Comparison of Efficacy and Safety of Levonorgestrel Intrauterine System with Oral Progesterone in Treatment of Dysfunctional Uterine Bleeding

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ABSTRACT

Introduction: Dysfunctional Uterine Bleeding (DUB) is defined as irregular uterine bleeding that occurs in the absence of recognizable pelvic pathology, general medical disease or pregnancy. DUB is one of the frequent conditions encountered in Gynaecology. The objective of present study was to compare the efficacy and safety of levonorgestrel-releasing intrauterine system (LNG-IUS) with oral progesterone in treatment of Dysfunctional Uterine Bleeding (DUB).

Material and Methods: The presented study was carried out in the Department of Obstetrics and Gynaecology, GSVM Medical College, Kanpur (U.P.). Hundred women of reproductive age group presenting with abnormal uterine bleeding without any organic or pelvic pathology were selected. All the selected patients were randomly divided into 2 groups each consisting 50 patients. Results were compared in terms of primary and secondary outcomes using student t-test, where values of ($p< 0.0001$) are considered as significant.

Results: In present study, majority of cases in both groups belonged to 30-35 years age group. Greater PBAC Score reduction was found with LNG-IUS in comparison of MDPA and results were highly statistically significant ($p<0.0001$). Increase in Hb levels was more with LNG-IUS in comparison of MDPA and results were statistically significant ($p<0.0001$). Mean endometrial thickness was more reduced in group 'A' after treatment.

Conclusion: The LNG-IUS can be considered more effective first choice for management of menorrhagia compared with conventional medical treatment.

Keywords: LNG-IUS, Oral progesterone, Dysfunctional Uterine Bleeding, PBAC Score.

INTRODUCTION

Heavy menstrual bleeding affects about one third of women in their reproductive period significantly impacting their quality of life and imposing financial burden.[1-3]

Patients with dysfunctional uterine bleeding (DUB) have constant, non-cycling estrogen levels that stimulate endometrial growth. Proliferation without periodic shedding causes the endometrium to outgrow its blood supply. The tissue breaks down and sloughs from the uterus. It is usually due to hormonal disturbances: reduced levels of progesterone causes low levels of prostaglandin F_2 alpha leading to menorrhagia, increased levels of tissue plasminogen activator (TPA) lead to more fibrinolysis.

Drug of choice for management of DUB is progestrone. It may be used locally or orally. Orally, it is available in various preparations like medroxyprogesterone acetate (MPA), norethindrone acetate, norethindrone, cyclic natural progestrone etc. Locally progestrone is available as vaginal suppositories, gel and progesterone releasing intrauterine devices (LNG-IUS) like MIRENA & EMILY.

UK National Institute for Health and Clinical Excellence recommended LNG-IUS as a first-line treatment for menorrhagia.[4] Recently several studies[5-8] done by various authors have shown the superiority of LNG-IUS over conventional medical treatments in reducing menstrual blood loss in dysfunctional uterine bleeding (DUB). Recently ECLIPSE study[9] observed that the LNG-IUS was more effective than conventional medical treatment in improving quality of life in DUB patients. However, Long-term randomized trials are required to further evaluate the outcomes and cost-effectiveness of the LNG-IUS and other medical treatments. Therefore, the aim of present study is to compare the efficacy and safety of effects of levonorgestrel-releasing intrauterine system (LNG-IUS) with oral progesterone in treatment of Dysfunctional Uterine Bleeding (DUB).

MATERIAL AND METHODS

The presented study was carried out in the Department of Obstetrics and Gynaecology, GSVM Medical College, Kanpur (U.P.). Hundred women of reproductive age group presenting with abnormal uterine bleeding without any organic or pelvic pathology were selected. Women of reproductive age group including the perimenopausal women with good compliance and ready to follow instructions are included in the study while women with pregnancy, any organic pathology of pelvic organs, with bleeding disorder,

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with systemic diseases like diabetes mellitus, hypertension etc. or having contraindication for progesterone therapy were excluded from the study.

All the selected patients were subjected to detailed history and examination (general, systemic and pelvic). All the selected patients were randomly divided into 2 groups each consisting 50 patients.

