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Randomised Controlled Trial to Evaluate Efficacy and Safety of Dienogest in Endometriosis with Dose Range of 2 Mg V/S 4 Mg

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KEYWORDS

RCT, Efficacy, Dose range and Follow-up period

ABSTRACT:

Introduction: Ten percent of women suffer with endometriosis, a persistent, painful disorder marked by the presence of tissue resembling the endometrium outside of the uterus, such as the ovaries and other pelvic structures. Premenstrual discomfort, dyspareunia, pelvic pain, and lower back pain are typical symptoms.

Aims: To Study Improvement In Dysmennorhoea In Endometriosis From Baseline To Study End Measured On Vas (A Validated Measure Of Endometriosis Related Pain).

Materials and method: It's an observer blind parallel group randomised controlled trial. It's conducted in SKIMS-MCH, Srinagar extending over a period of One Year (December 2021 To December 2022). Total of 190 samples have been included in this study.

Result: The mean heart rate difference between the two groups did not reach statistical significance (p=0.1652). Hence, the baseline heart rates of the two groups were similar. The mean arterial pressure difference between the two groups did not reach statistical significance (p=0.1255).,Thus, the mean arterial pressure of the two groups was similar.

Conclusion: In our investigation, we assessed the lowest dosage necessary to alleviate endometriosis symptoms while also taking associated adverse effects into account.For young patients who are wanting to preserve their fertility but are not inclined to have surgery, this procedure is quite successful.This is the first research of its sort in our community.

Introduction

Ten percent of women suffer with endometriosis, a persistent, painful disorder marked by the presence of tissue resembling the endometrium outside of the uterus, such as the ovaries and other pelvic structures. Premenstrual discomfort, dyspareunia, pelvic pain, and lower back pain are typical symptoms.

These symptoms often have a negative effect on one's social, mental, and physical health.As far as women are concerned, the main goal of therapy is to lessen the agonizing endometriosis symptoms. Nonsteroidal anti-inflammatory drugs (NSAIDs), which provide analgesia for a brief period of time, combined oral contraceptives (which are not approved for use in endometriosis), and progestins, androgens (like danazol), which create a hypoestrogenic environment, are examples of nonspecific medical therapies.

Due in part to their adverse event characteristics, none of the available therapy choices can be deemed perfect

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at this time. Danazol, for instance, may have unfavorable lipid alterations and androgenic effects, and GnRH agonists without "add-back" treatment result in a hypoestrogenic condition that increases the risk of bone loss, which precludes long-term usage.Progestins have a usually favorable tolerability profile and effectively treat endometriosis symptoms.

However, progestin tolerance varies with dosage, therefore each compound's lowest effective dose needs to be determined. Dienogest is a selective progestin with a half-life that varies from 8 to 10 hours in young cyclic women and from 11 to 12 hours in postmenopausal women. It combines the pharmacological qualities of progesterone derivatives and 19-norprogestins in a unique way, providing a strong local effect on endometrial tissue.

It only slightly suppresses systemic estrogenic levels while reducing endometriotic damage by fostering a local progesteronic environment.The present study compares the efficacy and safety of dienogest at 2, and 4 mg/day over 24 weeks, with the aim to define the lowest effective dose in the treatment of endometriosis.

Materials and Methods

Study Setting

patients in SKIMS-MCH, who come to G&O visits between menarche and menopause were eligible for enrolment if they had symptoms of endometriosis The study was an observer blind, parallel group, randomized controlled trial of dienogest at 2 mg v/s 4 mg once a day orally, to determine the optimal dose for efficacy and safety in the treatment of endometriosis.

Time Lines

One Year (December 2021 To December 2022)

Definition Of Population: Population were women between 20-40 years if they had symptoms related to endometriosis like pelvic pain, bleeding disorders etc. Safety variables like tolerability, assessed by directly questioning women on incidences of adverse events commonly associated with endometriosis and hormonal therapy like nausea, vomiting bloated feeling, headache, depression, acne, hirsuitism, etc.

Definition Of Problem

The main aim of treatment is to relieve symptoms with optimum possible dose.

