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ORIGINAL ARTICLE

A Comparative Study of Dienogest Versus Medroxyprogesterone Acetate in Endometriosis-Associated Dysmenorrhea and Menstrual Irregularities: A Randomized Trial

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Abstract

Background: Endometriosis is a chronic gynecologic disease that is dependent on estrogen and is associated with the existence of endometrial glands and stroma outside the uterus. It has been demonstrated that dienogest significantly and fairly effectively alleviates endometriosis-related symptoms such as dysmenorrhea and irregular menstruation. **Material and Methods:** This was a randomized, prospective, comparative, open-label study. For 12 weeks, Group A (n=30) received Dienogest 2 mg OD while Group B (n=30) received Medroxyprogesterone acetate (MPA) 10 mg BD. The patients were assessed at 4, 8, and 12 weeks to observe the VAS Score for dysmenorrhea, number of patients having dysmenorrhea, number of patients having irregular menstrual cycles. Adverse drug reactions(ADRs) were recorded for safety assessment.**Results:** After 12 weeks, VAS score & number of patients experiencing dysmenorrhea decreased in both groups significantly. Dienogest depicted better response than MPAin the reduction of VAS score(95.99% versus 84.91%; p-value=0.048) & reduction in the number of patients having dysmenorrhea after 12 weeks (6.67% versus 26.67%; p-value=0.038) and the difference was statistically significant.MPA group had a greater number of ADRs.**Conclusion:** Dienogest is significantly more effective than MPA, especially for dysmenorrhea. Dienogest shows better tolerability than MPA.

Keywords

Dienogest, Medroxyprogesterone Acetate, Endometriosis, Dysmenorrhea

Introduction

Endometriosis is an estrogen-dependent chronic gynaecologic disorder related to the presence of endometrial glands and stroma outside the uterus[1] resulting in dysmenorrhea and menstrual irregularities. Endometrial deposits most commonly occur in the pelvic cavity and the pouch of Douglas,[2] but may be present in distant locations such as the upper abdomen.[3,4] The lack of reliable diagnostic biomarkers contributes to the average diagnostic delay of 7 years after the symptoms first appeared.[5,6] It impacts 5–15% of women who are of reproductive age.[7,8]

Cyclical hormones stimulate growth but continuous hormones suppress it.[8,9]

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Abdominal cramps and pain that interfere with daily activities throughout the menstrual cycle are known as dysmenorrhea.[10] Endometriosis is the most frequent cause of secondary dysmenorrhea. It has been seen in 62–75% of adolescents having a laparoscopy for dysmenorrhea and/or chronic pelvic pain, as well as in 70% of teenagers whose pelvic pain did not get better after using NSAIDs and/or combination oral contraceptives (COC).[11-14] It is linked to midcycle or acyclic discomfort, irregular or heavy menstrual bleeding, and pain that worsens with time.[15,16] Among adolescents who complain of dysmenorrhea, approximately 70% are diagnosed with endometriosis, thus this symptom needs special attention in young women.[17] The main purpose of endometriosis management is to alleviate pain associated with the disease. This can be achieved surgically or medically, although in most women a combination of both is required.[18] All hormonal drugs like oral contraceptive pills (COCs), GnRH agonists, progestins, danazol, etc. are almost equally effective in treating pain related to endometriosis.[19] Progestins have been used for the last many years to treat endometriosis as they provide a combination of favorable efficacy and safety and thus can be administered as adjuvant therapy after surgery and are suitable for long-term use.[20] Medroxyprogesterone acetate (MPA) is a C21 steroid in the pregnane family with selective activity similar to progesterone.[21] MPA injectable suspension was given US FDA approval to treat endometriosis. A small oral dose of 2 mg/day of dienogest is currently authorized for the treatment of endometriosis in Europe, Japan, India, and other nations. DNG only slightly lowers systemic estrogen levels while reducing endometriosis lesions by fostering a local progestogenic environment.[22]

The study had been planned given the fact endometriosis is a frequent chronic gynecological illness that affects women of reproductive age. The majority of progestin medications used to treat endometriosis block the HPA axis. They also have androgenic adverse effects. A more recent progestin called dienogest has been demonstrated to be useful in treating the symptoms of endometriosis while having fewer adverse effects, particularly because it has anti-androgenic qualities.