Group-A: 50 cases selected in this group and LNG-IUS was inserted within first seven days of menses.

Group-B: In first cycle we prescribed norethisterone (Regesterone 5 mg) TDS for 7 days followed by 5mg BD for next 7 days then tapered to 5 mg OD for next 7 days. From the 2nd to 6th cycle we prescribed medroxy progesterone acetate 10 mg BD from 5th day to 25th day per cycle for maintenance therapy. Norethisterone (Regesterone 5mg) was freely available in our hospital.

The patients were called for follow up after 1 month, 3 months and after 6 months. At each follow up visit patients were assessed in terms of primary and secondary outcomes. Primary outcomes were menstrual diary, Pictorial blood loss assessment chart (PBAC) scores and subjective assessment of patient. The pictorial blood assessment chart (PBAC) consists of a series of diagrams representing lightly, moderately and heavily soiled towels and tampons. The chart is scored using the scoring system devised by Higham et al.[10] A baseline score is established, subsequent treatment cycles are then assessed and success can be indicated by a decreasing score. A PBAC score greater than or equal to 100 indicated a menstrual blood loss greater than or equal to 80 ml and was considered diagnostic for criteria.

Subjective assessment was done by considering 5 parameters i.e. general condition, satisfaction, duration and flow during menses, adverse effects and overall acceptability and grading was done as mild improvement**,** marked improvement, no improvement and further deterioration in the condition.

Secondary outcomes were Hb levels and side effects like nausea and vomiting, breast tenderness, impaired glucose tolerance, pelvic infection etc. At the end of visit, patient's acceptability was assessed by asking whether they wanted to continue with the same treatment modality. If patient answered NO then reason was asked and enquired. Cases in both groups are matchable in regards of age, parity, socio-economic status, clinical presentation. Results are compared in terms of primary and secondary outcomes using student t-test, where values of ($p< 0.0001$) are considered as significant.

RESULTS

Table 1 shows that in group 'A' after 1 month of treatment, the mean PBAC Score was 145.32 ± 79.29 and the reduction in mean PBAC Scores was by 40.32%. After 3 months of treatment in group 'A', the mean PBAC Score was 108.6 ± 70.887 and the reduction in mean PBAC Scores was by 55.14%. After 6 months, the mean PBAC Score was 77.28 ± 44.72 and the reduction in mean PBAC Scores was by 68.18%.

In group 'B,' after 1 month of treatment the mean PBAC Score was 206.52 ± 84.68 and the reduction in mean PBAC Scores was only by 15.85%. In group 'B' after 3 months of treatment the mean PBAC Score was 166.1 ± 77.78 and the reduction in mean PBAC Scores was by only 32.52%. After 6 months of treatment, the mean PBAC Score was 131 ± 61.46 and the mean reduction in PBAC Scores was by 46.92%.

The mean PBAC Scores for both groups were compared by applying unpaired t-test which showed that the group 'A' (LNG-IUS) was more effective in reducing the PBAC Scores and the difference between both groups is highly significant ($p <0.0001$).

Table 2 shows comparison of mean Hb levels in both groups during treatment. In group 'A', the mean Hb levels before treatment was 7.434 gm ± 0.933 gm% and after 1 month of treatment mean Hb was 8.16 ± 0.98 gm% and increase in mean Hb levels was by 9.76% After 3 months, the mean Hb levels increased by 20.50% from pre-treatment levels. After 6 months, the mean Hb levels showed a further increase by 29.19% from pre-treatment levels. In group 'B', the mean Hb levels during pre-treatment was 7.466 ± 1.041 gm% and after 1 month of treatment mean Hb levels increased by 4.55%, after 3 months the mean Hb levels increased by 7.04%. After 6 months of treatment, the mean Hb levels increased by only 10.76%.

The mean Hb levels obtained after treatment were compared by applying unpaired t-test. After comparing the post-treatment mean Hb levels in both groups, the group 'A' (LNG-IUS) was more effective in increasing Hb levels, and the difference is highly significant ($p <0.0001$).

