



ORIGINAL RESEARCH PAPER

Obstetrics & Gynaecology

METAANALYSIS TO STUDY THE EFFICACY AND SIDE EFFECTS OF CABERGOLINE, DIENOGEST AND LEUPROLIDE ACETATE IN THE MEDICAL MANAGEMENT OF ENDOMETRIOSIS.

KEY WORDS:

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ABSTRACT

Background- Endometriosis is a common, benign, estrogen dependent, chronic gynaecological disorder associated with pelvic pain and infertility. Symptoms typically include recurrent episodes of dysmenorrhea, dyspareunia and pelvic pain, while subfertility and infertility are frequent. Medical as well as surgical treatment is known for endometriosis, although recurrence of endometriosis is common. Therefore medical treatment is preferred where aim is to relieve the symptoms in order to improve quality of life. **Method-** 150 patients categorized into three groups randomly and managed by cabergoline, leuprolide acetate and dienogest respectively. **GROUP A-** Patients treated with cabergoline 0.5 mg twice weekly. **Group B -** Patients treated with dienogest 2 mg per day. **GROUP C -** Patients treated with leuprolide acetate 3.75 mg depot IM injection every 4 weeks. All three groups will be compared. Patients will be treated for 6 months with proper follow up and evaluation at the starting of treatment, 3rd month of treatment and finally at the end of 6th month of treatment with all three drugs respectively. Outcome will be analysed on the basis of Visual analog scale and ultrasonographic findings. **Result-** Change in size of endometrioma was seen maximum in cases treated with cabergoline in comparison to those treated with Leuprolide acetate and dienogest. Dienogest and Leuprolide acetate were associated with comparable reduction in back pain. Relief in pelvic pain was seen statistically significant in Leuprolide Acetate group after 3 months as well as 6 months of treatment. In dyspareunia, complete relief was found statistically significant after 6 months in patients who were taking Leuprolide acetate as compared to dienogest and cabergoline group. Dysmenorrhea - patients taking Leuprolide acetate was statistically significant after 3 months as well as 6 months of treatment as it leads to amenorrhoea. Side effects- Leuprolide acetate group cases had hot flushes and vaginal dryness in 50% females. Whereas abnormal uterine bleeding was the major side effect with use of Dienogest. Weight gain and gastrointestinal disturbances were mainly seen in cabergoline group. **Conclusion-** Leuprolide acetate was found more effective in relieving pelvic pain, dysmenorrhea and dyspareunia in patients of endometriosis in comparison to cabergoline and dienogest. While cabergoline was found effective in decreasing size of endometrioma.

INTRODUCTION

Endometriosis is a benign disease which is characterized by the presence of endometriotic lesions, consisting of functional abnormal growth of endometriotic glands and stroma outside the uterine cavity. Endometriosis is an estrogen dependent disease. When estrogen levels increase during the menstrual cycle the ectopic tissue grows and then regresses in the absence of estrogen similar to the activity of normal uterine endometrium. It is a female reproductive disorder present in approximately 15% of adult women between the ages of 25-35. The disease occurs in two forms 1) extra uterine organs and tissues; 2) the uterine wall. This abnormal growth of endometrial tissue, referred to as ectopic endometrium and can occur anywhere in the body, but is most commonly observed in the pelvis - on the outer surface of the ovaries, fallopian tubes or the uterus. The cyclic shedding of ectopic endometrium within the abdomen causes irritation, lower back pain, intestinal, or pelvic pain, heavy menstrual bleeding or spotting between periods, dysmenorrhoea, dyspareunia, and infertility.

The main purpose of treatment in endometriosis is alleviating pain associated with the disease. This can be done by medical or surgical means, although in most women a combination of both is required. As recurrence is very common in endometriosis even after surgery, so medical treatment is being preferred in this study. Long-term treatment is needed in most women; unfortunately in most women pain symptoms recur between 6 months to 12 months once a treatment is stopped. The approaches used for the treatment of endometriosis currently involve pharmacologic therapies and surgical removal of endometriotic implants. Because

proliferation along with long term survival of ectopic endometrium is oestrogen dependent, classic pharmacologic therapies are aimed at suppressing endogenous estrogen.

