11.42g/dl before treatment and 11.87g/dl after the 1st month respectively.

During follow up through PBAC after 1st month of treatment, there was a decrease in the amount of blood loss throughout the period in both groups based on history taken as a base line data before treatment but there was a high statistically significant decrease in group II compared to group I with (p value 0.000), This decrease was apparent in the total amount of blood loss with mean about 297 ml and 380 ml in group I and group II respectively with standard deviation around 100 ml. This SD was large due to extreme data due to failure of response in some cases.

However, after 3 months of treatment, we found that, the blood loss was decreased with high statistically significant in both groups compared with the 1st and the 3rd month in the total amount of blood loss (P value 0.000).

The mean blood loss in group I after 3rd month of treatment, was 154 ml compared with 297 ml after 1st month and in group II 284 ml compared with 380 ml after 1st month of treatment.

Also, there was decrease in standard deviation in the 1st group to be 53.8 and 96.8 in group II. This means that the extreme data decreased and so on after 3rd month of treatment, there was high statistically significant decrease in group II compared to group I (P value 0.000).

We recorded some complications as gastrointestinal discomfort after treatment in the two studied groups which was more in (group I) with statistically significant increased compared with (group II) with ($p<0.001$) 11 cases complaining of gastrointestinal discomfort representing 20% of (group I) compared with zero cases in (group II), Also nausea and vomiting were more in (group I) but with no statistically significant differences as (P value =0.243) as we found only 3 cases of group I were complaining of nausea/vomiting representing 5.5% , compared with zero cases in (group II).

There were some vaginal spotting during treatment period with statistically significant higher in (group II) compared to (group I) with (P value <0.001) as 23 cases complaining of spotting representing 41.8% of (group II) compared with only 4 cases representing 7.3% of (group I).

In both groups only two women complained of bleeding in spite of treatment but with no statistically significant differences, as P value = 1.00, with percentage 3.6% of both groups.

Finally we found that, 35 cases with no complications reported representing 63.6% of (group I) compared with 30 cases representing 54.5% of (group II) but also with no statistically significant value as (p-value =0.332).

***Comparison between the two studied groups regarding Hemoglobin level**

Hemoglobin level (g/dl)	Group I (n= 55)	Group II (n= 55)	P-value1
At baseline: Mean ± SD	11.36 ± 1.14	11.42 ± 1.08	0.791
Range	9.3-13.3	9.8-13.2	
After 1 month: Mean ± SD	12.32 ± 1.14	11.87 ± 1.13	0.038*
Range	10.4-14.7	10.2-13.8	
P-value[2]	0.000*	0.000*	
After 3 months: Mean ± SD	14.15 ± 1.20	13.13 ± 1.15	0.000*
Range	12.2-17.1	11.3-15.4	
P-value[2]	0.000*	0.000*	

***Comparison between the two studied groups regarding PBAC**

#PBAC (ml)	Group I (n= 55)	Group II (n= 55)	P-value[1]
After 1 month: Mean ± SD	296.84 ± 107.95	380.78 ± 117.57	0.000*
Range	110.0-448.0	168.0-549.0	
After 3 months: Mean ± SD	153.65 ± 53.84	283.78 ± 96.87	0.000*
Range	65.0-302.0	134.0-452.0	
P-value[2]	0.000*	0.000*	

#PBAC: pictorial blood loss assessment chart

***Comparison between the two studied groups regarding complications**

Complications	Group(n= 55)		Group II (n= 55)		P-value
	No.	%	No.	%	
Gastrointestinal discomfort	11	20.0%	0	0.0%	0.000*
Nausea/ vomiting	3	5.5%	0	0.0%	0.243
Spotting	4	7.3%	23	41.8%	0.000*
Still bleeding	2	3.6%	2	3.6%	1.000
No complication	35	63.6%	30	54.5%	0.332

DISCUSSION:

AUB is a frequent complaint in perimenopausal women and is also the most common cause of hysterectomy in this group. Abnormal bleeding may be chronic when it persists for more than 6 months, or acute when an episode of heavy bleeding requires immediate intervention.(5)

Medical options mentioned earlier such as hormonal contraceptives, DMPA, LNG-IUD, GnRH agonists, and tranexamic acid are all available therapies for AUB (6)**.**

In our study ,we reported that, after the 1st month, there was statically significant increasing in hemoglobin levels in (group I) compared to hemoglobin levels in (group II) with (p-value=0.038*) in comparison to the baseline hemoglobin levels. However ,there was a highly statically significant increasing in both studied groups based on the base line hemoglobin levels (p-value=0.000).

Moreover, after the 3rd month, we found that the hemoglobin levels were increasing with high statically significant levels in both groups compared with the baseline hemoglobin levels and the 1st month hemoglobin levels with (p-value=0.000).

In agreement with **Kriplani et al., 2006** (7) **,** who note that, there was decrease of blood loss in both treated groups as the mean (PBAC) score decreased from 356.9 to 141.6 in the TXA group and from the pre-treatment 370.9 to 156.6 with MPA and mean reduction of blood loss was 60.3% with TXA and 57.7% with MPA after 3 months ($p < 0.005$ in both groups).

