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Medroxy-Progesterone acetate in AUB-O: is the intramuscular route better suited for low and middle income countries? An open-labelled randomised controlled trial

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Abstract: *Objective:* Our purpose was to evaluate the efficacy of oral medroxy progesterone acetate and intramuscular depot medroxy progesterone acetate in patients presenting with heavy menstrual bleeding in terms of reduction in the amount of blood loss, side effect profile and compliance. *Study design:* 50 patients with heavy menstrual bleeding were randomized into two groups, patients in group 1 (25 Patients) were given i/m depot medroxyprogesterone acetate on day 3 of menses after recruitment (total dosage 2) and Group 2 (25 patients) were given oral medroxyprogesterone acetate 10mg from day 3 of menses 8 hourly for 7 days followed by 12 hourly for 14 days cyclically for 6 months (total 294 dosages). Patients were assessed on two monthly intervals for next 6 months on the basis of change in haemoglobin levels and menstrual blood loss on the basis of PBAC score and side effects, if any. *Results:* No significant difference was found in the efficacy and side effect profile of i/m depot medroxyprogesteroneacetate and oral medroxyprogesteroneacetate in treatment of heavy menstrual bleeding. *Conclusion:* The findings of present study showed that both DMPA and oral MPA could be offered as an alternative owing to no difference in their clinical efficacy, however DMPA has better compliance and overall cost benefit as compared to oral MPA.

Keywords: Heavy Menstrual Bleeding, Depot Medroxy Progesterone Acetate, PBAC score

Introduction

Excessive bleeding during menstruation affects 1 in 20 women of reproductive age group. It alone accounts for 12% of all gynaecological consultations in a referral facility [1]. When the excessive blood loss results in deterioration of the quality of life, inclusive of physical, social and emotional quality, it is termed as heavy menstrual bleeding [HMB] [2-3]. Globally, HMB remains one of the most common indications for hysterectomy [4].

Since the problem is all pervasive, research for newer methods of management as well as innovations of the existing methodologies is common. High dose oral progestogens have been the standard management of HMB for a long time [5-6]. The treatment necessitates daily ingestion of medication which is expensive and is cited to decrease compliance. This becomes relevant in the context of low and middle income countries [LMIC]. This has therefore let to an increased focus on injectable progestogens as an alternative to oral medication for treatment of HMB.

We aimed to compare the efficacy of oral versus intramuscular depot medroxy-progesteroneacetate [DMPA] in management of HMB by studying the PBAC scores. As a secondary objective, we aimed to analyse the cost benefit ratio and assess the compliance to treatment with the two different methods of drug delivery.

Material and Methods

The present study was an Open-labelled Randomised Controlled Trial [RCT] conducted at Era's Lucknow Medical College for a period of 18 months after due clearance from the institutional ethical committee. Subjects were recruited after informed, written consent, as per the defined inclusion criteria. We studied 50 women from 18 to 45 years who presented with HMB and a Pictorial blood assessment chart [PBAC] score above 100. Exclusion criteria included undiagnosed vaginal bleeding, infertility, women planning a pregnancy, known hypersensitivity to MPA or any of its excipients, known or suspected malignant or pre malignant lesions of breast or genital tract, uterine leiomyomas more than 2mm in size, medical disorders including any history of thromboembolism.

After recruitment, a detailed history including PBAC scoring, examination and transvaginal sonography was done. Women with endometrial thickness of 12mm or more were biopsied using Pipelle to exclude atypia. The subjects were randomly allocated into 2 groups using sequentially numbered opaque sealed envelope [SNOSE] technique. In group 1, the subjects were given 150mg of DMPA intramuscularly [IM] on day 3 of menstrual cycle. This was repeated after 3 months. In group 2, the subjects were given oral Medroxy progesterone acetate [MPA] 10mg, from day 3 of menstrual cycle every 8 hourly for 7 days followed by every 12 hourly for 14 days in every cycle for a total of 6 months. The women were assessed bimonthly for the next 6 months for PBAC scoring, any side effects and haemoglobin levels.

Data was analysed using chi square test for categorical data, paired t test for comparison of pre- and post-treatment PBAC score and hemoglobin level and unpaired t-test for comparison of improvement (post treatment–pre treatment) in PBAC score and hemoglobin level. SPSS Version 21.0 was used for analysis.

Results

50 women were randomly allocated to two groups, both of which were similar in socio-demographic characteristics [Table 1]. Group 1 [n=25] was given injection DMPA 2 doses at 3 months interval intramuscularly. Group 2 [n=25] was given oral MPA in multiple doses over a period of 6 months. We compared clinical as well as non-clinical parameters of the two groups. The clinical parameters included PBAC score, haemoglobin, any adverse effects. The non clinical parameters included compliance to treatment and cost-benefit analysis. Table 2 and 3 compares the clinical parameters between the two groups.

