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Original Article

Obstetrics and Gynaecology Section

Evaluation of Efficacy and Safety of 2 mg vs 4 mg Dienogest in Endometriosis: A Randomised Single-blind Dose-ranging Trial

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ABSTRACT

Introduction: Endometriosis is a recurring chronic inflammatory condition that affects females of reproductive age. Endometriosis-associated Pelvic Pain (EAPP) adversely impacts physical, mental, and social well-being. Currently, there is no ideal treatment option. Dienogest, a selective progestin, shows a pronounced effect on endometriosis.

Aim: To compare the efficacy and safety of Dienogest at doses of 2 mg and 4 mg/day orally in the treatment of endometriosis.

Materials and Methods: An observer-blind, parallel-group, randomised clinical trial was conducted in the Department of Obstetrics and Gynaecology at IPGME&R, SSKM Hospital, Kolkata, West Bengal, India, from April 2016 to December 2017. A total of 190 women aged 20-45 years suffering from endometriosis were recruited and divided into two treatment groups, A and B, receiving daily doses of 2 mg and 4 mg, respectively, for 24 weeks. Relief of EAPP was assessed using the Visual Analogue Scale (VAS) score, and improvement in Quality of Life (QoL) was measured. Treatment-related adverse events were also recorded. Numerical variables were compared using Student's t-test or the Mann-Whitney U Test, and categorical variables were compared using the Chi-square test or Fisher's-exact test.

Results: The absolute reduction in pelvic pain VAS score was 39.71±8.60 at 24 weeks from the initial score of 70.88 (Mean VAS score before treatment with Dienogest) in Group A, compared to 34.80±6.45 from 69.34 (Mean VAS score before treatment with Dienogest) in Group B (p=0.0001). The difference in mean VAS at 24 weeks between the two groups was statistically significant (p=0.0002). At 24 weeks, 18 (24.66%) patients in Group A experienced an irregular bleeding pattern compared to 27 (40.30%) in Group B, with spotting being the most common issue. Adverse effects such as weight gain, acne, alopecia, depression, and decreased libido were observed in both groups, but they were more pronounced in the 4 mg group.

Conclusion: The efficacy and safety results from this dose-ranging study of Dienogest indicate that 2 mg/day is the effective dose for treating endometriosis and offers better tolerability compared to the 4 mg dose.

Keywords: Endometrioma, Ovary, Pelvis, Progestin, Uterus

INTRODUCTION

Endometriosis, a chronic inflammatory condition afflicting nearly 10% of women of reproductive age, is characterised by the presence of endometrium-like tissue in regions outside the uterus, including the ovaries and other pelvic structures [1,2]. Typical symptoms include pelvic pain, dysmenorrhoea, dyspareunia, premenstrual pain, and lower back pain. This condition adversely impacts physical, mental, and social well-being. In terms of QoL, the primary aim of treatment is to reduce the painful symptoms associated with endometriosis. The diagnosis of endometriosis typically requires a combination of laparoscopic inspection of the pelvis with histopathology of the lesion, but recent guidelines recommend a non invasive clinical diagnosis based on clinical symptoms and patient history [3-5]. Currently, no treatment options are considered ideal as they are associated with suboptimal safety and tolerability, which limit their long-term use. Dienogest is a selective progestin that uniquely combines the pharmacological properties of 19- norprogestins and progesterone derivatives, offering a pronounced local effect on endometrial tissue [6]. It reduces endometriotic lesions by creating a local progesterone environment while only moderately suppressing systemic oestrogenic levels. However, the tolerability of progestins is dose-dependent. Unfortunately, well-designed trials of long-term Dienogest use in endometriosis are lacking, especially in the Indian context. The present study was conducted to define the lowest effective dose of Dienogest in the treatment of endometriosis, comparing the efficacy and safety at 2 mg and 4 mg/day over 24 weeks.

MATERIALS AND METHODS

The present study was an observer-blind, parallel-group, randomised clinical trial conducted in the Department of Obstetrics and Gynaecology at IPGME&R, SSKM hospital in Kolkata, West Bengal, India from April 2016 to December 2017, after approval by the Institutional Ethics Committee (Inst/IEC/2026/288). Written informed consent was obtained from all patients.

Inclusion criteria: Women aged 20-45 years experiencing EAPP with or without abnormal bleeding patterns and with or without complaints of infertility were included in the study.

