e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(5); 198-206

Original Research Article

Study on the Management of Heavy Menstrual Bleeding by Low Dose Dexamethasone

Vinay Mirajkar
(MD, DGO.)
Associate Professor, Dep. of Obstetrics and Gynaecology, Pacific Institute of Medical Sciences Umarda, Udaipur, Rajasthan

Received: 09-02-2023 / Revised: 04-03-2023 / Accepted: 23-04-2023
Corresponding author: Dr.Vinay Mirajkar
Conflict of interest: Nil

Abstract

Introduction: Menstruation that is so severe it interferes with a woman's physical, emotional, social, and material well-being is referred to as heavy menstrual bleeding (HMB). Estimates place the prevalence of excessive menstrual bleeding in impoverished countries at 4-9%. It has figured out the causes of HMB and around 48% of patients that are sent to secondary care do not have any evident pathology.

Aims and objectives: The purpose of this research study has been explored to the management of heavy menstrual bleeding by low dose dexamethasone.

Methods: This prospective Randomized Controlled Trial enrolled 100 female patients with heavy menstrual bleeding (HMB) from May 2022 to April 2023. Patients were randomly assigned to receive either placebo or dexamethasone, a synthetic glucocorticoid, in different dosages (0.4 mg, 0.8 mg, 1 mg, 1.2 mg, 1.5 mg, or 1.8 mg) during the luteal phase of three menstrual cycles. Menstrual blood loss was evaluated using a lab-validated method. Inclusion and exclusion criteria were applied, and statistical analysis was performed using SPSS 25 software, including Chi-square and ANOVA tests. Significance level was set at $p<0.05$.

Results: The researcher was divided into two different groups of patients such as placebo and dexamethasone with 20 and 80 patients respectively. Furthermore, the age categories of patients are from 22 to 56 years old. Again, the mean blood loss during menstruation is high around 136.5 mL of dexamethasone. The greatest impact was seen at a 25 mL reduction in menstrual blood loss with the 1/8 mg total daily dose, with a 95% credible interval of 1 to 49 mL. The posterior odds for any benefit over placebo, or at least a 10 mL benefit, for this dose, were 0.98 and 0.89, respectively.

Conclusion: The study has concluded that 0.8mg of dexamethasone taken twice daily for 5 days during the luteal phase of the menstrual cycle would reduce menstrual blood does volume.

Keywords: heavy menstrual bleeding, dysmenorrheal, dexamethasone, endometrium.

Introduction

Menstruation that is so severe it interferes with a woman's physical, emotional, social, and material well-being is referred to as heavy menstrual bleeding (HMB). Estimates place the prevalence of excessive menstrual bleeding in impoverished countries at 4-9% [1]. HMB lowers the quality of life and has a negative effect on jobs, family responsibilities, and caring roles. HMB causes morbidity in otherwise fit mid-aged women, but the cumulative effect upon the quality of life of older

persons (QOL), typically surpasses 30 days yearly, would be unacceptable in the majority of other health problems [2]. It is widely accepted that menstruation has expenses that make poverty worse. So, recent government attempts to promote/finance the supply of free menstruation protection have been implemented [1,2].

HMB's cause or causes are not fully known. Nearly 48 percent of HMB cases that are sent to secondary care don't have any evident pathology. The growth of blood vessels in the endometrium, which occurs throughout a typical menstrual cycle, differentiation, & vasoconstriction are rigorously regulated to make certain that the endometrial shed is confined and controlled [3]. After endometrial injury, there is a self-limiting inflammatory response that helps the tissue recover quickly and return to its normal structure in time for the next cycle of vascular expansion. These cyclical activities are dynamically regulated by sex hormones and their interactions with the immunological, endocrine, and circulatory systems. [4]. There is a chance that severe and/or prolonged bleeding will occur as a result of the premenstrual cellular and molecular alterations listed below: (1) reduced vasoconstriction; (2) reduced vascular homeostasis; (3) a high level of inflammation at menses; and (4) inadequate postmenstrual endometrium repair. In women with HMB, inadequate vascular growth and aberrant angiogenesis have been seen [5]

The current standard of care for treating HMB symptoms involves conservative, medicinal, or surgical (hysterectomy and endometrial ablation) treatments. Since there are numerous probable causes of HMB, finding a cure frequently requires trial and error. In ordinary clinical practice, especially primary care, medical care (non-hormonal or hormonal) is typically the first line of treatment, however, this may be unsuccessful or not tolerated, for example, due to typical adverse reactions of hormonal medications [6,7].