Material and Methods

Subjects and study design

This was a randomized, prospective, open-label, comparative study conducted by the Department of Pharmacology and Obstetrics &Gynaecology, Pt.B.D.Sharma PGIMS, Rohtak on 60 patients. The study was conductedby the principles of good clinical practice (ICH-GCP) and the declaration of Helsinki.All patients who were included in the study provided informed consent, and the study was only carried out with approval from the Institutional Ethical Council (IEC) with approval no. IEC/Th/17/pharma 03.

Objectives

Primary Objective*:* To assess and compare the efficacy of dienogest with medroxyprogesterone acetate in dysmenorrhea associated with endometriosis.

Secondary Objectives:

1. To assess and compare the efficacy of dienogest with medroxyprogesterone acetate in menstrual irregularities with endometriosis.
2. To assess and compare the safety profile of dienogest with medroxyprogesterone acetate in endometriosis.

Sample Size Calculation

The study by Al-Jefout M et al. was taken as a reference to calculate sample size.[16] Endometriosis prevalence in the general population is 2.5 % of women as per the study. Taking this value as a reference, the minimum required sample size with an absolute error which is taken as 4% and a confidence interval of 95% was 60 patients. To increase the power of the study, we enrolled 71 patients out of which 11 were lost to follow up.

The formula used: N e" 4´pq/e^2, Where p is the prevalence rate, q is 1-p, and e is an absolute error.

A sufficient amount of patients underwent screening and were selected as per the inclusion and exclusion criteria for the study. The eligible patients were split into two study groups at random i.e. Group A and Group B. Each study group minimally had 30 patients who were receiving one of the following treatments orally for a period of 12 weeks: Group A: Dienogest 2 mg OD, Group B: Medroxyprogesterone acetate 10 mg BD (same brand of the drugs were used). All the patients were explained about the study through a patient information sheet and every patient provided written informed consent. During the study, patients were not permitted to take any non-study hormonal drugs.

Randomization: Simple randomization was done according to a computer-generated list of random number groups prepared using Statistical Analysis System Software. Every participant was assigned at random to one of the two groups.Blinding was not done.

The inclusion criteria were: Females of reproductive age group subjects diagnosed with endometriosis either by clinical criteria and Ultrasonographyor Laparoscopy,

and patients willing to give written informed consent. Exclusion criteria were pelvic inflammatory disease, progestin allergies, progestin contraindications, and neoplastic diseases, nursing or pregnant mothers, anyone who has used hormone medication during the last three months, alcohol and tobacco use, as well as the inability to show up for routine follow-ups.

Efficacy Assessment

The patients were assessed for the drug response at 4, 8, and 12 weeks to observethe VAS Score for dysmenorrhea, the number of patients having dysmenorrhea, number of patients having irregular menstrual cycles. Safety assessment was done after 4,8, and 12 weeks by recording adverse drug reactions.Adverse drug reactions (ADR) can be defined as an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product.

Statistical Analysis

Data was expressed as Mean ± SEM. Both intragroup and intergroup statistical analyses were done. A p-value of less than 0.05 was deemed statistically significant.

Results

Enrolment of the study population is shown in *flow chart 1* As shown in *Table 1*, baseline parameters did not differ statistically significantly between the two groups (p>0.05).

As shown in *Table 2*, there was a statistically significant reduction in VAS score at the end of 4, 8, and 12 weeks compared to baseline values in both groups. (p-value =0.048).

As shown in *Table 3*, there was a statistically highly significant difference observed in comparison with baseline in both the groups after 8 and 12 weeks (p<0.001).While after comparing both groups, after week 12 there was a statistically significantly smaller number of patients having dysmenorrhea observed with dienogest (Group A) (p=0.038).

As shown in *Table 4*,Group A demonstrated a statistically significant difference from base line values after eight weeks, and both groups exhibited a significant difference at the twelve-week mark (p<0.05). There was no statistically significant difference in the number of patients experiencing irregular menstrual cycles between the two groups.