GnRH-agonists, like buserelin, leuprolide acetate and triptorelin, are currently the most widely used medical therapies for endometriosis. They decrease the production of gonadotropins and they suppress ovulation, so they induce a pharmacological menopause. Therefore, long term use of GnRH-agonists is associated with hypo-estrogenic side effects: irregular menstrual period, hot flushes, vaginal burning, decreased libido and decreased bone mineral density.

Dienogest (DNG) is a fourth-generation selective progestin that exhibits high selectivity for binding to progesterone receptors. It has a potent oral progestational activity and little androgenic, estrogenic, glucocorticoid or mineralocorticoid activity and minimal impact on metabolic parameters. It reduces endometriotic lesions by creating a local progestogenic environment, suppressing the systemic estrogen level moderately.

Basu et al (2001) made an interesting discovery that the neurotransmitter dopamine selectively inhibits the vascular permeability and angiogenic effect of VEGF at nontoxic levels, revealing a new link between the nervous system and angiogenesis.

This led to the idea to use dopamine agonists for anti-angiogenic therapy. They found that daily oral treatment with

cabergoline over 14 days causes regression of endometriotic lesions by suppression of cell proliferation and VEGF mediated angiogenesis.

MATERIAL AND METHODS

150 patients categorized into three groups randomly and managed by cabergoline, leuprolide acetate and dienogest respectively.

GROUP A – Patients treated with cabergoline 0.5 mg twice weekly.

GROUP B – Patients treated with dienogest 2 mg per day.

GROUP C – Patients treated with leuprolide acetate 3.75 mg depot IM injection every 4 week.

All three groups will be compared. Patients will be treated for 6 months with proper follow up and evaluation at the starting of treatment, 3rd month of treatment and finally at the end of 6th month of treatment with all three drugs respectively. Outcome will be analysed on the basis of Visual analog scale and ultrasonographic findings

Inclusion Criteria :

Women in reproductive age group, with pain in the lower abdomen or pelvis for at least 6 months duration, occurring continuously or intermittently, dysmenorrhoea, pain during

Table 1-Complaint of patients in terms ofVAS Scale

Complaint	VAS									f-value	p-value
	Group A Cabergoline			Group B Dienogest			Group C Leuprolide Acetate				
	No.	Mean	SD	No.	Mean	SD	No.	Mean	SD		
Dysmenorrhoea	30	5.20	0.92	26	5.38	1.47	34	5.74	1.28	3.138	0.051
Dyspareunia	36	5.67	0.89	28	5.07	1.05	26	5.62	1.17	3.085	0.051
Pelvic Pain	29	5.55	1.26	38	5.53	0.95	30	5.20	0.85	4.360	0.052
Back Pain	18	6.11	0.76	14	6.14	0.66	16	5.75	1.00	1.101	0.341

Table 2-Size change at the end of 3 months of treatment

Size change	Group A Cabergoline	Group B Dienogest	Group C Leuprolide Acetate
<25%	20 (43.48)	32 (68.08)	28 (60.87)
>25%	26 (56.52)	15 (31.91)	18 (39.13)
Total	46 (100.00)	47(100.00)	46(100.00)

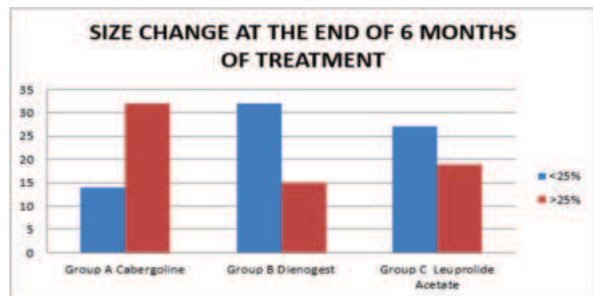


Chart 1-

Table 3-Relief in Pelvic Pain at the end of 3 months of treatment

	Group A Cabergoline	Group B Dienogest	Group C Leuprolide Acetate
Not relieved	18 (69.23)	7 (20)	0
Partially relieved	8 (30.77)	25 (71.43)	17(65.38)
Completely relieved	0	3(8.57%)	9(34.61)
Total	26 (100.00)	35(100.00)	26(100.00)

Table 4-Relief In Back Pain at the end of 3 months of treatment

	Group A Cabergoline	Group B Dienogest	Group C Leuprolide Acetate
Not relieved	11(64.71)	3 (21.43)	5(33.33)

sexual intercourse, increased menstrual bleeding, cyclical intestinal complaints, fatigue and weakness and with non gynaecological cyclical symptoms as dyschezia, dysuria, rectal bleeding, shoulder plain. Patients with acute Pelvic inflammatory disease whose symptoms persists even after treatment.