Hysterectomy is an expensive major surgery that ends fertility and is one of the surgical therapies for HMB. In adults between the years of 30 and 40, fibroids in the uterus are a common reason for HMB, and they frequently necessitate surgery. Even in the absence of significant fibroids, a hysterectomy is still a routine procedure [8]

HMB medical treatment is either ineffective or has unacceptably negative side effects. Women who want to get pregnant should not use the Levonorgestrel intrauterine device (LNG-IUS), a hormonal contraception that is currently approved as a treatment for HMB. The side effects of LNG-IUS, which include amenorrhea and persistent, unexpected, unplanned bleeding for some users, may not be acceptable to women [9,10].

Angiogenesis is slowed down by endogenous glucocorticoids. Endometrial blood vessel structure must be controlled to lessen endometrial bleeding & menstrual blood loss. Therefore, increased menstrual blood loss could be caused by local endometrial glucocorticoid insufficiency [11]. 11b-hydroxysteroid dehydrogenase type 2 (11bHSD2), a protein that renders cortisol inactive, is expressed during the luteal phase, has grown within the endometrium of HMB-afflicted women. In order to "rescue" luteal stage endometrial cortisol insufficiency, a novel therapy involving synthetic glucocorticoids was proposed. This treatment would boost the endometrium (spiral arteriole) arterial differentiation, local constriction of blood vessels at the start of menses, and initial endometrium repair/angiogenesis while reducing menstrual bleeding. Dexamethasone was selected because it converts to 11-dehydro-Dex, which is still bioactive, rather than being inactivated by 11bHSD2 [12,13].

Materials and methods

Study design

This is a prospective Randomized Controlled Trial conducted on 100 patients from May, 2022 to April, 2023. The patients who visited the outpatient department of our hospital were considered. The patients with heavy menstrual bleeding were grouped randomly. Some patients were given placebo while others were managed with dexamethasone to treat heavy menstrual bleeding. Twenty and eighty patients in each of the two groups—placebo and dexamethasone—were assigned to the study population. Again, these 80 patients received dexamethasone at 6 different dosage, namely, 0.4 mg, 0.8 mg, 1mg, 1.2 mg, 1.5 mg, and 1.8 mg. The comparative analysis was conducted between placebo and dexamethasone group and also the pharmaco-effect was assessed between the dosages.

One among 6 doses of dexamethasone, a synthetic glucocorticoid produced by Tayside Pharmaceuticals in Dundee, was given orally twice every day for five days during the luteal phase of three menstrual cycles as just a treatment option. The other two alternatives were placebo.

Inclusion and exclusion criteria

The trial group consisted of females over the age of 18 who desired treatment again for symptoms of excessive menstrual bleeding. (HMB). The mean menstrual blood loss over 2 screening menstruation cycles was 50 mL or more. A modified alkaline-haematin approach was utilized to evaluate menstrual blood loss in such an objective, lab-validated evaluation of collected, applied for sanitary protection.

The main exclusion criteria included planning to try for pregnancy within the next five months, a mean cycle length ranging from 21 to 42 days, menstrual periods that have been "very irregular," nursing, pregnancy that was "possible" but unwilling to be using methods of contraception, prior or present cervix, diabetes mellitus, ovary, uterus, or breast cancer, in addition to seven prohibited medications, such as taking systemic, inhaled, or potent topical glucocorticoids

Statistical analysis

The study used SPSS 25 software for statistical analysis. The continuous data was expressed as mean ± sd while the discrete data was expressed as frequency and percentage. The study has employed Chi-square as the statistical tool for comparing the effect between the two groups and ANOVA was used for analyzing between the dosages. The average scores, standard deviations, student's t-test, & Chi-square were used to make the appropriate percentage comparisons seen between various groups. The level of significance was considered to be $p<0.05$.

Ethical approval

The authors gave the patients a full explanation of the study. The patients' consent has been obtained. The study's methodology has been approved by the ethical committee of the involved hospital.

Results

Table 1 presents the baseline characteristics of patients in two groups: the Placebo group, consisting of 20 patients, and the Dexamethasone group, consisting of 80 patients. The characteristics include age, weight, menstrual cycle-related variables, blood pressure, obstetric history, presence of fibroids, smoking status, and presence of painful periods. In terms of age and weight, both groups have similar median and mean values, with a median age of 45 years and a median weight of 70.1 kg in the Placebo group, and a median age of 45 years and a median weight of 75.1 kg in the Dexamethasone group. The weight values are presented as a range with minimum and maximum values in square brackets. The minimum period of menses in the preceding three months is slightly lower in the Dexamethasone group (5.2 days) compared to the Placebo group (5.7 days), with a