Table-1: Comparison of sociodemographic characteristics in group 1 and group 2

Sociodemographic factors	Group 1	Group 2	P value
Age (mean±SD)	33 ± 7.52	33.48 ± 9.15	0.840
BMI (mean±SD)	23.42 ± 4.69	23.71 ± 4.96	0.829
Nutritional status–			
Underweight	3 (12%)	3 (12%)	
Normal	13 (52%)	12 (48%)	0.990
Overweight	6 (24%)	7 (28%)	
Obese	3 (12%)	3 (12%)	
Socioeconomic status-			
Upper	0 (0%)	0 (0%)	
Upper Middle	2 (8%)	3 (12%)	0.830
Lower Middle	5 (20%)	6 (24%)	
Upper Lower	8 (32%)	9(36%)	
Lower	10 (40%)	7 (28%)	

Table-2: Comparison of pictorial blood assessment chart score and Haemoglobin level between group 1 and group 2 : pre-treatment and at different follow ups					
Timeline [months]	**Group 1**	**Intra group change [Group 1]**	**Group 2**	**Intragroup change [Group 2]**	**P value**
	PBAC score				
0	495.64 ± 332.04		476.76 ± 361.24		0.848
2	195.08 ± 128.62	-300.56 ± 247.79 (p value <0.001)	266.36 ± 264.61	-210.40 ± 194.59 (p value <0.001)	0.232
4	108.32 ± 101.08	-387.32 ± 302.19 (p value <0.001)	177.92 ± 189.76	-298.84 ± 291.31 (p value <0.001)	0.112
6	80.64 ± 59.77	-415.00 ± 328.81 (p value <0.001)	97.20 ± 74.47	-379.56 ± 314.58 (p value <0.001)	0.390
Hemoglobin					
0	10.09±1.05		10.32±1.24		0.493
6	10.17±1.01	0.08±0.35 (p value-0.290)	10.38±1.11	0.06±0.29 (p value-0.288)	0.483

Table-3: Comparison of side effects between group 1 and group 2			
Timeline [months]	**Group 1 No. (%)**	**Group 2 No. (%)**	**P Value**
Weight gain			
6	0 (0%)	1 (4%)	1.000
Drowsiness			
6	0 (0%)	2 (8%)	0.490
Inter menstrual spotting			
6	2 (8%)	3 (12%)	1.000
Breast tenderness			
6	2 (8%)	2 (8%)	1.000

PBAC score: The mean pre-treatment PBAC score was similar in group 1[495.64±332.04] and group 2 [476.76±361.24]. The decline in scores at 2, 4 and 6 months was similar, with no statistical difference between the two groups. After 6 months, mean PBAC score in group 1 was 80.64±59.77 and group 2 was 97.20±74.47.

Hemoglobin levels: The change in pre treatment haemoglobin level was clinically higher in group 1 as compared to group 2. However, this difference was not statistically significant. Both pre- and post- treatment hemoglobin levels were comparable between the two groups.

Adverse effects: Weight gain, drowsiness, breast tenderness and inter menstrual spotting were the commonly reported adverse effects. A clinically higher proportion of women with adverse effects was noted in group 2. However the difference between the two groups were not significant statistically.

The non clinical parameters studied included compliance to treatment and cost benefit analysis. Difference in compliance between the two groups was not significant [Group 1- 100%; Group 2- 92.1%] [Table 4]. The average economic cost of DMPA was 1280 [INR] and oral MPA was 2364 [INR]. The cost-benefit analysis favoured group 1 by a difference of 1084 [INR] [Table 5].

Table-4: Compliance to treatment protocol			
Group	**Total events**	**Events completed as per schedule**	**% compliance**
Group 1	50	50	100%
Group 2	7350	6762	92%
P value - 0.144			

Table-5: Cost benefit analysis for 3 months treatment					
Component		**Group 1**	**Group 2**	**Difference per patient**	**Direction of benefit**
Direct cost		Rs 680	For 7 Days TDS @6/-per tab=Rs 126/- For 14 days BD Rs=168 For 6 months =294*6 Rs.1764	Rs. 1084	In favour of injectable
Indirect cost	1. Cost of medical consultation	0	0	0	Same
	2. Work opportunity loss	4 hours @ 100/- per hour Rs.400/-	4 hours @ 100/-per hour Rs.400/-	0	Same
	3. Average transportation cost	Rs.200/-	Rs.200/-	0	Same

Discussion

Heavy menstrual bleeding [HMB] is a common gynaecological complaint in LMIC which adversely impacts the quality of life and places considerable economic burden on the health care system. In a multinational cross-sectional evaluation in LMIC of southern Asia and sub-Saharan Africa, the investigators found a prevalence ranging from 38 to 77% [7].

