Safety and Efficacy of Dinogest in Long Term Treatment of Endometriosis

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ABSTRACT

Introduction: Endometriosis is a chronic disease characterized by the proliferation of endometrial tissue outside the uterine cavity, and it occurs in 6% to 10% of women of reproductive age and in 50% of infertile women. Current research aimed to study the safety and efficacy of dinogest 2mg daily in patients of endometriosis for a period of 12 months.

Material and methods: This study was a retrospective non placebo randomized trial done in the department of obstetrics and gynaecology, RMCH. Patient data was collected in a span of 1year i.e; February 2018 to January 2019 and dinogest was given for 12 months thereafter. Total 100 women post surgery (cystectomy) with endometriosis were taken who had been treated with 2mg of dinogest once a day for 12 months. We evaluated changes in endometriosis associated pain, endometrioma size, recurrence rate and adverse events.

Result: Pain was significantly reduced at 12 months after dinogest medication. The size of endometrioma was significantly decreased at the 12th month. Only 1 case of sonographic recurrence was seen. The most common adverse drug reaction was uterine bleeding (1%) with minor side effects which became gradually tolerable.

Conclusion: Administration of dinogest for a one year period seems to be highly effective in preventing recurrence after surgery, there was marked reduction in endometriosis associated pain and decreasing the size of recurrent endometrioma. So, it is very safe and tolerable drug for treatment of endometriosis

Keywords: Dinogest, Endometriosis, Long Term, Recurrence

INTRODUCTION

It often causes infertility and/or pain symptoms (dysmenorrhea, deep dyspareunia, chronic pelvic pain and dyschezia). In some patients, pain symptoms are extremely severe and negatively affect quality of life (QoL), work efficiency and sexual life.[1-4]

Despite the presence of many controversies regarding the mechanisms responsible for its pathogenesis and progression, it is widely accepted that endometriosis is an estrogen-dependent chronic inflammatory disease.[5]

Several hormonal therapies have been proposed for the treatment of endometriosis-related pain, including oral contraceptive pill and other estroprogestin formulations (such as the vaginal ring and the transdermal patch), progestins (including medroxyprogesterone acetate, norethisterone acetate, desogestrel and the levonorgestrel-releasing intrauterine device), gonadotrophin-releasing hormone (GnRH) agonists and hyperandrogenic compounds (such as danazol and gestrinone).[6] These traditional endocrine therapies for endometriosisinhibit estrogens production in the ovary. However, medical therapy is a purely symptomatic treatment. Dinogest is a progestin indicated as monotherapy at an oral dose of 2 mg once daily for patients with endometriosis.[7] Dinogest is highly selective for the progesterone receptor, exhibiting strong progestational effects and moderate antigonadotrophic effects, with limited androgenic, glucocorticoid, or mineralocorticoid activity. Dinogest suppresses estradiol levels only moderately.[8-9]

The safety and efficacy of dinogest for providing pain relief in the adult population has been highlighted in several clinical trials, differing in design and ethnicity of populations.[9,10,11-15] Current research aimed to study the safety and efficacy of dinogest 2mg daily in patients of endometriosis for a period of 12 months.

MATERIAL AND METHODS

Data was collected retrospectively from medical record in which the patients treated with 2mg dinogest once a day for 12 months from February 2018 to January 2019 in the department of Obstetrics and Gynaecology in Rohilkhand medical college and hospital, Bareilly.

The subjects included 100 patients, 80 of whom had undergone unilateral cystectomy and 15 had undergone a bilateral cystectomy and 5 had undergone adnexectomy. Diagnosis was confirmed on the basis of ultrasound.

Oral administration of dinogest was initiated on day 3 of the first menstruation following surgery for each patient.

The present study was based only on a retrospective review of medical records, so written informed consent was not obtained, Trans Vaginal Sonography was used to measure large diameter of endometriotic cyst. The serum cancer antigen125 (CA125), CA 19-9 and Estradiol (E_2) and Anti Mullerian Hormone concentration were determined at baseline before the dinogest therapy. These investigations were repeated after 6 months period to assist in assessing the clinical status of the patients.