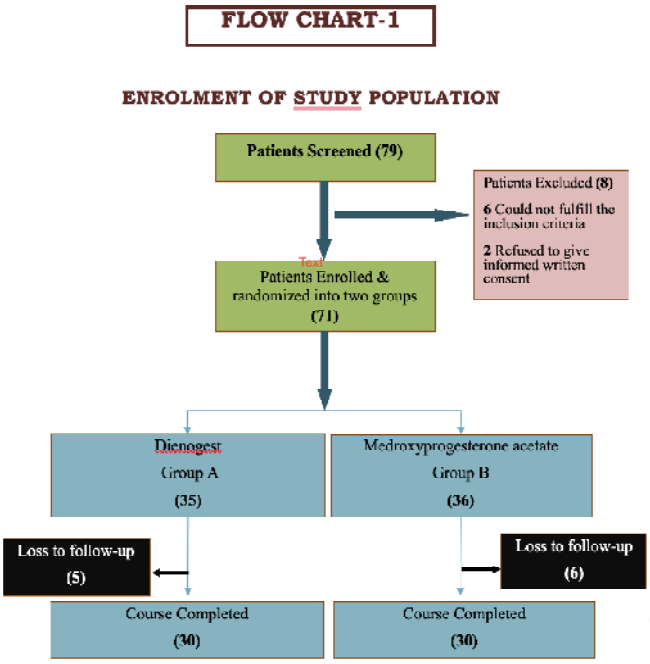

Table-1 Comparison of Study Population Characteristics in both the Groups

Variables	Group A (n=30)	Group B (n=30)	'p' value
Age in years	26.03±1.11	26.9±1.01	0.564
Weight (Kgs)	54.2±1.83	54.23±1.82	0.991
Marital Status			-
Married	25	28	
Unmarried	5	2	
Education			-
Literate	26	24	
Illiterate	4	6	
Age at menarche	11.9±0.21	12.03±0.19	0.648
History of drug allergy	0	0	-

Comparison of values after 4, 8, and 12 weeks with baseline values showing a statistically significant difference (p<0.05).

The incidence of various adverse effects in Group A versus Group B is shown in *Table 5*.

Discussion

A painful menstrual cycle is referred to as dysmenorrhea. In the number of patients experiencing dysmenorrhea (p-value<0.001), there was a statistically significant decrease in both groups. Dienogest was

Table-2. Comparion of VAS Score for assessment of Dysmenorrhea in both the Groups

VAS score	Dienogest (Group A) (n=30)		Medroxyprogesterone acetate (Group B) (n=30)		p-value (intergroup)
	Mean±SEM	Reduction from baseline (%)	Mean±SEM	Reduction from baseline (%)	
Baseline	5.73±0.38	-	5.3±0.58	-	0.537
Week 4	3.17±0.33**	2.56 (44.68%)	3±0.41*	2.3 (43.40%)	0.747
Week 8	1.1±0.26**	4.63 (80.80%)	1.4±0.32**	3.9 (73.58%)	0.469
Week 12	0.23±0.11**	5.5 (95.99%)	0.8±0.26**	4.5 (84.91%)	0.048#

*INTRAGROUP ANALYSIS: *Comparison of values by the end of weeks 4, 8, and 12 with baseline values showing a statistically significant distinction(p<0.05).*

*** Comparison of values after weeks 4, 8, and 12 with baseline values showing a statistically highly significant difference (p<0.001).*

INTERGROUP ANALYSIS: # Comparison of values between A and B Group showing a statistically significant distinction(p<0.05)

Table-3. Distribution of Patients With Dysmenorrhea in Both Patients Patients with Dysmenorrhea in both Groups

DYSMENORRHEA	Dienogest (Group A) (n=30)	MPA (Group B) (n=30)	p-value (Intergroup)
	No. of patients (%)	No. of patients (%)	
Baseline	28 (93.33%)	24 (80%)	0.129
4 weeks	20 (66.67%)*	22 (73.33%)	0.065
8 weeks	10 (33.33%)**	12 (40%)*	0.299
12 weeks	2 (6.67%)**	8 (26.67%)**	0.038#

INTRAGROUP ANALYSIS: Comparison of values after weeks 4, 8, and 12 with baseline values showing a statistically significant distinction (p<0.05).*

*** Comparison of values after weeks 4, 8, and 12 with baseline values showing a statistically highly significant difference (p<0.001).*

INTERGROUP ANALYSIS:# Comparison of values betweenA and B Group showing a statistically significant distinction (p<0.05).

associated with a greater reduction in the number of patients with dysmenorrhea than MPA when comparing the two groups, but at the 12-week mark, the difference was statistically significant (6.67% versus 26.67%; p-value =0.038).

