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Efficacy and safety of Dienogest versus Medroxyprogesterone Acetate in the treatment of endometriosis-associated pelvic pain

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ABSTRACT

Objectives

Endometriosis is a chronic gynaecological disorder that requires a management plan consisting of pharmacological treatment and surgical procedures. This study aimed to observe and compare efficacy and safety of dienogest with medroxyprogesterone acetate in the treatment of endometriosis associated pelvic pain.

Methods

A prospective, randomized, comparative clinical study was conducted on 60 patients. They were randomly divided into groups of 30 to receive either Dienogest 2 mg OD (Group A) or Medroxyprogesterone acetate (MPA) 10 mg BD (Group B) orally for 12 weeks. Efficacy assessment was done by VAS Score for chronic abdominal pain, number of patients having symptoms of chronic abdominal pain, Biberoglu and Behrman scale. Safety assessment was done by recording adverse drug reactions.

Results

At the end of 12 weeks, dienogest depicted better response than medroxyprogesterone acetate in the reduction of VAS score for chronic pelvic pain (reduction in 92.90% versus 81.87%; p value=0.012). Number of patients having chronic pelvic pain was less in the Dienogest group than Medroxyprogesterone Acetate (13.33% versus 33.33%), but the difference wasn't statistically significant. Dienogest depicted better response than medroxyprogesterone acetate in reduction of Biberoglu & Behrman's score but the difference was not statistically significant (86.53% versus 83.98%). Medroxyprogesterone acetate led to more adverse effects than dienogest which are mainly vaginal dryness, decreased libido, hirsutism & hot flushes.

Conclusions

Both treatment groups i.e. dienogest and medroxyprogesterone acetate were found to be safe and efficacious in patients suffering from endometriosis. Dienogest was significantly more effective & safe than medroxyprogesterone acetate especially for treatment of chronic pelvic pain.

Keywords: Biberoglu & Behrman's score; dienogest; endometriosis; endometriosis associated pelvic pain; medroxyprogesterone acetate (MPA).

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INTRODUCTION

Endometriosis is a common benign and chronic gynaecological condition that occurs when endometrial glands and stroma are present outside of their typical locations[1], most frequently in the pelvic cavity, which contains the ovaries, the uterosacral ligaments, and the pouch of Douglas[2]. Patient mainly presents with pelvic pain, dysmenorrhea, dyspareunia, bladder and bowel problems or infertility[3,4]. The prevalence of pelvic endometriosis ranges from 6 to 10%. The average age at diagnosis is between 25 and 29 years[5,6]. Early menarche (before age 11), shorter periods (less than 27 days), and heavy, protracted cycles are risk factors for developing endometriosis. The common hypothesis proposed for pathogenesis include retrograde menstruation, haematogenous or lymphatic transport, bone marrow stem cells, and coelomic metaplasia[3].The American Society for Reproductive Medicine (ASRM) Practice Committee recommended that "endometriosis should be recognised as a chronic condition that requires a life-long care strategy with the goal of optimising the use of medical treatment and avoiding repetitive surgical procedures"(Johnson, 2013). The primary goal of endometriosis management is to reduce disease-related pain. This can be done surgically or medically, all though for the majority of women, both are required [6]. The majority of current medical treatments for endometriosis, which is an estrogen-dependent condition, include combined oral contraceptive pills (COCs), GnRH agonists, progestins, danazol and nonsteroidal anti-inflammatory medicines (NSAIDs) for symptomatic treatment[4]. Progestins play a crucial role in the management of endometriosis and are extremely effective in reducing the incidence of endometrial hyperplasia and carcinoma brought on by unopposed estrogens[7], being utilised as a monotherapy with significant success in the treatment of endometriosis[8]. These medications have the major benefits of not raising the risk of thrombosis[9,10] and being safe to use in women who are contraindicated to oestrogen[11,12] use.