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The adverse event profile and patient satisfaction regarding dienogest treatment was determined through a questionnaire. Menstrual pain was determined before surgery, after surgery, before dienogest treatment, and after dienogest treatment. The severity of pain was measured on a 10-point visual analog scale (VAS; 0 mm, absence of pain; 100 mm, unbearable pain) during the outpatient visits.

Transvaginal ultrasonography was conducted on the patients every 6 months to assess the presence of endometrioma.

Parameter	Patients no: - 100
Age (yr) (mean +/- SD)	38.2 +/- 8.1
Body mass index	19.8 +/- 2.5
Previous surgery of endometriosis	15

Table-1:

ASRM stage of endometriosis	
Stage 1-2	28
Stage 3-4	72
Type of endometriosis	
Deep infiltrating	6
Unilateral	66
Bilateral	28
Presence of other disease	
Leiomyoma	20
Adenomyosis	12
Ovarian cyst	12
Paratubal cyst	5

Table-2: ASRM stage of endometriosis

Recurrent endometriosis was diagnosed when a round mass was identified with a thick wall, having a diameter of 2 cm or more, regular margins, and a homogenous low echogenic fluid content with scattered internal echoes. The patients were also evaluated according to the r-ASRM stage classification. Adverse events were defined as any unfavorable or unintended signs or symptoms like nausea, weight gain, abdominal pain or uterine bleeding, occurring with the use of dinogest. Serious adverse events were defined and documented according to the international standards.

Body weight was measured during the initial visit, and then after every 6 months. Weight gain was defined as an increase of over 1 kg.

The patients were instructed to record bleeding events daily on a diary card to provide information on the mean number of days, number of episodes, and duration of episodes of bleeding.

RESULT

Table 1 Shows baseline and demographic characterstics. Total 100 patients were taken for study and mean age of 100 patients was 38 years +/- 8 years and mean body mass index was 19.8 +/- kg/m^2.

According to the ASRM stage of endometriosis 78 out of 100 patients were found in stage 3/4 and 28 patients of 100 in stage 1 / 2 (table-2).

Table-2 is suggestive that 6 out of 100 patients had deep infiltrating endometriosis, 66 out of 100 patients had unilateral endometriosis, and 28 out of 100 patients

Blood test	Pre treatment	Post treatment 6 months	P- value
CA 125(U/ml)	90.25 +/- 18.99	25.2 +/- 15.40	<0.001(HS)
CA 19-9 (U/ml)	60.20 +/- 16.60	20.3 +/- 8.20	<0.001(HS)
E_2 (Pmol/L)	96.3 +/- 20.82	80.80 +/- 30.80	<0.001(HS)
Values are presented as mean +/- standard deviation or number (%)			

Table-3: Shows laboratory parameters (categorized based on treatment period

Blood Test	Pre Treatment	Post Treatment 12 Months	P- Value
CA 125(U/ml)	90.25 +/- 18.99	18.0 +/- 13.50	<0.001(HS)
CA 19-9 (U/ml)	60.20 +/- 16.60	16.6 +/- 11.20	<0.001(HS)
E_2 (Pmol/L)	20.82 +/- 96.3	25.50 +/- 52.20	<0.001(HS)
Blood Test	Post Treatment 6 Months	Post Treatment 12 Months	P- Value
CA 125(U/ml)	25.2 +/- 15.40	18.0 +/- 13.50	<0.001(HS)
CA 19-9 (U/ml)	20.3 +/- 8.20	16.6 +/- 11.20	<0.001(HS)
E_2 (Pmol/L)	80.80 +/- 30.80	25.50 +/- 52.20	<0.001(HS)

Table-4: Blood Investigations

Drug reaction	No of pateints
Headache	6
Breast discomfort	2
Depressed mood	1
Acne	4
Nausea	3
Weight gain	15
Abdominal pain	3
Abnormal uterine bleeding	1

Table-5: Adverse drug reactions

had bilateral endometriosis. 20 out of 100 patients had leiomyoma associated with endometriosis, 12 out of 100 patients showed association with adenomyosis, 12 out of 100 showed association with ovarian cyst and 5 out of 100 patients showed association of endometriosis with paratubal cyst.