Exclusion criteria: • Pregnancy; • Breastfeeding; • Amenorrhea within 3 months of enrollment; • Previous use of hormonal agents; • History of severe adverse drug reactions or hypersensitivity to steroid hormones; • History of thrombosis/embolism; • Depressive psychology; • Patients at risk of decreased Bone Mineral Density (BMD).

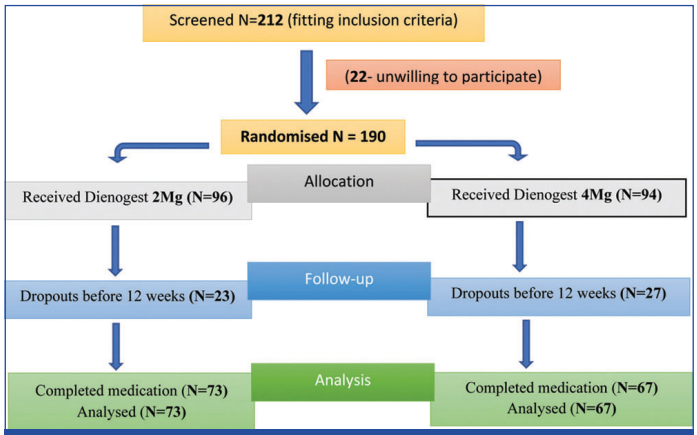
Sample size calculation: The sample size was calculated based on the combined frequency of progressive dysmenorrhoea and menorrhagia as a primary outcome measure, assuming that 80% of untreated subjects are likely to suffer from these problems, with a 20% reduction in frequency deemed to be a clinically important

reduction. The difference between the groups for a two-sided alpha value of 0.05 and a power of 80 was assumed, considering a dropout rate of 15%. The recruitment target was set at a minimum of 95 subjects per group or 190 overall.

Study Procedure

Randomisation: The blinded investigator evaluated the inclusion and exclusion criteria. Eligible subjects were randomly assigned at a ratio of 1:1 into two groups: Group A received 2 mg and Group B received 4 mg of Dienogest, once daily orally for 24 weeks. The randomisation list was automatically generated based on a computer-generated randomisation sequence using Microsoft Visual Basic 6 software. Allocation concealment was done by an independent statistician and maintained the blinding for the investigator until all data were collected.

The study screened 212 women aged between 20 to 45 years complaining of EAPP [Table/Fig-1]. The diagnosis of endometriosis was made clinically (women with dysmenorrhoea, dyspareunia, chronic pelvic pain infertility, and reduced QoL) with or without surgery and histopathologically (presence of endometrial glands and/or stroma, with or without haemosiderin-laden macrophages in the endometriotic lesions). A detailed history was taken with special attention to the EAPP. EAPP was assessed by a VAS (VAS; 0 mm = absence of pain, 100 mm = unbearable pain). The VAS score has proven to be a well-established tool for the measurement of pelvic pain associated with endometriosis [7]. Transvaginal Ultrasound Sonography (USG) was done for the detection of uterine size, endometrial thickness, with an evaluation of the ovaries for the presence of endometriomas.



[Table/Fig-1]: Patient flowchart.

Outcomes: The primary outcome measured was the change in the severity of pelvic pain, back pain, and dyspareunia from baseline to the end of 24 weeks, as assessed by a VAS score. Other study variables included: 1) uterine bleeding patterns assessed over 12 and 24-week periods; 2) the effect on the size of endometrioma, if present. Women documented the presence and intensity of bleeding on daily cards, from which the frequency and duration of bleeding events were calculated. Safety variables, like tolerability, were assessed by directly questioning women on incidences of adverse events commonly associated with endometriosis and hormonal therapy, such as nausea, vomiting, bloated feeling, headache, depression, acne, hirsutism, etc. The secondary outcomes measured aimed to compare: 1) adverse effects; 2) improvement in overall QoL between the two doses.

Physical health score was assessed by QoL analyses based on the short questionnaire form for health survey, a non disease-specific tool widely used in clinical trials [8]. The 12-Item Short Form Health Survey (SF-12) contains psychometrically based physical and mental health component scores analysing the eight domains, which include general health, physical functioning, role physical, bodily pain, vitality, social functioning, mental health, and role emotional. QoL analyses were done at baseline, after 12 weeks, and after 24 weeks of treatment. An individual's composite score was determined by taking an average of the two scores, where a higher score represented better health status.