MPA is a 17-hydroxy derivative progestogen with weak effects on the lipoproteins and moderate androgenic activity[11]. Oral MPA 30 and 50 mg/day has been successful in treating endometriosis[12,13]. A progestin called Dienogest (DNG) is a semi-synthetic 19-nortestosterone derivative. Its main activity is progestational and due to the absence of the C19 methyl group, it lacks androgenic activity[14,15]. A modest oral dose of 2 mg/day of this selective progestin has lately been authorised for the treatment of endometriosis in Europe, Japan, India, and other nations[14].

As most of the progestin drugs available for treatment of endometriosis lead to suppression of HPA axis, they lead to infertility and show androgenic side effects accompanied by alteration of lipid profile, liver dysfunction, weight gain and BMI (Vannuccini, 2022). Hence, the search continues for safer alternatives for the treatment of endometriosis and to prevent its complications. A more recent progestin called dienogest has demonstrated to be effective in treating endometriosis symptoms with lower side effects. This is primarily because dienogest does not have any androgenic effects; instead, it has advantageous anti-androgenic qualities that are linked to negligible changes in lipid and carbohydrate levels.In order to examine the effectiveness and safety of dienogest versus medroxyprogesterone acetate in the treatment of pelvic pain related to endometriosis, the present study was undertaken.

MATERIAL AND METHODS

This was a prospective, open label, randomized, comparative clinical study conducted by the Department of Pharmacology and Obstetrics & Gynaecology, Pt.B.D.Sharma PGIMS, Rohtak on 60 patients. Study was in accordance with the principles of good clinical practice (ICH-GCP) and declaration of Helsinki. An informed consent was obtained from all patients enrolled for the study. This study was done after obtaining the ethical clearance from institutional ethical committee (IEC) with approval number IEC/Th/17/pharma03.

Sample Size Calculation

The study by Al-Jefout M et al. et al. was taken as 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 reference, the minimum required sample size with absolute error which is taken as 4% and confidence interval of 95% was 60 patients. To increase the power of study, we enrolled 71 patients out of which 11 were lost to follow up.

Formula used: $N \geq 4 \cdot pq/e^2$, Where p is prevalence rate, q is 1-p, e is absolute error.An adequate number of patients were screened and selected as per the inclusion and exclusion criteria for the study. The eligible patients were randomly divided into two study groups i.e. Group A and group B. Each study group minimally had 30 patients and 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 (Available commercial preparations (same brand) of the drugs were used.). A patient information sheet was used to inform each patient about the study, and each patient's signed informed consent was obtained. 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. All participants were randomly allocated to any of the two groups.

The inclusion criteria were: Females of reproductive age group (18-40 yrs), subjects diagnosed with endometriosis either by clinical criteria (Definitive presence of nodule in pouch of Douglas or cervix or fixed retroverted uterus) and Ultrasonography (USG criteria for diagnosis depended on the published ultrasound characteristics of ovarian endometrioma by Van Holsbeke, et al. which required the presence of ground glass echogenicity and one to four compartments, along with no papillary structures with detectable blood flow[17]. Patients willing to give written informed consent was necessary. The exclusion criteria were: Pelvic inflammatory disease, allergy to progestin, contraindications to progestin, neoplastic disease, pregnant and nursing mothers, any history of hormonal agent intake in the last 3 months, smokers and alcoholic subjects, inability to attend regular follow ups.