Table-3 shows the decline in CA 125 levels from 90.25 +/- 18.99 to 25.2 +/- 15.40, decline in CA 19-9 levels from 60.20 +/- 16.60 to 20.3 +/ - 8.20, decline in estradiol levels from 96.3+/-20.82 to 80.80 +/- 30.80 post six month of treatment with dienogest and were found to be statistically significant.

Table-4 shows the decline in CA 125 levels from 90.25 +/- 18.99 to 18.0 +/- 13.50, decline in CA 19-9 levels from 60.20 +/- 16.60 to 16.6 +/ - 11.20, decline in estradiol levels from 96.3+/-20.82 to 52.20 +/- 25.50 post twelve month of treatment with dienogest and were found to be statistically significant. The persistent decline in levels of all the markers i.e. CA 125 levels from 25.2 +/- 15.40 to 18.0 +/- 13.50, CA 19-9 levels from 20.3 +/ - 8.20 to 16.6 +/ - 11.20, decline in estradiol levels from 80.80 +/- 30.80 to 52.20 +/- 25.50 post six month and twelve month of treatment with dienogest and were found to be statistically significant.

Table-5 shows adverse drug reactions of the drug, 15 out of 100 patients had weight gain as the adverse effect, 6 of 100 patients had headache, 4 of 100 patients had acne as the adverse drug reaction, 3 of 100 patients had nausea and abdominal pain each and 1 out of 100 patients had depressed mood as the adverse drug reaction.

DISCUSSION

Treatment of endometriosis after surgery for stage endometriosis through surgery is still not completely cured, follow-up treatment mainly play an inhibitory effect rather than therapeutic effect, combined with the characteristics of endometriosis recurrence, so in the long period of treatment, not only to consider the effectiveness of drug therapy also want to consider the safety of drug treatment.

GnRH-a drugs and dienogest is recognized as a safe and effective drug, but they take effect in different mechanisms. Aims to study the safety and efficacy, this research measure GnRH-a drug and dienogest in endometriosis using meta-analysis. The results showed that the efficacy in GnRH-a drug and dienogest for pain control are similar, adverse reactions in patient perform different, such as in headache, hectic fever. Dienogest is a selective progesterone, which combines the pharmacological properties of 19-progesterone and progesterone derivatives, have significant effect on endometrium and ovarian androgen, no moderate inhibitory activity, due to modification of dienogest in structure, compared with the other progesterone, side effects are fewer. GnRH-a is a hypothalamic preparation, as an inhibition of ovarian release.[16-19]

Compared with dienogest, GnRH-a take IOTA advantage in increase of weight gain and decrease of hot flashes. But this study has some limitations: According to the analysis of the above statistics, while measuring the pain control efficacy, we do not include the analysis of the remaining four studies[17,18,19,20] which also showed the dienogest and GnRH-a in advantage in endometriosis but higher and miscellaneous pain happen. From forest grams, we saw that most of the result contain invalid line (the middle line), with a small number of suggesting statistical significance. In the compare in adverse reaction, mainly from dienogest and GnRH-a groups in endometriosis patients, due to the outcoming measure difference in articles, the numbers of samples and studies asymmetry.

CONCLUSION

There is no statistically significance in weight gain, and not enough evidence that the different cause by gender or dose. It may need further research. With regard to the incidence of hectic fever, in RevMan software make a hiatus funnel map, which mention the data deficient in our study. In this study, the quality of the most included studies is not high. Dienogest and GnRH-a was used in Japan and Europe, but there is a few data in China or other Asian countries, that may make a bias in race.

Because the dienogest is novelty relatively, its efficacy and safety for endometriosis requires a scientific clinical study yet.

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