But our results were not matched with **Kriplani** (7) results as regards the degree of reduction in both groups as they were reported that, the mean reduction of blood loss was 60.3% with TXA and 57.7% with MPA after 3 months ($p < 0.005$ in both groups).

Also, Kriplani et al., 2006, reported that, there was lack of response during treatment was seen in three patients (6.1%) TXA and in 13 patients (28.9%) with MPA ($p = 0.003$). Moreover, they noted that, during the 6 months study period more hysterectomies were performed in the MPA than in the TXA group (17.8% vs 4%; $p = 0.002$).

However, he reported that, 3 months after stopping the treatment, 66.7% in TXA group and only 50% in MPA had a recurrence of menorrhagia, ($p = 0.155$).

The results of **Kriplani et al., 2006** was with the use of cyclical 10 mg twice-daily medroxyprogesterone acetate (MPA) for 3 cycles not with 150 mg of
medroxyprogesterone acetate once intramuscular as we use which may the cause of the difference in the results.

Moreover, follow up not extended after the 3 month of treatment which may add more data for comparison.

However, **Goshtasebi et al., 2013** (8) demonstrated that both treatments (long-term MPA and Tranexamic acid) reduced HMB, improved women's quality of life, and increased Hb concentrations. There were no statistical differences between outcomes of TXA and MPA. However, TXA was better tolerated and had a higher level of patient satisfaction. This may be due to the decline in duration of bleeding, lower side-effects, and significant improvement in general health, and shorter period of using drug in a cycle.

Our results were in line with the study by **Goshtasebi et al., 2013** who reported that Menstrual blood loss determined with the PBAC, duration of bleeding, and hematological assessment decreased significantly in both groups over the follow-up period. There was a significant statistical difference in duration of bleeding between TA group compared with MPA group (7.8 days decreased to 6.68 days vs. 8.4 to 8.06 days, respectively, $P = 0.05$), but in other criteria we did not find any difference between the two groups. In addition, a patient's baseline PBAC score had a statistically significant effect on the change in PBAC from baseline. Other variables yielded minimal differences.

However, **Goshtasebi et al., 2013** reported that of the 90 patients who used study medication for at least one cycle, 25.5 % ($n = 23$) experienced adverse effects in both groups; nausea with vomiting, headaches, vertigo, spotting, increase blood loss, and breast tenderness.

Also, the Randomized controlled trial by **Batool et al., 2018** (9) aimed to determine efficacy of tranexamic acid in heavy menstrual bleedings, the study included 80 patients. Patients were randomly divided into two groups; Group A, oral dosage of tranexamic acid 3.9-4 g/day for 4-5

days starting from the first day of the menstrual cycle and Group B (Placebo), folic acid supplementation dose 400µg. In agreement with our results, they reported that a significant difference in mean blood loss was found between two groups. Patients treated with tranexamic acid, 83% of them had <80 ml blood loss as compared to placebo (p=0.00). In line with our results **Ammerman & Nelson, 2013(10)** reported that All 48 women stopped bleeding within 5 days; 4 women had spotting only at the time of their last contact during the 5-day follow-up. Mean time to bleeding cessation was 2.6 days.

While the study by **Jenni et al., 2020** (11) revealed that the pre-treatment PBAC score compared with the first 3-month PBAC score in Tranexamic acid showed a decrease also but was not statistically significant(p=0.051). The PBAC scores at 3 months and at 6 months of drug usage in group 2 also did not show any major difference (p=0.775). However, compared to the pre-treatment score, at the end of 6 months there was significant improvement in the PBAC score (p=0.006).

In the line of our results, **Gultekin et al., 2009** (12) , reported that, oral tranexamic acid is a reasonable treatment option for patients with excessive dysfunctional perimenopousal bleeding with a 66.0% response rate. As they found that Median bleeding time was nine days (range 8-12 days) and median Hb was 10.6 g/dL (range 8.2-11.7) before starting the treatment. During follow-up 45 patients were unresponsive to transamine and needed further treatments (overall response rate was 65.9%). Among responsive patients, after three cycles of transamine usage median bleeding time was five days (range 3-8 days) and median Hb values were 12.1 g/dL.

Also Naoulou B&Tsai MC,2012 (13) were reported in there systemic review about the efficacy of Tranexamic acid in the treatment of idiopathic and nonfunctional heavy menstrual bleeding that, the available evidence indicates that treatment with TA is effective and could potentially improve the quality of life of patient presenting with idiopathic and secondary heavy menstrual bleeding. TA appears to be superior to placebo, the non-steroidal anti-inflammatory drug mefenamic acid, the hemostatic agent ethamsylate and luteal phase norethisterone for the treatment of idiopathic heavy menstrual bleeding.

CONCLUSION: Long-term use of MPA is as effective as Tranexamic acid in the treatment of perimenopausal irregular uterine bleeding and increasing quality of life.

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