Figure 1 shows reduction in mean endometrial thickness before treatment and after 6 months of treatment in both groups. In group 'A, pre-treatment endometrial thickness was 10.68 ±1.977 mm and post-treatment was 8.154 ± 1.71 mm. The mean reduction in endometrial thickness was by 2.53 mm in group 'A'. While in group 'B', pre-treatment thickness was 11.04 ± 2.187 mm and post-treatment was 9.39 ± 2.37 mm. The mean reduction in endometrial thickness was by 1.65 mm in group 'B'.

Post-treatment endometrial thickness in both groups were compared by applying unpaired t-test which shows that group 'A' (LNG-IUS) was more effective in reducing the endometrial thickness and the difference is highly significant ($p <0.0001$).

Figure 2 depicts that in group 'A', 20% patient experienced marked improvement after 1 month of treatment followed by 60% patients feeling improvement after 3 months treatment. 88% patients experienced improvement after 6 month of treatment in group 'A'. While in group 'B', improvement after 1, 3 and 6 months of treatment was in 12%, 22& and 60% patients respectively.

Figure 3 shows that group ' A' patients reported less side effects in comparison to group 'B' patients after 6 months of treatment except hypomenorrhoea which was more common in group 'A.'

Groups	Mean PBAC Scores			
	Pre-treatment	After 1 month treatment	After 3 months treatment	After 6 months treatment
Group A (LNG-IUS)	242.88 ±93.36	145.32 ± 79.29	108.6 ± 70.887	77.28 ± 44.72
Group-B (Oral Progesterone)	246.84 ± 89.97	206.52 ±84.68	166.1 ± 77.78	131 ± 61.46
Highly significant (p <0.0001)				

Table-1: Comparison of mean PBAC scores in both groups during treatment

Groups	Mean Hb levels (gm%)			
	Pre-treatment	After 1 month treatment	After 3 months treatment	After 6 months treatment
Group A (LNG-IUS)	7.434 ± 0.933	8.16 ± 0.98	8.958 ± 0.88	9.604 ± 0.857
Group-B (Oral Progesterone)	7.466 ± 1.041	7.806 ± 1.02	7.992 ± 1.0078	8.27± 1.03
Highly significant (p <0.0001)				

Table-2: Comparison of Mean Hb levels in both groups during treatment

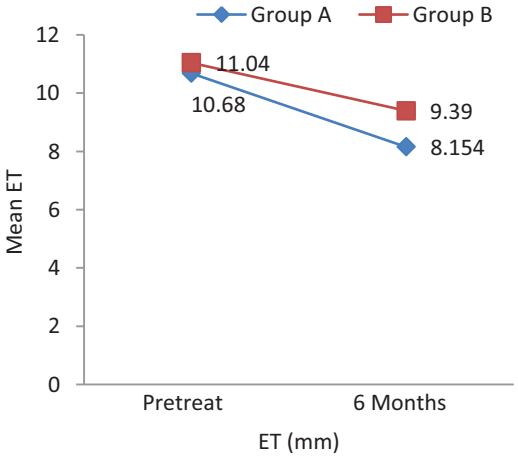

Figure-1: Comparison of reduction in endometrial thickness in both groups

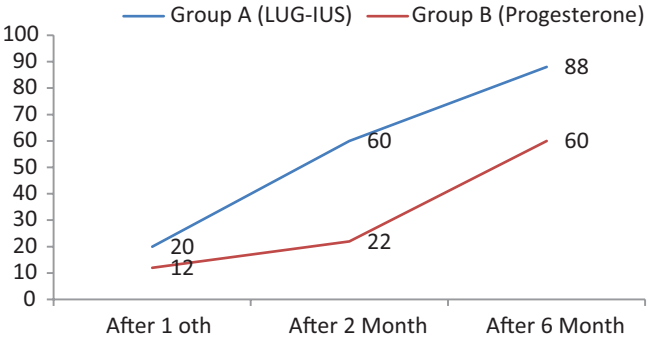

Figure-2: Comparison of patient's subjective assessment of improvement in both groups