STATISTICAL ANALYSIS

Data were summarised using usual descriptive statistics, namely mean and Standard Deviation (SD) for normally distributed numerical variables, median and interquartile range for skewed numerical variables, and counts and percentages for categorical variables. Numerical variables were compared between study groups by student independent samples t-tests when normally distributed, or by Mann-Whitney U Test when skewed. The Chi-square test or Fisher's-exact test will be employed for inter group comparison of categorical variables. The analysis was two-tailed, and a p-value less than 0.05 was considered statistically significant.

RESULTS

Total of 212 patients were screened as per criteria, but 22 cases were unwilling to participate in the study. Therefore, 190 patients were randomised into two groups, A (96) and B (94). A total of 50 cases were dropped out (23 from Group A and 27 from Group B) before completing 12 weeks of treatment; they were removed from the data analysis, and the final sample size was 140 (Group A n=73, Group B n=67).

Patients were of comparable age, weight, and Body Mass Index (BMI) between the two studied groups [Table/Fig-2]. There was no significant difference in the visual analogue score in both groups at the beginning of the study regarding pelvic pain [Table/Fig-3]. Both groups showed highly significant reduction in VAS for pelvic pain by the end of the study (p-value <0.0001). The difference in mean VAS at 24 weeks between the two groups was statistically significant (p=0.0002) [Table/Fig-3].

Parameters	Group A (n=73)	Group B (n=67)	p-value
Age (Years) (Mean±SD)	26.84±4.10	27.45±5.80	**0.47**
Weight (kg) (Mean±SD)	56.23±6.58	54.78±5.85	**0.17**
Height (cm) (Mean±SD)	149.05±11.57	151.37±8.79	**0.19**
BMI (kg/m^2) (Mean±SD)	26.92±5.42	25.84±6.76	**0.30**
History of infertility n (%)	28 (38.36%)	31 (46.27%)	**0.35**
CA125 level (IU/mL) (Mean±SD)	92.7±19.6	97.5±25.4	**0.21**

[Table/Fig-2]: Distribution of demographic data in two groups.

VAS score	Group A (n=73)	Group B (n=67)	t-test p-value
Baseline score (Mean±SD)	70.88±11.65	69.34±14.44	0.4870
12 weeks score (Mean±SD)	43.11±14.32	43.48±11.65	0.8678
24 weeks score (Mean±SD)	39.71±8.60	34.80±6.45	0.0002
p-value before and after 24 weeks of treatment in both the groups	<0.0001	<0.0001	

[Table/Fig-3]: Distribution of VAS score in two groups.

The difference in mean physical health score (QoL) between the two groups was not statistically significant (p=0.1238), indicating that these two groups were comparable [Table/Fig-4]. However, the difference in mean physical health score at 12 weeks between the two groups was statistically significant (p<0.0001). There was an increase in health score from 41.33 to 54.89 in Group A and from 43.12 to 47.76 in Group B, with the difference being statistically significant, revealing a slightly greater efficacy of the 2 mg dose. The difference in mean physical health score at 24 weeks between the two groups was also statistically significant (p<0.0001) [Table/Fig-4]. There was an increase in health score from 41.33 to 59.02

Physical health score (QoL)	Group A (n=73)	Group B (n=67)	t-test p-value
Baseline score (Mean±SD)	41.33±7.55	43.12±5.95	0.1238
12 weeks score (Mean±SD)	54.89±7.14	47.76±6.53	<0.0001
24 weeks score (Mean±SD)	59.02±5.50	55.73±3.25	<0.0001
t-test p-value before and after treatment in both the groups	<0.0001	<0.0001	

[Table/Fig-4]: Distribution of physical health score {Quality of life (QoL)} in two groups.

in Group A and from 43.12 to 55.73 in Group B, with this difference being statistically significant and showing a slightly greater efficacy of the 2 mg dose [Table/Fig-4].

The difference in the presence of Endometrioma in the two groups was not statistically significant [Table/Fig-5], indicating that they were comparable. The change in the size of endometrioma at 24 weeks in the two groups was not statistically significant (p=0.0893) [Table/Fig-5]. In Group A, a reduction in the size of endometrioma was seen in 19 (65.52%) patients, while in Group B, reductions were found in 26 (78.79%) patients, and a statistically significant reduction in the size of endometrioma was seen in both groups.