Exclusion Criteria :

1. Women with infertility
2. Women with Inflammatory Bowel disease.
3. Women with Chronic Pelvic Inflammatory Diseases.
4. Women with genital malformation that makes physical examination and TVS impossible.
5. History of gynaecological malignancy.

Patients treated for 6 months with proper follow and evaluation at the end of 1st month of treatment, 3rd month of treatment and finally at the end of 6th month of treatment with all three drugs respectively

Outcome analysed on the basis of

1. Visual analog scale for chronic pelvic pain
2. Ultrasonographic findings both abdominal and trans vaginal ultrasound
3. Magnetic Resonance Imaging (MRI)

RESULTS

Relief Status	Group A Cabergoline	Group B Dienogest	Group C Leuprolide Acetate
Partially relieved	06(35.29)	11 (78.57)	10(66.66)
Completely relieved	0	0	0
Total	17 (100.00)	14(100.00)	15(100.00)

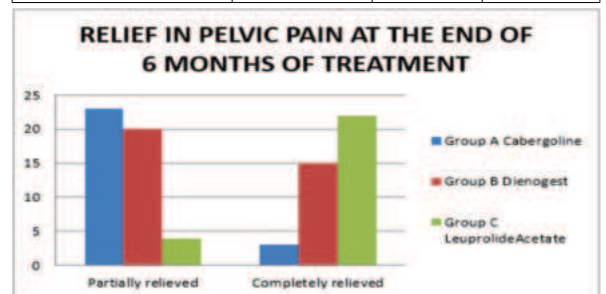


Chart 2-

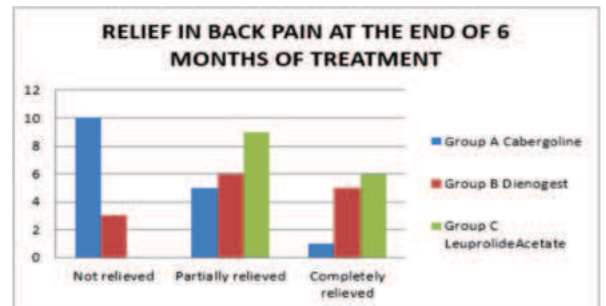


Chart 3

Table 5-Relief in Dyspareunia at the end of 3 months of treatment

	Group A Cabergoline	Group B Dienogest	Group C Leuprolide Acetate
Not relieved	7(21.21)	3(12)	1(4)
Partially relieved	26(78.78)	22(88.00)	24 (96.00)

Completely relieved	0	0	0
Total	33 (100.00)	25(100.00)	25(100.00)

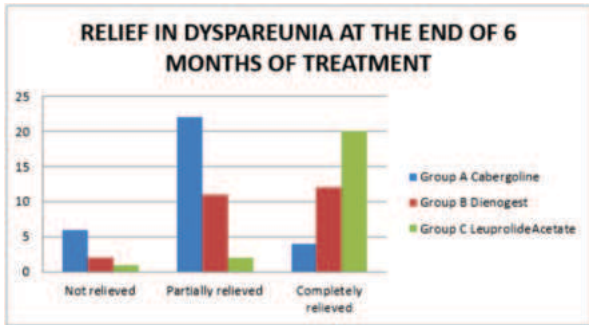


Chart 4-

Table 6-Relief in Dysmenorrhoea at the end of 3 months of treatment

VAS	Group A Cabergoline	Group B Dienogest	Group C Leuprolide Acetate
Not relieved	20(71.42)	0	0
Partially relieved	7 (25.00)	6(23.08)	2(6.25)
Completely relieved	1 (3.57)	20(76.92)	30(93.75)
Total	28 (100.00)	26(100.00)	32(100.00)

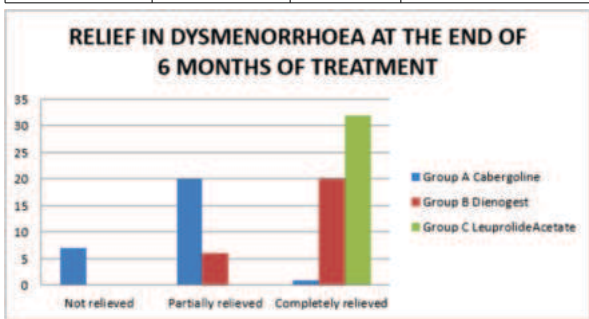


Chart 5-

Table 7-Table showing various side effects of all three drugs used.