Similar results were shown in a study done by Wong Y *et al*, After treatment, the mean score for menstrual pain reduced in both the dienogest and medroxyprogesterone acetate groups, with the dienogest group achieving a greater absolute reduction (6.6 vs. 4.69, p=0.044).[17]

In a study done by Kim *et al*, the evaluation of dienogest for dysmenorrhea associated with endometriosis was done in 89 patients for a duration of 6 months. By the time the course of treatment was over, the verbal rating scale's overall dysmenorrhea scores in this study significantly decreased (p<0.001).[18] In a study done by Kohler G *et al*, dienogest was associated with a statistically significant reduction in the incidence of dysmenorrhea (p-value <0.05).[19]

Progesterone and its synthetic analogs are already known to be effective in treating irregular menstrual flow and abnormal uterine bleeding [1-3]. A statistically significant reduction in the number of patients having irregular menstrual cycles was observed in both groups (p<0.05). On comparing both the groups, more reduction in the number of patients with irregular menstrual cycle was seen with dienogest than MPA but it was not statistically significant at the end of 12 weeks (6.67% versus 10%; p-value =0.552). Similar results were shown in a previous study done by Yang *et al*, dienogest's efficacy in treating adenomyosis in 85 patients was evaluated, and Dienogest effectively reduces menstrual flow.[20] As per Murji *et al*, dienogest offers an effective and tolerable alternative or adjunct to surgery and provides many advantages over combined hormonal contraceptives for the treatment of endometriosis.[21] In our study, neither dienogest nor medroxyprogesterone acetate were shown to cause serious

side effects and were both well tolerated. The most common adverse effect reported was weight gain in both groups.

Conclusion

Dienogest is significantly more effective than medroxyprogesterone acetate, especially for the treatment of dysmenorrhea. Although both dienogest and medroxyprogesterone acetate were found to be efficacious in dysmenorrhea and irregularity of menstrual cycle in endometriosis patients. Dienogest shows better tolerability than medroxyprogesterone acetate.

Table 4. Distribution of Patients with Irregular Menstrual Cycle in Both Groups

IRREGULAR MENSTRUAL CYCLE	Dienogest (Group A) (n=30)	MPA (Group B) (n=30)	p-value (Intergroup)
	No. of patients (%)	No. of patients (%)	
Baseline	12 (40%)	10 (33.33%)	0.592
4 weeks	7 (23.33%)	7 (23.33%)	0.571
8 weeks	3 (10%)*	5 (16.67%)	0.225
12 weeks	2 (6.67%)*	3 (10%)*	0.552

Limitations

Limited sample size may not fully represent the general population and blinding was not done.

Generalizability of study

The generalizability of this study may be influenced by cultural differences across populations.

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***Conflict of Interest**: Nil*

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Table-5 Incidence of Adverse Drug Reactions

Adverse Drug Reactions (ADRs)	Dienogest (Group A) n=30 (%)	MPA (Group B) n=30 (%)	p-value (inter-group)
Weight gain	9 (30%)	11 (36.67%)	0.584
Acne	1 (3.33%)	4 (13.33%)	0.161
Hirsutism	0	3 (10%)	0.237
Vaginal dryness	1 (3.33%)	8 (26.67%)	0.011#
Breast discomfort	4 (13.33%)	8 (26.67%)	0.197
Headache	5 (16.67%)	1 (3.33%)	0.085
Hot flushes	0	4 (13.33%)	0.112
Insomnia	0	0	-
Mood changes (Aggression)	1 (3.33%)	5 (16.67%)	0.085
Depression	5 (16.67%)	1 (3.33%)	0.085
Dizziness	1 (3.33%)	2 (6.67%)	0.554
Decrease libido	1/25 (4%)	7/28 (25%)	0.033#
Lower abdominal pain	0	0	-
Epigastric pain	2 (6.67%)	6 (20%)	0.129
Bloating	2 (6.67%)	7 (23.33%)	0.070
Nausea	1 (3.33%)	3 (10%)	0.301

#Comparison of values between Group A and B showing a statistically significant difference (p<0.05)

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