range of 3, 5, 7, and 15 days in the Dexamethasone group. The mean duration of Heavy Menstrual Bleeding (HMB) has been similar in both groups, with an average of 6 years. The maximum duration of the menstrual cycle in the preceding three months is also similar in both groups, with a value of 9 days. When it comes to obstetric history, the years since the last birth are approximately higher in the Dexamethasone group (12 years) compared to the Placebo group (7 years). The mean menstrual blood loss test is higher in the Dexamethasone group (136.5 mL) compared to the Placebo group (113.1 mL). The number of alcohol units consumed weekly is also higher in the Dexamethasone group (4 units) compared to the Placebo group (2 units). Blood pressure and heart rate variables are slightly higher in the Dexamethasone group compared to the Placebo group, with higher mean values for systolic blood pressure (125.2 mmHg vs. 123.1 mmHg) and diastolic heart rate (77.9 mmHg vs. 76.5 mmHg) in the Dexamethasone group. In terms of obstetric history, the number of births and terminations are higher in the Dexamethasone group compared to the Placebo group. Specifically, a higher percentage of patients in the Dexamethasone group have given birth 1 or more times (31.2% vs. 40% for none, and 18.75% vs. 10% for one birth). Similarly, a higher percentage of patients in the Dexamethasone group have had terminations (81.2% vs. 80% for none, and 12.5% vs. 15% for one termination). The number of miscarriages is also higher in the Dexamethasone group, with 75% of patients having no miscarriages compared to 65% in the Placebo group. The presence of painful periods is more prevalent in the Dexamethasone group, with 80% of patients reporting painful periods compared to 20% in the Placebo group. The presence of fibroids, as detected by ultrasound or MRI, is slightly higher in the Dexamethasone group, with 31.2% having fibroids less than 3 cm and 12.5% having fibroids greater than or equal to 3 cm, compared to 30% and 5% respectively in the Placebo group.

Table 1: Baseline characteristics of the patients in each group

Characteristics	**Placebo**	**Dexamethasone**
	n=20	**n=80**
N	Median	Mean
Age (years)	45	45
Weight (kg)	70.1 [49, 61.1, 93, 131]	75.1 [48, 65.2, 85.6, 125]
The minimum period of menses in the preceding three months (days)	5.7	5.2 [3, 5, 7, 15]
Answer to the question of how long HMB has been an issue (years)	6	6
Maximum duration of the menstrual cycle in the preceding three months (days)	9	9
Years since the last birth, approx.	7	12
Mean menstrual blood loss test (mL)	113.1	136.5
alcohol units presently consumed weekly.	2	4
blood pressure in systole (mmHg)	123.1 ± 13.8	125.2 ± 12.7
Diastolic heart rate (mmHg)	76.5 ± 13.6	77.9 ± 10.7
at menarche age (years)	12.8 ± 1.8	13.2 ± 1.8
Maximum cycle duration beyond three months (days)	31.3 ± 4.8	30.2 ± 3.8

Past 3-month minimum cycle length in days	27.0 ± 3.1	26.7 ± 2.9
Number of births		
None	8 (40)	25 (31.2%)
1	2 (10)	15 (18.75%)
2	6 (30)	22 (27.5%)
3	3 (15)	14 (17.5%)
04	1 (5)	4 (5%)
Number of terminations		
None	16 (80)	65 (81.2%)
1	3 (15)	10 (12.5%)
2	1 (5)	4 (5%)
3	0	0
4	0	1 (1.2%)
Number of miscarriages		
None	13 (65)	60 (75%)
Once miscarriage	5 (25)	15 (18.7%)
Twice miscarriages	2 (10)	5 (6.2%)
Answer to the question if the patient is having painfu periods		
Yes	16 (80)	60 (5%)
no	4 (20)	20 (25%)
Fibroids present		
Fibroid < 3 cm	6 (30)	25 (31.2%)
Fibroid >= 3 cm	2 (5)	10 (12.5%)
No fibroids detected	12 (60)	39 (48.7%)
No recent USS/MRI	2 (5)	6 (7.5%)
Smoking		
Current (1-20 cigars per day)	4 (20)	6 (7.5%)
Previous	2 (10)	20 (25%)
Never	14 (70)	54 (67.5%)

The primary outcome NDLM data are shown separately per dose in the bottom half of Table 2. treatment benefit in all dose groups. The greatest impact was seen at a 25 mL reduction in menstrual blood loss with the 1/8 mg total daily dose, with a 95% credible interval of 1 to 49 mL. The posterior odds for any benefit over placebo, or at least a 10 mL benefit, for this dose, were 0.98 and 0.89, respectively.