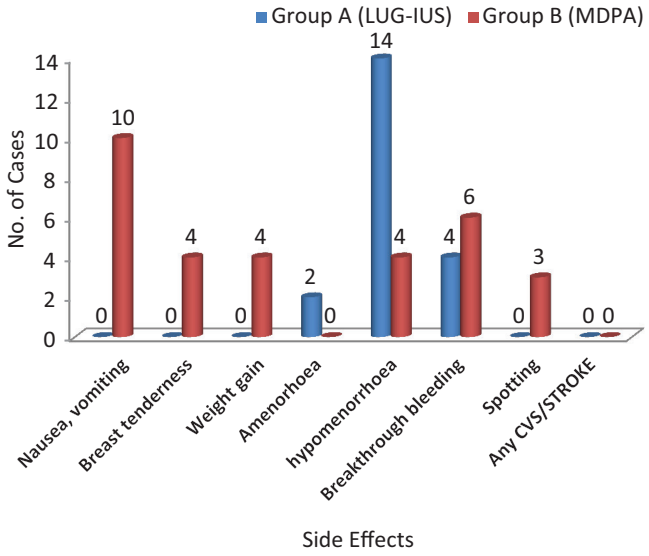

Figure-3: Comparison of side effects in both groups after 6 months of treatment

DISCUSSION

Abnormal uterine bleeding is one of the most common reasons for women to seek for care. DUB is responsible for about half of the women with abnormal uterine bleeding in reproductive age group. In present study, 100 women of reproductive age group presenting with dysfunctional uterine bleeding were selected from outpatient department. These 100 women were divided in two groups and different treatment modalities were provided.

Group-A: It included 50 patients in whom LNG-IUS was inserted within first seven days of menses.

Group-B: It also included 50 patients and in first cycle we prescribed norethisterone (Regestrone 5 mg) TDS for 7 days then 5mg BD for next 7 days then tapered to 5 mg OD for next 7 days. From the 2nd to 6th cycle we prescribed medroxy progesterone acetate 10 mg BD from 5th day to 25th day per cycle for maintenance therapy.

In present study, the mean age in group 'A' (LNG-IUS) was 35.22 ± 5.817 years and in group 'B' was 35.88 ± 5.32 years. Studies done by Shaaban et al.[6] and Naeema et al.[11] also showed mean age in groups using LNG-IUS treatment modality was 39.3±6.7 years and 35.98±7.66 years respectively which is comparable to our study. It shows that dysfunctional uterine bleeding (DUB) is more common in reproductive age groups particularly between 30-40 years of age.

In present study, maximum cases presented with complaint of menorrhagia (56% in group A and 50% in group B) followed

by polymenorrhoea (14% in group A and 22% in group B). Study done by Jetley S et al.[12] also found menorrhagia (46.4%) as most common clinical presentation in women suffering from DUB.

PBAC scores

It is a tedious job to quantify menstrual blood loss objectively therefore menorrhagia is defined subjectively in clinical practice. In present study, we have used PBAC Chart which is used by Higham et al. It is a simple and accurate tool for semi-objective assessment of menstrual blood loss and it can be used in clinical practice to aid the decision about treatment and follow-up.

Comparison of PBAC scores in both groups:

In present study, all cases in both groups have PBAC Scores > 100 before treatment. In group 'A', pre-treatment mean PBAC Score was 242.88 ±93.36. In group 'B', pre-treatment mean PBAC Score was 246 ± 89.87. Study done by Robert et al.[13] also observed that all patients with menorrhagia had PBAC Scores > 120 which is similar to present study.

In group 'A', mean PBAC score was reduced by 40.32%, 55.14% and 68.18% in comparison of pre-treatment value after 1 month, 3 month and 6 month treatment respectively while in group 'B', mean PBAC score was reduced by 15.85%, 32.52% and 46.92% in comparison of pre-treatment value after 1 month, 3 month and 6 month treatment respectively. The mean PBAC Scores obtained were compared by applying unpaired t-test. The difference in mean PBAC Scores in both groups was statistically significant ($p< 0.0001$) and at the end of 6 months both the treatment modalities were found effective but reduction was significantly better with LNG-IUS in group A. Studies done by various authors (Shaw RW et al,[14] Kucuk et al[7], Saygili H et al [15], Shaaban et al[6]) showed statistically significant reduction ($p < 0.05$) in PBAC score after treatment with LNG-IUS and they also observed that LNG-IUS is more effective in PBAC score reduction in comparison of MDPA or low dose oral contraceptives. These findings are in consistent with the present study.