Study Variables

The main study variables were

1. Endometriosis associated pain assessed by VAS score every 12 weeks

2. Uterine bleeding pattern assessed over 12 week period , women documented presence and intensity of bleeding on daily cards from which the frequency and duration of bleeding events were calculated.

3.safety variables like tolerability, assessed by directly questioning women on incidences of adverse events commonly associated with endometriosis and hormonal theraphy like nausea, vomiting bloated feeling, +headache, depression, acne, hirsuitism, etc.

Inclusion Criteria

Women aged 20-45 years experiencing de novo or recurrent pain associated with endometriosis or menorrhagia with or without complain of infertility.

Exclusion Criteria

1. Contraindications to progestins

2. Severe metabolic diseases

3. Known alcohol or drug abuse

4. Pregnancy

5. Concurrent treatment with other hormonal preparations

Sample Size

Sample size of this study was calculated on basis of combined frequency of progressive dysmenorrhoea and menorrhagia as primary outcome measure,assuming that 80% of untreated subjects likely to suffer fom these problems,20% reduction in frequency is deemed to be clinically important reduction ,with these assumptions it is calculated that 81 subjects will be required for each group in order to detect such a difference between groups for a two sided alpha value of 0.05 and power of 80 patients assuming a dropout rate of 15%recruitment target is being kept as 95 subject per group or 190 overall.

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Result

Table 1: Distribution of mean Heart Rate in two groups, Arterial Pressure in two groups, Vas(beginning) in two groups, Vas at 12 weeks in two groups, Vas at 24 weeks in two groups

		Number	Mean	SD	Minimum	Maximum	Median	p-value
Heart Rate	Group-A	96	78.4632	7.1753	67	88	78	0.1652
	Group-B	94	79.8105	6.1129	68	88	78	
Mean Arterial Pressure	Group-A	96	91.6737	8.4394	70	106	94	0.1255
	Group-B	94	93.3905	6.8543	82	103.3	93.3	
Vas	Group-A	96	72.2189	12.5314	50	100	70	0.6428
	Group-B	94	71.2674	15.5402	50	103.3	74	
Vas At 12 weeks	Group-A	79	41.4177	17.8409	20	84	40	0.1346
	Group-B	71	45.4085	14.2042	30	82	48	
Vas At 24 weeks	Group-A	73	39.7055	8.6075	20	50	30	0.0001
	Group-B	67	32.7985	6.4497	24	50	33.5	

Table 2 : Distribution of mean Physical health score (beginning) in two groups, Physical health score (12 weeks) in two groups, Physical health score (24 weeks) in two groups

		Number	Mean	SD	Minimum	Maximum	Median	p-value
Physical health score (ADM)	Group-A	96	43.9947	6.6474	31	60	42.5	0.7814
	Group-B	94	44.271	6.9477	30	62	44	
Physical health score (12 weeks)	Group-A	79	53.9284	6.7976	40	66.5	52.4	0.0278
	Group-B	71	51.8333	4.0152	46	60.6	50	
Physical health score (24 weeks)	Group-A	73	59.023	5.5044	44	70.2	58.1	<0.00001
	Group-B	67	55.7261	3.2468	40	64	54	

Since there was no statistically significant difference in the mean heart rates of the two groups (p=0.1652), the baseline heart rates of the two groups were similar. The mean arterial pressure difference between the two groups did not reach statistical significance (p=0.1255).Thus, the mean arterial pressure of the two groups was similar. The mean arterial pressure difference between the two groups did not reach statistical significance (p=0.1255). Thus, the mean arterial pressure of the two groups was similar. The

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mean Vas difference between the two groups at 12 weeks was not statistically significant (p=0.1346).The VAS score decreased in the 2 mg group from 71 mm to 41.4 mm on the VAS scale, while it decreased in the 4 mg group from 72 mm to 45 mm. However, this difference was not statistically significant, indicating that both dosages were effective in reducing pain. The mean Vas difference between the two groups at 12 weeks was not statistically significant (p=0.1346).The VAS score decreased in the 2 mg group from 71 mm to 41.4 mm on the VAS scale, while it decreased in the 4 mg group from 72 mm to 45 mm. However, this difference was not statistically significant, indicating that both dosages were effective in reducing pain.