	Group A (N=50)	Group B (N=50)	Group C (N=50)	
Weight Gain	25 (50%)	20 (40%)	5 (10%)	< 0.05
Hot Flushes	2 (4%)	0 (0%)	25 (50%)	< 0.001
Abnormal Menstrual Bleeding	5 (10%)	28 (56%)	1 (2%)	< 0.001
Vaginal Dryness	2 (4%)	2 (4%)	25 (50%)	< 0.001
G.I. Disturbances	22 (44%)	18 (36%)	2(4%)	< 0.001
Headache	14 (28%)	18 (36%)	2 (4%)	< 0.05

DISCUSSION

While evaluating the pain in patients of endometriosis the following four types of pain was considered i.e dysmenorrhoea, dyspareunia, back pain and pelvic pain. Most of patients had complaint of dyspareunia (36 out of 50) with mean VAS (5.67) in patient treated with cabergoline followed by complain of dysmenorrhea i.e (30 out of 50) with mean VAS of 5.20

Change in size of endometrioma-

While following these patients further to the end of 6 months of treatment, results were found significant and shown in Table 10. The patients being treated with cabergoline had significant change in size of endometrioma i.e 32 out of 46 cases had >25% decrease in size after 6 months of treatment. Whereas only 31.91% in group B and 41.30% in group C had >25% reduction in size. After statistically

evaluating result significant decrease in size was seen in group A and p value being =0.001.

Improvement in pelvic pain-

Maximum relief of pelvic pain was seen in group C i.e. patient treated with Leuprolide acetate with highly significant p value < 0.001.

Improvement in Back pain-

During evaluation of back pain in patient of endometriosis, most of the patients treated with dienogest i.e. 78.57% (11 out of 14) has partial relief at the end of 3 months whereas 66.66% in group C and 35.29% in group A were partially relieved as shown in table 13. Results were statistically significant. This was further compared at the end of 6 months as shown in table 14 in term of reduction in back pain. Patient in group B had comparable relief in pain with that of group C where as in group A only 6.250% had complete relief of pain at the end of 6 months, the results were statistically significant as p value 0.003.

Improvement in Dyspareunia-

Observation shows that there was comparable relief in dyspareunia in all three groups after 3 month of treatment. In group A 78.78%, in group B 88% and in group C 96% of females were partially relieved. No patients had complete relief in pain after 3 month of treatment .

But the end of 6 month of treatment results was significantly different. Patients treated with Leuprolide acetate showed complete relief in 86.95% of women as only 48% (12 out of 25) has complete relief in group B and minimum relief was seen with patient treated with cabergoline i.e. only 12.50% has complete relief

Improvement in Dysmenorrhoea-

While after 6 month of treatment 100% of the patient had complete relief in dysmenorrhoea in group C due to amenorrhoea while 76.92% completely relief in group B, while only 3.57% were completely relieved and 71.43% partially relieved in group A

Side effects-

While considering the side effects of all the three drugs, weight gain was seen in 50% of patient in group A and 40% of patient in group B while least in (10%) group C. Hot flushes and vaginal dryness was seen in 50% of the patient treated with Leuprolide acetate.

Whereas abnormal uterine bleeding was seen mostly in patient treated with Dienogest i.e in 56% of the cases. Dienogest treated people also had headache as one of the complaint in 36% of the patient, GI disturbances seen in 36% the total treated patient.

Cabergoline has major side effect weight gain in the 50% of patient and GI disturbance in 44% of the total patient in the group.

Irregular uterine bleeding is a known adverse effect of treatment with progestin which have been compared in trial against Leuprolide acetate

CONCLUSION

In our study injectable Leuprolide acetate was found more effective in relieving pelvic pain, dysmenorrhea and dyspareunia in patients of endometriosis in comparison to cabergoline and dienogest. While cabergoline was found effective in decreasing size of endometrioma.

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