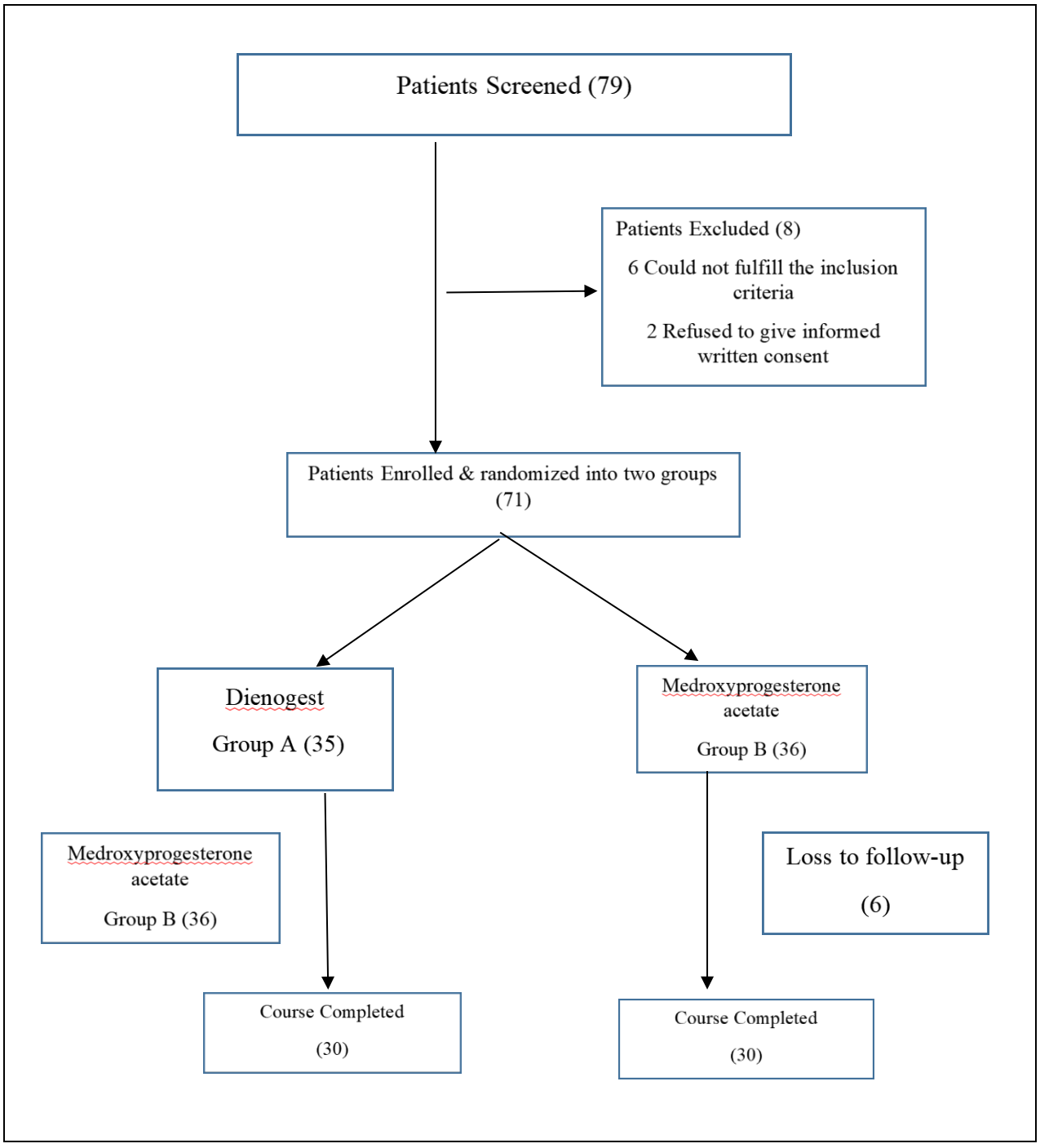
Efficacy assessment was done by VAS Score for chronic pelvic pain, number of patients having symptoms of chronic pelvic pain, Biberoglu and Behrman scale. The Biberoglu and Behrman scale consists of three patient-reported symptoms (dysmenorrhea, dyspareunia, and pelvic pain not related to menses) and two signs assessed during pelvic examination (pelvic tenderness and induration). Each of these is graded on a scale from 0 to 3, with higher numbers indicating more severe symptoms. Safety assessment was also done by recording adverse drug reactions. Adverse drug reactions of both the treatments were recorded in a pre-prepared adverse drug monitoring proforma.

