ORIGINAL ARTICLE

EFFCTIVENESS OF LEVONORGESTREL INTRAUTERINE SYSTEM VERSUS NORETHISTERONE IN IDIOPATHIC HEAVY MENSTRUAL BLEEDING

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ABSTRACT

BACKGROUND: Heavy Menstrual Bleeding (HMB) is defined as menstrual blood loss for more than 7 days and/or blood loss greater than 80 ml. Women having HMB who have no demonstrable organic pathology are diagnosed as having idiopathic heavy menstrual bleeding. Abnormal uterine bleeding is one of the commonest reasons for which women are referred to hospitals by general practitioners. This study was conducted to compare levonorgestrel intrauterine system and norethisterone in idiopathic heavy menstrual bleeding.

METHODS: The study was carried out at the Department of Gynecology and Obstetrics, Fauji Foundation Hospital, Rawalpindi, Pakistan. A Randomized Controlled Trial (RCT) was chosen in order to achieve the above-mentioned objective. Duration of this study was 8 from December 26, 2014 to August 30, 2015. All women with idiopathic heavy menstrual bleeding presented at the Department of Gynecology and Obstetrics, were enrolled in the study. A computer generated table of random numbers was used to randomize the enrolled women into two study groups – Group A and Group B. In group A levonorgestrel intrauterine system was inserted and in group B oral norethisterone was given. Norethisterone tablet was prescribed at dose of 5 mg 3 times daily from day 1-21 over 6 cycles in group B. Once treatment started data were collected on the especially designed profroma by the principal investigator herself. Total number of pads used per cycle, hemoglobin level (g/dl) at presentation and total number of pads used per cycle, hemoglobin level (g/dl) and patient satisfaction n terms of whether they wanted to continue the treatment or wanted other option like hysterectomy) at 6 months were recorded. For follow up, patients contact number and address were noted.Data were entered and analyzed using SPSS version 20.

RESULTS: During the study period , a total of 110women with idiopathic heavy menstrual bleeding (55 in each study arm) presented at the Department of Gynecology and Obstetrics, Fauji Foundation Hospital, Rawalpindi, were enrolled. The mean (SD) age of women enrolled in levonorgestrel intrauterine system group was 41.1 (± 3.3) years while in norethisterone group, it was 41.0 (± 3.5) years. In levonorgestrel intrauterine system group, 21 (38%) women were less than 40 years of age, while in norethisterone group 16 (30%) women were less than 40 years of age. In levonorgestrel intrauterine system group 54 (98%) women were multigravida whereas in norethisterone group all 55 (100%) women were multigravida. The comparison of mean difference in various parameters from baseline to end of treatment between two study groups showed that women in levonorgestrel intrauterine system group had significantly less mean number of sanitary pads used/ cycle ($p<0.0001$), significantly lower mean blood loss ($p<0.0001$) and significantly mean higher hemoglobin level ($p=0.018$) compared to women in norethisterone group. Similarly, a significantly higher number of women in levonorgestrel intrauterine system group showed satisfaction with treatment than women in norethisterone group ($p=0.007$) at the end of treatment (after 6 months).

CONCLUSION: In conclusion, our study shows that women who were given levonorgestrel releasing intrauterine system showed a significantly lower use of sanitary pads, significant lower volume of blood loss, significantly improvement in hemoglobin levels and a significantly higher percentage of them showed satisfaction with the treatment after 6 months of treatment compared to women who were given norethisterone treatment for the management of HMB.

KEY WORDS: Heavy Menstrual Bleeding, Levonorgestrel Releasing Intrauterine System, Norethisterone, Hemoglobin.

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INTRODUCTION

Heavy menstrual bleeding (HMB) is defined as menstrual blood loss for more than 7 days and/or blood loss greater than 80 ml[1, 2]. Women having HMB who have no demonstrable organic pathology are diagnosed as having idiopathic heavy menstrual

bleeding[3]. Abnormal uterine bleeding is one of the commonest reasons for which for which women are referred to hospitals by general practitioners[2]. In USA, more than 600,000 hysterectomies are performed annually. Approximately 90% of these were for benign diseases including menstrual disorders[3].

The treatment options are medical and surgical. Among medical and non-hormonal methods as prostaglandin synthetase inhibitors reduces blood loss by 25%, inhibitors of fibrinolysis by 50%, COCP by 40%, Gondotrophin releasing hormone analogues by 75%[4]. Among medical hormonal treatment oral norethisterone and levonorgestrel intrauterine system both were effective.

Norethisterone tablets are given in a dose of 5mg three times daily from day 1 to 21 of cycle over 6 cycles. Its adverse effects include nausea, vomiting, bloating, mastalgia and depression[4]. The levonorgestrel intrauterine system is an effective way to bypass systematic side effects and consists of T shaped polyethylene frame with a reservoir containing 52mg of levonorgestrel. It releases 20 microgram of levonorgestrel/day and acts by causing endometrial gland atrophy and stromal decidualization(4). The side effects of LNG IUS are irregular vaginal spotting, pelvic pain, expulsion and amenorrhea[5,6] but most of the patients become asymptomatic in first three months[7]. The percentage decrease in mean menstrual blood loss and satisfaction with levonorgestrel intrauterine system is 70.8% (±88.3) and 90% as compared to norethisterone which is 21.5%(±35.8) and 20% respectively[3,8]. Mean (SD) increase in hemoglobin levels from baseline to cycle6 is 13.372(± 1.0020) in LNG intrauterine system and 12.512(±1.2875) in oral norethisterone[9].