In present study, 86% cases in group 'A' achieved PBAC Scores < 100 after 6 months of treatment whereas in group 'B' only 36% cases achieved the desired effect. So, the effective outcome i.e. reduction in PBAC Scores can be achieved more effectively in lesser time. The results obtained are comparable to study done by Chattopadhyaya B et al.[16] (73.68% in LNG-IUS group)

Comparison of Hb levels in both groups

In present study, in group 'A', mean Hb level was 7.434 ± 0.933 gm% while in group 'B' it was 7.466 ± 1.041 gm% before treatment. In group 'A', mean Hb level was increased by 9.76%, 20.5% and 29.19% in comparison of pre-treatment value after 1 month, 3 month and 6 month treatment respectively while in group 'B', mean Hb level was increased by 4.55%, 7.04% and 10.76% in comparison of pre-treatment value after 1 month, 3 month and 6 month treatment respectively. The mean Hb levels obtained were compared by applying unpaired t-test. The difference in mean Hb levels in both groups was statistically significant ($p< 0.0001$). All the patients of DUB in this study showed improvement but results were significantly better in LNG-IUS groups. Studies done by various authors (Kriplani A et al,[17] Taru G et al[18]) also showed increase in mean Hb levels after treatment with LNG-IUS in DUB patients and these results are in accordance with the results of present study.

Comparison of subjective improvement in both groups

In group 'A', 90% patient experienced marked improvement in their general condition after 6 months of treatment while 55% patients reported marked improvement in group 'B. In study of Kaunitz AM et al.[19], 84.8% of women in the levonorgestrel-releasing intrauterine system group had treatment success vs 22.2% of women in the medroxyprogesterone acetate group ($P < .001$). In a study by Erika B et al,[20] the number of women expressing that they were very satisfied with the LNG-IUS was 69% and 77% after six months and 36 months of use, respectively.

Comparison of endometrial thickness in both groups:

Present study shows that in group 'A', pre-treatment endometrial thickness was 10.68 ±1.977 mm and post-treatment it was 8.154 ± 1.71 mm. The mean reduction in endometrial thickness was by 2.53 mm. While in group 'B', pre-treatment endometrial thickness was 11.04 ± 2.187 mm and post-treatment it was 9.39 ± 2.37 mm. The mean reduction in endometrial thickness was by 1.65 mm. The difference in mean endometrial thickness post-treatment was statistically significant ($p< 0.0001$) in both groups. Studies done by various authors (Alka K et al, Michelli M et al and Suhairwreikat et al.) also showed decrease in mean endometrial thickness after treatment with LNG-IUS in DUB patients and these results are in consistent with present study.

Side-Effects

In group 'A', 4% cases reported amenorrhoea, 28% cases developed hypomenorrhoea and 6% cases reported breakthrough bleeding after 6 months of treatment with LNG-IUS while in group 'B', 20% cases complained of nausea and vomiting, 8% cases developed hypomenorrhoea, 12% cases breakthrough bleeding and 6% cases complained of spotting. Kriplani A et al.[17] developed amenorrhoea in 28.57% cases after 1 year of treatment with LNG-IUS while Taru G et al.[18] developed amenorrhoea in 33.87% cases after same treatment. Naeema et al.[11] developed amenorrhoea in 73.3% cases after 3 year of treatment with LNG-IUS.

CONCLUSION

In present study, majority of cases in both groups belonged to 30-35 years age group and most common clinical presentation seen was menorrhagia. On comparing the mean PBAC scores in both groups, greater reduction was found with LNG-IUS in comparison of MDPA and results were highly statistically significant ($p<0.0001$). Increase in Hb levels was more with LNG-IUS in comparison of MDPA and results were statistically significant ($p<0.0001$). Mean endometrial thickness was more reduced in group 'A' after treatment. 90% patients in group 'A' reported marked improvement in comparison of group 'B' (only 10%). The

LNG-IUS can be considered more effective first choice for management of menorrhagia compared with conventional medical treatment. Long-term studies are required to evaluate outcomes and cost-effectiveness of the LNG-IUS and other medical treatments.

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