Data was expressed as Mean ± SEM. Both intragroup and intergroup statistical analyses were done. Intragroup analysis for repeated measures was done using ANOVA for parametric data. Intergroup analysis was done using unpaired 't' test for parametric data. Categorical data like incidence of adverse events in both the groups was analysed using Chi-square test or Fisher Exact test. A p-value <0.05 was considered as statistically significant.

RESULTS

A total of 79 patients with symptoms of endometriosis were screened for this study. (Flow chart-1).

Flow chart-1: Distribution of patients



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As shown in table 1, the mean age of the patients in years was 26.03±1.11 and 26.9±1.01 (Mean±SEM) in Group A and Group B respectively. The difference in the age between the two groups was not statistically significant (p=0.564). There was no statistically significant difference in the study population characteristics namely age and weight, between the two groups (p>0.05).

On intragroup analysis, it was observed that there was statistically highly significant reduction in VAS score for chronic pelvic pain with both the drugs i.e. dienogest and medroxyprogesterone acetate at 8 weeks which continued for 12 weeks. Reduction observed with dienogest was 92.90% whereas with medroxyprogesterone acetate it was 81.87% at the end of 12 weeks as compared to baseline values. Intergroup analysis showed that dienogest showed statistically significant better response than medroxyprogesterone acetate in reduction of VAS score for chronic pelvic pain at the end of 12 weeks (92.90% vs 81.87%; p-value=0.012) as shown in table-1.

TABLE-1: COMPARISON OF VAS SCORE FOR ASSESSMENT OF CHRONIC PELVIC PAIN 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	5.63±0.49	-	5.13±0.38	-	0.423
Week 4	3.6±0.37*	2.03 (36.06%)	3.77±0.29*	1.36 (26.51%)	0.719
Week 8	1.3±0.29**	4.33 (76.91%)	1.6±0.27**	3.53 (68.81%)	0.452
Week 12	0.4±0.13**	5.23 (92.90%)	0.93±0.16**	4.2 (81.87%)	0.012#

INTRAGROUP ANALYSIS:

** Comparison of values at the end of week 4, 8 and 12 with baseline values showing statistically significant difference (p<0.05).*

*** Comparison of values at the end of week 4, 8 and 12 with baseline values showing statistically highly significant difference (p<0.001).*

INTERGROUP ANALYSIS:

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

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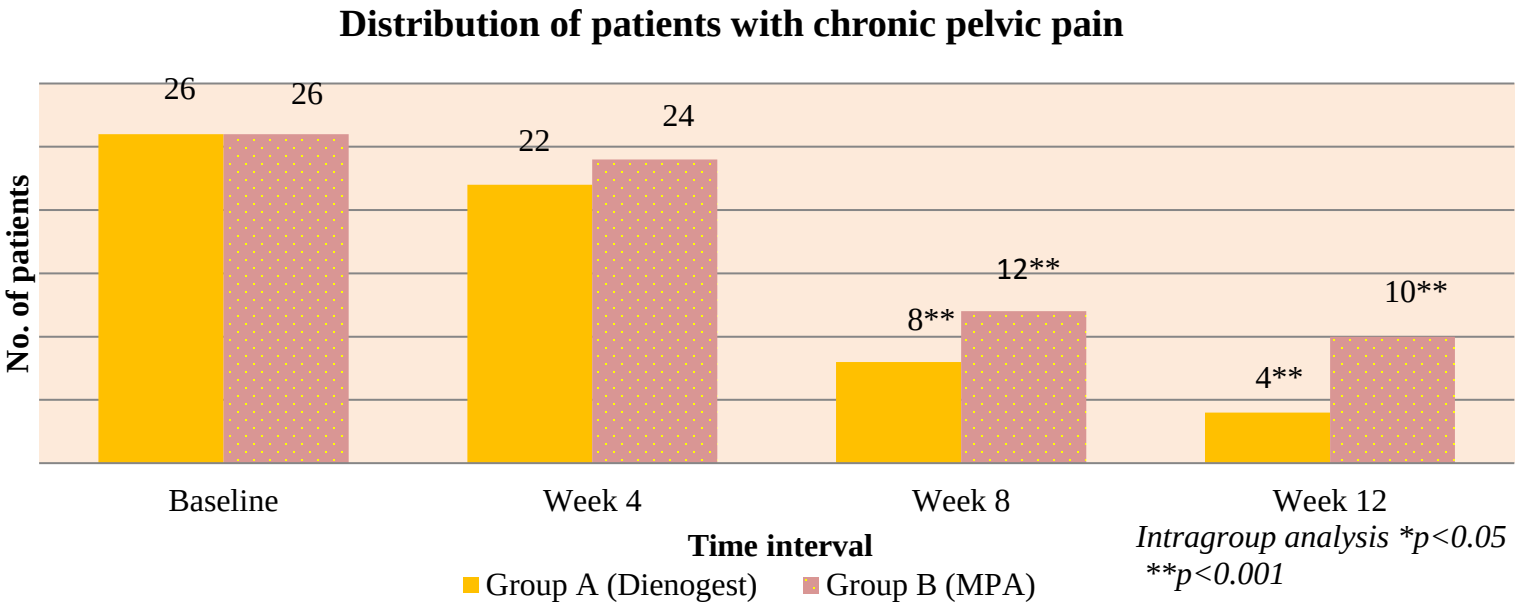
There was also a highly significant reduction in the number of patients having pain in both the groups at the end of 12 weeks. In the dienogest group, the number of patients having pain was 4 (13.33%) vs 26 (86.67%) whereas in medroxyprogesterone acetate group, it was 10 (33.33%) vs 26 (86.67%) as compared to baseline values. Dienogest showed better response than medroxyprogesterone acetate as number of patients having pain at the end of 12 weeks was less as compared to medroxyprogesterone acetate 4 (13.33%) versus 10 (33.33%) but the difference was not statistically significant as shown in figure-1.

Figure-1



There was a statistically highly significant reduction in Biberoglu & Behrman's score with both the drugs i.e. dienogest and medroxyprogesterone acetate at the end of 4 weeks which continued for 12 weeks. Reduction observed with dienogest was 86.53% whereas with medroxyprogesterone acetate it was 83.98% as compared to baseline values. Dienogest depicted better response than medroxyprogesterone acetate in reduction of Biberoglu & Behrman's score at the end of 12 weeks but the difference was not statistically significant (reduction in 86.53% versus 83.98%; p-value=0.752) as shown in table-2.

TABLE-2

Comparison of Biberoglu and Behrman's score in both groups

BIBEROGLU AND BEHRMAN'S SCORE	Dienogest (Group A) (n=30)		MPA (Group B) (n=30)		P-value (Intergroup)
	Mean±SEM	**Reduction from baseline (%)**	**Mean±SEM**	**Reduction from baseline (%)**	
Baseline	7.2±0.36	-	6.87±0.39	-	0.5365
4 week	3.97±0.35 **	3.23 (44.86%)	4.4±0.33 **	2.47 (35.95%)	0.3751
8 week	1.6±0.27 **	5.6 (77.77%)	1.9±0.32 **	4.97 (72.34%)	0.4765
12 week	0.97±0.28 **	6.23 (86.53%)	1.1±0.30 **	5.77 (83.98%)	0.7525

INTRAGROUP ANALYSIS:

** Comparison of values at the end of week 4, 8 and 12 with baseline values showing statistically significant difference (p<0.05).*

*** Comparison of values at the end of week 4, 8 and 12 with baseline values showing statistically highly significant difference (p<0.001).*

The most common ADR observed was weight gain. With the exception of headache and depression, which were more common with dienogest, the overall number of patients experiencing different adverse drug reactions (ADRs) was higher in medroxyprogesterone acetate than in dienogest. Hot flushes & hirsutism were seen only in medroxyprogesterone acetate.The incidence of vaginal dryness and decreased libido was observed more in medroxyprogesterone acetate and this difference was statistically significant (p< 0.05).