Endometrioma	Group A (n=73)	Group B (n=67)	Chi-squared p
Endometrioma present (n%)	29 (39.73%)	33 (49.25%)	0.259
Unilateral (N%)	16 (21.92%)	18 (26.87%)	0.497
Bilateral (N%)	13 (17.81%)	15 (22.39%)	0.500
Baseline size (Mean±SD) cm	6.48±4.34	5.27±5.49	0.1486
24 weeks size (Mean±SD) cm	3.11±1.94	1.78±1.89	<0.0001
Reduction of size at 24 weeks (cm) Mean (%)	3.37 (52%)	3.49 (66.2%)	0.0893
p-value in each group	<0.0001	<0.0001	

[Table/Fig-5]: Presence and change in size of endometrioma in two groups.

The most commonly reported treatment-related adverse event was abnormal uterine bleeding. Among the 4 mg group, the most common problem reported was irregular spotting and metrorrhagia, as complained by those patients, while in the 2 mg group, the majority of patients complained of spotting (p=0.0486), thereby showing a better safety profile of the 2 mg dose compared to the 4 mg [Table/Fig-6].

Adverse events detected at 24 weeks	Group A (n=73)	Group B (n=67)	Chi-squared p-value
Irregular bleeding n (%)	18 (24.66%)	27 (40.30%)	0.0486
Weight gain n (%)	3 (4.12%)	7 (10.45%)	0.1479
Depression 2 n (%)	2 (2.74%)	4 (5.98%)	0.3464
Decreased libido n (%)	1 (1.37%)	2 (2.99%)	0.5102
Acne n (%)	3 (4.12%)	4 (5.98%)	0.6156
Alopecia n (%)	0 (0%)	1 (1.49%)	0.2970

[Table/Fig-6]: Treatment-related adverse events detected at 24 weeks.
Chi-squared test

DISCUSSION

Progestins are used as first-line therapy for the treatment of endometriosis [9]. They exhibit an antigonadotropic effect, which inhibits ovarian function and creates a hypoestrogenic environment. By directly acting on endometrial progesterone receptors, they induce decidualisation of the endometriotic lesion. They have also been shown to reduce peritoneal inflammation.

Progestins have demonstrated results comparable to surgery in treating dyspareunia associated with endometriosis, are effective in reducing pain in patients with intestinal endometriosis [10], are successful in alleviating symptoms and inducing regression of recurrent endometriomas [11], and have proven effective in the treatment of rectovaginal endometriosis. However, they do have some adverse effects, including acne, weight gain, headaches, and irregular menstrual bleeding.

A dose-finding study examined Dienogest at 1, 2, or 4 mg/day in divided doses, using measures of symptom change and physical examination, and reported that the 2 mg OD dose provided optimal efficacy [12]. Köhler G et al., compared the efficacy and safety of Dienogest at doses of 1, 2, and 4 mg/day orally in the treatment of endometriosis [4]. The study was designed to estimate the lowest effective dose of Dienogest in the treatment of endometriosis. The outcomes measured were changes in the stage of endometriosis, patient-reported symptoms of dysmenorrhoea, dyspareunia, diffuse pelvic pain, and tolerability. They showed that Dienogest 2 mg, in an easy-to-use once-daily regimen, is effective for improving the underlying pathology and symptoms of endometriosis, which is consistent with the present study. Symptoms of endometriosis impact many aspects of a woman's life, including work and education, relationships, and social functioning [13]. As symptoms become more severe, quality of life is further reduced.

In the QoL analysis, the improvements in physical health scores in the 2 mg and 4 mg daily groups were compared. The outcome of the present study corroborated with previous studies by Strowitzki T et al., Momoeda M and Taketani Y, and Schindler AE, which investigated the efficacy of Dienogest in relieving the symptoms of endometriosis and improving QoL [5,12,14]. Strowitzki T et al., showed a significant mean reduction in EAPP (VAS score) between baseline and 12 weeks with a daily dose of 2 mg of Dienogest [5]. Schindler AE et al., expressed that a daily dose of 2 mg of Dienogest effectively alleviates the painful symptoms of endometriosis, reduces endometriotic lesions, and improves QoL indices [14]. According to the present study, there was a significant improvement in QoL in the 2 mg group compared to the 4 mg group because patients tolerated 2 mg more due to minimal side-effects, and pain reduction was almost similar in both groups.