Table 2: Statistical analysis of in changes of factors or parameters related to menstrual blood loss for placebo and for each dosage of dexamethasone

Randomized treatment								
	Placebo	**Dexamethasone**	**Dosage of dexamethasone overall**					
			0.4 mg	**0.8 mg**	**1 mg**	**1.2 mg**	**1.5 mg**	**1.8 mg**
Parameter								
N	20	80	6	10	22	9	15	18

Mean menstrual blood loss change* (mL)	-6.4	-21.3	-8.2	-24.2	-18.9	6.1	-24.9	-36.9
SD	51.9	44.5	55.1	42.3	38.3	50.9	32.8	54.4
Maximum	97.6	89.9	75.8	37.4	48.2	90.3	35.8	27.6
Minimum	-172	-189	-66.8	-92.4	-145	-59.1	-85.8	-189
NDML- modelled effects of treatment								
Dexamethasone minus placebo difference in mean menstrual blood loss change from anterior median (mL)			-4	-15	-9	-5	-16	-27
95% Crl *** (mL)			-28, 56	-42, 3	-30, 12	-29, 14	-39, 34	-50, 10
chance that dexamethasone will be superior to placebo by at least 10 mL in the future.			0.31	0.6	0.47	0.38	0.71	0.92
Probability of any benefit of dexamethasone over control in the future			0.72	0.9	0.83	0.68	0.95	0.99

Discussion

For instance, it is believed that Prednisolone 5 mg once daily can provide a physiological replacement for Dexamethasone at a dose of 0-75 mg once daily. Dexamethasone was accepted favorably; Throughout every stage of the trial, 80% - 91% of the participants completed all prescribed treatments, and there were no serious side effects (AEs) while receiving active therapy [14]. Long-term consumption of older person-physiological doses of glucocorticoids, however, has been associated with increased fracture and cardiovascular disease risk as well as risks from blocking endogenous cortisol secretion. In order to maintain an appropriate luteal phase local glucocorticoid-permitting endometrial blood vessel creation is required to prevent monthly blood loss, there is a contradiction between treating a putative local endometrial cortisol insufficiency and minimizing cumulative globally glucocorticoid dose. [15].

Dexamethasone dosages between 0 and 9 mg had the biggest effects on menstrual blood loss. (twice daily). According to a published report, a corresponding reduction in menstrual blood loss percent of 22.4% compared with the base is "meaningful," and this study demonstrated an average relative reduction in menstrual blood loss quantity of 19.5% of individuals who received menstrual blood loss screening. [15].

The use of dexamethasone as a treatment for the HMB symptom is very promising,

and it may be welcomed by women who choose not to have surgery, who have unfavorable side effects from hormone treatment, or who want to try for a baby. To demonstrate that the systematic dexamethasone regimen employed wouldn't result in the drug's renowned side effects, more long-term trials will be required in the future. To address worries regarding cumulative dosages of dexamethasone over time, localized topical dexamethasone administration may minimize the dose required and thereby systemic levels [16,17]. Dexamethasone could be delivered intrauterinally by modifying current intrauterine delivery techniques, however, this would require continuous administration. Short-term management prior to the onset of menses might be possible using intravaginal forms of site-targeted administration, which could significantly reduce the dose [18,19].

Dexamethasone treatment for HMB may have the benefit of being approved for use by HMB patients who want to manage their symptoms while trying to conceive. At the general community, women may become pregnant while taking common steroid medicines for medical purposes (non-HMB), frequently at larger dosages than in DexFEM [20,21]. In the earliest days of pregnancy, particularly early dosage for the management of recurrent miscarriage, the use of steroids has been researched. In dexamethasone for excessive menstruation (DexFEM), HMB treatment would last whereas the daily doses often required to prevent miscarriages, frequently for the whole initial period, are administered for only five days in the single fertile cycle, at doses that are around two or three times those used in DexFEM [22,23].

Middle-aged women frequently experience excessive bleeding during their periods (HMB), which considerably lowers their standard of life and places a burden on society. We looked into our hypothesis that endometrial glucocorticoid insufficiency causes defective endometrial vasoconstriction in HMB. Exogenous glucocorticoids (dexamethasone) were used in a trial to examine whether addressing this deficiency for a limited length of time during the luteal phase would enhance HMB. The research discovered that proof that dexamethasone 1/8 milligram every day reduced menstrual blood loss in a modified study in HMB. Further research is needed to understand dexamethasone's involvement in the management of HMB fully [24].

Heavy menstrual bleeding (HMB) significantly burdens society and lowers the individual quality of life. The inactivation of cortisol in HMB endometrium may result in a local endometrial glucocorticoid shortage, which would then lead to increased angiogenesis and decreased vasoconstriction. According to a previous study, menstrual bleeding could be decreased by "rescuing" luteal phase endometrial glucocorticoid insufficiency. The study's main result is a decrease in menstrual blood loss following the screening [25,26].

Conclusion

The study has concluded that 0.8 mg of dexamethasone taken twice daily for 5 days during the luteal phase of the menstrual cycle would reduce menstrual blood does volume. The study has also shown that the significant adverse impact occurs due to heavy menstrual bleeding in the lives of the patients. Mostly the hormonal treatment and surgical interventions are declined by the patients to preserve their fertility for the future. Similar studies should be conducted with more varied population for bringing more comprehensive results. This current research would contribute in the management of heavy menstrual bleeding which is one of the primary complaints among the patients of menstrual age.

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