DISCUSSION

The presence of endometrial tissue outside of their typical locations, most frequently in the pelvic cavity, causes endometriosis, a common benign and chronic gynaecological condition[1]. Progestins are suited for long-term use and offer a favourable mix of efficacy and safety[18] (Vercellini et al, 2016). As a result, they can be used as an adjuvant therapy following surgery[18]. Major worldwide guidelines state that progestins, whether they contain estrogens or not, should be used as the first line of treatment for symptomatic endometriosis[19].The present study showed that dienogest depicted a statistically significant better response than medroxyprogesterone acetate in reduction of VAS score for chronic pelvic pain at the end of 12 weeks (92.90% vs 81.87%; p-value=0.012). Almost similar results were depicted in a study done by Oh ST[20] (Oh ST, 2015), in which the impact of 2 mg dienogest and high dose MPA (30- 60 mg) on endometriosis were compared. For a period of six months, 98 patients received dienogest whereas 120 patients received MPA. Dienogest was observed to have a VAS score >3 in 29/98 (29.59%) patients, whereas MPA had a VAS score >3 in 78/120 (65%) patients. In the dienogest group patients had pain disappearance in 68.36% of cases compared to 35% of cases in MPA group, or pain that persisted in 31.64% of cases compared to 65% of cases in MPA groups[20]. The results of our investigation are comparable to those of the aforementioned study as in both studies, pain reduction was more in dienogest than MPA.

The outcomes from this study support previous studies which investigated the efficacy of dienogest. In the study conducted by Vahid-Dastjerdi M et al., two groups of 48 and 53 women respectively, were assigned to the Dienogest (2 mg once daily) and MPA (10 mg twice daily) groups. After six months of follow-up evaluations, the pelvic pain score was significantly lower in the Dienogest group than the MPA group (P < 0.001)[21].Regarding Biberoglu and Behrman's scale scores (B&B scale), similar studies with comparable treatment groups were not available. In a study by Strowizki T et al, the dienogest (2mg) group experienced a more pronounced decline than the placebo group (7.8% versus 2.1%, respectively)[22]. In another trial conducted by Crosignani PG et al, DMPA caused a statistically significant decrease in B&B scale score. Our study's findings are comparable to the above mentioned studies in the context that both dienogest and MPA led to statistically significant decrease in B&B scale scores[23].

In a study by Oh ST, the impact of 2 mg dienogest and high dose (30–60 mg) MPA on endometriosis was studied. The results of our analysis are consistent with this study as weight gain and breast discomfort were considerably more common in the MPA group than in the dienogest group. Weight gain was the most frequent ADR observed in both studies. In our study, depression was observed in both groups, while in the study referenced above, it was only observed in the MPA group. Alopecia was not seen in any of the groups in our investigation, but it was seen in the MPA group in the study previously mentioned[20].Limitations of this study include the relatively small number of patients. Additionally, blinding was not done and long term follow-up was not completed.

CONCLUSION

Both the treatment groups i.e. dienogest and medroxyprogesterone acetate were found to be safe and efficacious in patients suffering from endometriosis (led to statistically significant improvement in chronic pelvic pain). Dienogest was significantly more effective than

medroxyprogesterone acetate especially for the treatment of chronic pelvic pain. Medroxyprogesterone acetate led to more adverse effects than dienogest mainly in vaginal dryness, decreased libido, hirsutism & hot flushes.However, more research on the effect of treatment on pelvic pain would be helpful in providing guidance to physicians when making clinical decisions.

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