Irregular bleeding is characteristic of progesterone therapy and is thought to be due to breakthrough bleeding from pseudo decidua, an inevitable effect of progestational agents [15]. Dienogest at 2 mg and 4 mg once daily was generally well-tolerated. Adverse events were mostly mild to moderate in intensity. There were slight differences in treatment-related complications between the two groups regarding side-effects, other than abnormal uterine bleeding.

Strengths of the study include the investigator in the present study adhering strictly to the protocol, non significant differences in baseline characteristics regarding endometriosis between the groups, notably, a large number of patients screened and subsequently randomised, and a single-blind design for treatment. A double-blind, multicentre, placebo-controlled trial with a large number of cases may provide more definite results.

Limitation(s)

Potential limitations of the present study include a smaller number of cases analysed, a short treatment duration, and the lack of a placebo-controlled trial.

CONCLUSION(S)

The efficacy and safety in this dose-ranging study of Dienogest indicate that 2 mg/day is the optimal and effective dose for the treatment of endometriosis and has better tolerability compared with the 4 mg dose.

REFERENCES

[1] Kennedy S, Bergqvist A, Chapron C, Hooghe T, Dunselman G, Greb R, et al. ESHRE guideline for the diagnosis and treatment of endometriosis. Hum Reprod. 2005;20(10):2698-704.
[2] Gerlinger C, Faustmann T, Hassall JJ, Seitz C. Treatment of endometriosis in different ethnic populations: A meta-analysis of two clinical trials. BMC Womens Health. 2012;12:9.
[3] Dai Y, Li X, Shi J, Leng J. A review of the risk factors, genetics and treatment of endometriosis in Chinese women: A comparative update. Reprod Health. 2018;15(1):82.

[4] Köhler G, Faustmann TA, Gerlinger C, Seitz C, Mueck AO. A dose-ranging study to determine the efficacy and safety of 1, 2, and 4 mg of Dienogest daily for endometriosis. Int J Gynaecol Obstet. 2010;108(1):21-25.
[5] Strowitzki T, Faustmann T, Gerlinger C, Seitz C. Dienogest in the treatment of endometriosis-associated pelvic pain:a 12-week, randomised, double-blind, placebo-controlled study. Eur J Obstet Gynecol Reprod Biol. 2010;151(2):193-98.
[6] Oettel M, Carol W, Elger W. A 19-norprogestin without 17α-ethinyl group II: Dienogest from a pharmacodynamic point of view. Drugs Today. 1995;31(7):517-36.
[7] Fauconnier A, Fritel X, Chapron C. Endometriosis and pelvic pain: Epidemiological evidence of the relationship and implications. Gynecol Obstet Fertil. 2009;37(1):57-69.
[8] Lins L, Carvalho FM. SF-36 total score as a single measure of health-related quality of life: Scoping review. SAGE Open Med. 2016;4:2050312116671725.
[9] Vannuccini S, Clemenza S, Rossi M, Petraglia F. Hormonal treatments for endometriosis: The endocrine background. Rev Endocr Metab Disord. 2022;23(3):333-55.
[10] Brown J, Kives S, Akhtar M. Progestagens and anti-progestagens for pain associated with endometriosis. Cochrane Database Syst Rev. 2012;2012(3):CD002122.
[11] Gezer A, Oral E. Progestin therapy in endometriosis. Women's Health. 2015;11(5):643-52.
[12] Momoeda M, Taketani Y. Randomised double-blind, multicentre, parallel-group dose-response study of Dienogest in patients with endometriosis. Jpn Pharmacol Ther. 2007;35(7):769-83.
[13] Missmer SA, Tu FF, Agarwal SK, Chapron C, Soliman AM, Chiuve S, et al. Impact of endometriosis on life-course potential: A narrative review. Int J Gen Med. 2021;14:09-25.
[14] Schindler AE. Dienogest in long-term treatment of endometriosis. Int J Womens Health. 2011;3:175-84.
[15] Irahara M, Harada T, Momoeda M, Tamaki Y. Hormonal and histological study on irregular genital bleeding in patients with endometriosis during treatment with Dienogest, a novel progestational therapeutic agent. Reprod Med Biol. 2007;6(4):223-28.

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