For a problem as rampant as HMB, it becomes important that due attention be given towards identifying and addressing the causes of HMB in LMIC. This would include finding alternatives for treatment so that it becomes affordable and easily available, policy making measures and appropriately directed research. Oral progestogens, which have been extensively used in HMB have two major constraints - daily drug intake and high cost. The short half life [t1/2] necessitates that the drug be given frequently which adversely affects compliance. High cost of the drug is another limitation which becomes important in the context of affordability of women in LMIC.

DMPA has emerged as an alternative that can provide long term efficacy after one time injection. Compared to oral MPA that has to be taken daily for three weeks in every cycle, DMPA has a convenient dosage of three monthly injection. The present study was planned as an open-labelled RCT which tested the relative efficacy of the two modalities in terms of reduction in bleeding, cost and compliance level. Subjects were randomised to either of the two study groups - 1 or 2, and given DMPA or oral MPA for a period of 6 months. Both the groups were similar in socio-demographic and clinical parameters. Both the groups had a significant decrease in menstrual blood loss with MPA. The difference in pre- and post-treatment PBAC score was 415.00+/-328.81 in Group 1 and 379.56+/-314.58 in Group 2. The percentage reduction in mean PBAC score was 83.73% and 79.61 %in Group 1 and Group 2. Arathy et al [8] found a similar [73.85%]percentage reduction in mean PBAC score compared to baseline after 3 months of MPA.

The mean PBAC scores and mean rise in hemoglobin was similar in both the groups at the end of 6 months. The same was observed by Kucuk and Ertan [9] when they compared the efficacy of DMPA with oral MPA in HMB. They concluded that oral MPA and DMPA have similar impact on reduction of bleeding during menstruation, and rise in hemoglobin levels. Bofill et al [10] conducted a systematic review which included 15 RCT comparing oral progestogens to other medical treatment for HMB. They concluded that oral progestogen therapy from day 5 to day 26 of the menstrual cycle was comparable in

efficacy to combined hormonal vaginal ring. However, levonorgestrel intra-uterine system [LNG-IUS] and Ormeloxifene therapy were superior in reducing menstrual blood loss.

In another study by Erkayiran et al [11], efficacy of DMPA and LNG-IUS was compared in patients with heavy menstrual bleeding due to uterine leiomyoma and they found significant reduction in menstrual blood loss and significant increase in hemoglobin levels in both groups at the end of one year.

We observed a higher proportion of adverse effects [weight gain, drowsiness, inter-menstrual spotting] in women given oral MPA as compared to DMPA. However we did not find this to be statistically significant. It could be because of the small sample size, and low incidence of side effects. Other studies have also not reported any difference in adverse effect profile of oral MPA and DMPA [9]. Common side effects of oral MPA reported by investigators are nausea, vomiting, vertigo, spotting, breast tenderness etc. [12-14]. Goshtasebi et al [12] found 23.5% women reporting at least one side effect while Viesi et al [13] found the number to be as high as 66.7% in oral MPA group. Among studies reporting use of DMPA, no such side effects have been reported [11, 15]. We found 12% women reporting at least one adverse effect with oral MPA and 8 % with DMPA.

With regards to compliance, we found a major clinical difference between DMPA and oral MPA. All women taking DMPA reported for their second dosage, however a total of 588 doses out of 7350 were missed [as reported by patients from memory] in oral MPA group. Comparing the two groups, we had 100% compliance in Group 1 and 92% in Group 2. The difference though clinically relevant, was not significant statistically.

Due to the necessity of daily drug intake, oral progestogens are often not acceptable to many patients. This problem in compliance leads to inadequate treatment and increased chances of fallacious failed medical management. DMPA provides us another route of administration of MPA and relieves the patient of the compulsion for remembrance and daily administration of medication. Besides the convenience of three-monthly dosage, DMPA has benefits in terms of lesser cost than oral MPA for three months. The overall economic benefit in Group 1 was 27,100 [INR]. This figure attains significance when the average monthly income in the state of UP is 20,730 [INR] [per capita income], 5.23 % of salary.

Conclusion

The findings of present study showed that both DMPA and oral MPA could be offered as an alternative owing to no difference in their clinical efficacy, however DMPA has better compliance and overall cost benefit as compared to oral MPA.

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