The two groups were comparable since there was no statistically significant difference in the mean physical health score (at starting) between them (p=0.7814). The mean physical health score at 12 weeks differed between the two groups in a statistically significant way (p=0.0278). The health score increased from 43 to 53.9 in group A and from 44 to 51.833 in group B. This difference was statistically significant and suggested that the 2 mg dose was somewhat more effective. The mean physical health score at 24 weeks varied between the two groups in a statistically significant way (p<0.00001). The health score increased from 43 to 59.02 in group A and from 44 to 55.72 in group B. This difference was statistically significant and suggested that the 2 mg dose was somewhat more effective.

Discussion

It's an observer blind parallel group randomised controlled trial. It's conducted in SKIMS-MCH extending over a period from One Year (December 2021 To December 2022). Total of 190 samples have been included in this study.

When treating endometriosis, progestins are the initial line of treatment. They exhibit an antigonadotropic action, which suppresses ovarian production and fosters a hypoestrogenic atmosphere. They cause decidualization of the endometriotic lesion by directly acting on endometrial progesterone receptors. Furthermore, they have been demonstrated to lessen peritoneal inflammation. When it comes to treating endometriosis-related dyspareunia, progestins have demonstrated outcomes that are on par with surgery [1], are successful in relieving pain in patients suffering from intestinal endometriosis [2], are successful in curing symptoms and causing recurrent endometriomas to shrink, and have even shown promise in treating rectovaginal endometriosis. Progestins do, however, have some side effects, such as acne, weight gain, migraines, and irregular menstrual flow.

The purpose of my investigation was to assess the safety and efficacy of both groups for endometriosis. A total of 190 patients were included in the study. They were randomly assigned to two groups and administered Tab DIENOGEST at doses of 2 mg for group A and 4 mg for group B. These groups were comparable in terms of age, weight, height, and BMI.The primary goal was to compare how endometriosis patients' decrease of pelvic discomfort and bleeding issues differed. A few individuals were referred for RAFS staging of endometriosis and diagnostic laproscopy because they also had concomitant infertility.

We monitored them by giving the two dosages at random and measuring the reduction in cyst size using ultrasonography at 12 and 24 weeks when it was discovered that some of them also had endometriomas.

The study found that both groups showed comparable reductions in pelvic pain in endometriosis, with the absolute reduction in pelvic pain VAS score after therapy being 29 (± 8.60)mm at 24 weeks from 72mm at admission in the 2 mg group and 34.7 (± 6.44) at 24 weeks from 71.6mm at admission in the 4 mg group. This difference was statistically significant, suggesting that 4 mg led to slightly greater pain reduction, but it cannot be said to be the optimum dose because there was a greater association of side effects and bleeding disorders in this group.Given that pelvic discomfort is one of the most significant signs of endometriosis, this study has significant therapeutic implications.

Dienogest's effectiveness and safety in treating endometriosis at oral dosages of 1, 2, and 4 mg/day were compared by Kohler et al. [3]. a 24-week comparative experiment that was open-label, randomized, multicenter, and required histological confirmation of endometriosis in women. Second-look laparoscopy and patient-reported symptoms were used to evaluate effectiveness. Tests for statistical analysis included Wilcoxon signed rank and $\chi 2$. The mean revised American Fertility Society scores were lowered by dienogest in the 2-mg group from 11.4 to 3.6 (n=29;

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P<0.001) and in the 4-mg group from 9.7 to 3.9 (n=35; P<0.001). Significant percentages of women reported significant symptom improvements after using dienogest at 2 and 4 mg/day. There was minimal treatment discontinuation owing to adverse effects for either of the dienogest dosages, and they were both generally well tolerated. Because the 1-mg dosage arm could not adequately reduce bleeding, it was stopped. Future endometriosis research should aim to determine the ideal dose of dienogest, which is 2 mg once day.

The gains in physical health scores for both groups were equivalent when analyzed in terms of quality of life. Dienogest versus Decapeptyl at 3.75 mg was evaluated by Cosson M. et al. [4] for effectiveness as consolidation therapy following surgery for endometriosis. A parallel-group, open, randomized, multicenter clinical experiment. For the therapeutic treatment of endometriosis, dienogest is an alternative to GnRH analogs. Dienogest was shown to be equally effective as Decapeptyl in treating endometriosis four months after surgery, with no androgenic side effects. Dienogest's safety and effectiveness as a long-term endometriosis therapy were examined by Petraglia et al. [5] along with follow-up following medication termination. Women with endometriosis who had finished a 12-week dienogest placebo-controlled trial were enrolled in the study and may take part in an open-label extension study for a maximum of 53 weeks. Following the termination of treatment, a patient subgroup was assessed during a 24-week follow-up.With gradual reductions in pain and irregular bleeding with ongoing therapy, long-term dienogest demonstrated a satisfactory effectiveness and safety profile. Notably, the decrease in pelvic discomfort remained for at least 24 weeks after treatment termination.

At 12 weeks, there was a statistically significant (p<0.00001) difference in the two groups' bleeding patterns. In group A, 95% of patients had normal bleeding, while in group B, only 48% of patients had normal bleeding. The most common complaint among patients in the 4 mg group was spotting, while in the 2 mg group, only 2.7% of patients complained of spotting, indicating a better safety profile for the 2 mg dose than the 4 mg. The difference in the bleeding patterns after 24 weeks between the two groups was statistically significant (p<0.00001). In group A, 97.1% of patients had normal bleeding patterns, whereas in group B, only 50% of patients had normal bleeding patterns. The most common complaint among patients in the 4 mg group was spotting, which they reported having, but none of the patients in the 2 mg group complained of spotting, indicating a

As per our study there was significant improvement in quality of life in 2 mg group as compared to 4 mg group .The mean physical health score at 24 weeks was 59.0 in 2 mg and 55.7 in 4 mg group which was statistically significant(p>0.00001),it is because patients tolerated 2 mg more as there were minimal side effects and pain reduction was almost similar in both of them.

As far side effects were concerned 19.1% patient reported weight gain in 4 mg group as compared to 6.8% in 2 mg group which was significant .Similarly 17.6% patients in 4 mg group complained of depression ,while in 2 mg it was just 2%. Decreased libido was reported in 16.2 % patients in 4 mg group and even some patients stopped the treatment due to it. 22.1% of patient reported acne in 4 mg group which led to greater level of dissatisfaction among patients. Similarly 20% patients reported alopecia in this group. The effects of two hormonal treatments (a novel progestin called dienogest and a GnRH agonist called leuprolein acetate) on endometriosis symptoms in individuals with varying clinical grades of the illness were investigated by Kaminski et al. [6]. Leuprolein acetate and dienogest both reduced dyspareunia and pelvic discomfort. These influences did not differ from one another. Dienogest did not show any signs of androgenic activity, including hirsutism, voice tone, or severe seborrheic lesions. Hot flashes were not seen with Dienogest. Dienogest therapy-induced bleeding had no effect on hematologic indices or the patients' choice to terminate treatment prematurely.

Conclusion

We came to the conclusion that, in addition to taking into account any associated side effects, our study assessed the lowest dose necessary to alleviate endometriosis symptoms.For young patients who are wanting to preserve their fertility but are not inclined to have surgery, this procedure is quite successful.This is the first research of its sort in our community. The results of this randomized controlled trial (RCT) assessing dienogest's safety and effectiveness in

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endometriosis indicate that the symptom alleviation and safety profiles of both the 2 mg and 4 mg dosages are significantly improved. Though there are less reported side effects and a promising efficacy with the 2 mg dosage, the 4 mg dose indicates a somewhat greater efficacy in controlling some symptoms. Clinicians should carefully weigh these factors when prescribing dienogest for endometriosis, considering both symptom control and patient tolerability

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