HMB is the commonest complain of women of reproductive group for which they consult gynecologists. Different treatments are given but hysterectomy is considered as last resort. Most of the women want to conceive and preserve their uterus so we want to make a suitable alternative to hysterectomy and treat the patient until the women attains menopause by conducting a trial to evaluate the role of oral norethisterone and levonorgestrel intrauterine system in terms of decreasing blood loss and patients satisfaction.

This study was conducted to compare levonorgestrel intrauterine system and norethisterone in idiopathic heavy menstrual bleeding.

MATERIAL & METHODS

The study was carried out at the Department of Gynaecology and Obstetrics, Fauji Foundation Hospital, Rawalpindi. All women with idiopathic heavy menstrual bleeding (heavy menstrual bleeding ,blood loss more than 80ml/cycle assessed by number of pads a woman used/cycle at regular interval in the absence of organic pathology) presented at the Department of Gynaecology and Obstetrics, and who fulfilled the following inclusion criteria were enrolled in the current study. A Randomized Controlled Trial (RCT) was chosen in order to achieve the above-mentioned objective.

Total duration of the study was eight months. Enrolment of women started from December 26, 2014 and data collection was completed by August 30, 2015.Data was collected on:

• Number of sanitary pads/cycle at presentation and at the end of treatment (6 months) as mean number of pad.

• Hemoglobin level at presentation and at the end of treatment (6 months) as mean hemoglobin.

• Satisfaction with the treatment and it will be assessed by asking whether the patient wants to continue the treatment or other options such as hysterectomy

Sample size was calculated by using the World Health Organization (WHO) sample size calculator with the following values:

• Level of significance = 5%

• Power of test = 80%

• Population mean(P1)= 70.80[3]

• Anticipated population mean (P2) = 21.50(3)

• Pooled SD = 62.37

The required sample size was 55 women in each study group, leading to a total of 110 women[3,8,9].

Non-probability, consecutive sampling technique was used. Women aged 30 – 45 years with idiopathic heavy menstrual bleeding, and willing to participate were included.Following criteria was used for exclusion:

• Menstrual irregularity (by taking history from patient)

• Breastfeeding

• Congenital or acquired uterine abnormalities including fibroids

• History of organic causes of uterine bleeding (e.g. endometriosis, adenomyosis, endometrial polyp)

• Use of levonorgestrel releasing intrauterine system or copper intrauterine device during 30 days before the study

• History of vascular or coagulation disorder

• Concomitant use of medication or presence of underlying disease/condition known to effect the metabolism or pharmacokinetics of study

• BMI > 35 kg/m^2

Administrative permission from Hospital Research and Ethical Committee, Fauji Foundation Hospital, was sought and informed consent for inclusion in the study was obtained from each patient. All women 30–45 years with idiopathic heavy menstrual bleeding presented at the outpatient department of Gynaecology and Obstetrics, Fauji Foundation Hospital, Rawalpindi were recruited in the current study. Women who had changes in menstrual irregularity, were breastfeeding, had congenital or acquired uterine abnormalities including fibroids, had history of organic causes of uterine bleeding (e.g. endometriosis, adenomyosis, endometrial polyp), were using levonorgestrel releasing intrauterine system or copper intrauterine device during 30 days before the study, had history of vascular or coagulation disorder, were using medication or presence of underlying disease/condition known to effect the metabolism or pharmacokinetics of study and those who had BMI > 35

kg/m^2 were excluded from the study.

Women should have a normal pelvic examination, negative cervical cytology, normal ultrasound pelvis and normal endometrial sampling. After enrolment, patients were randomized by lottery method to either of two treatment groups. In group A levonorgestrel intrauterine system was inserted and in group B oral norethisterone was given. LNG intrauterine device was inserted into uterus within 7 days of menstrual period in group A. Norethisterone tablet was prescribed at dose of 5 mg 3 times daily from day 1-21 over 6 cycles in group B. Once treatment started data were collected on the especially design proforma by the research herself by recording total number of pads used per cycle, hemoglobin level (g/dl) at presentation and total number of pads used per cycle, hemoglobin level (g/dl) and patient satisfaction (by asking whether they want to continue the treatment or wants other option such as hysterectomy) at 6 months. For follow up patient contact number and address were noted.

The data were entered and analyzed using SPSS version 20. For continuous variables such as age, total number of sanitary pads/cycle at baseline and after 6 months of treatment, hemoglobin levels at baseline and after 6 months of treatment, and blood loss at baseline and after 6 months of treatment, mean with standard deviation and median was calculated. Frequencies and percentages were measured for categorical variables such as parity, and subjective feeling (satisfaction with treatment).

For comparison of mean difference in blood loss, number of sanitary pads/cycle and hemoglobin concentration from baseline to end of treatment between the two study groups, i.e. levonorgestrel intrauterine system and oral norethisterone, unpaired two sample Student t test was used and p-values were obtained. For comparison subjective between two study groups, Chi-square test was used and p-values were obtained.Effect modifiers such as age was controlled by stratification. Post stratification independent sample t-test and Chi-square test were applied keeping p-value ≤ 0.05 as significant.

RESULTS

During the study period of 8 months, a total of 110women with idiopathic heavy menstrual bleeding (55 in each study arm) presented at the Department of Gynaecology and Obstetrics, Fauji Foundation Hospital, Rawalpindi were enrolled.

Baseline data (at Presentation)

Total number of sanitary pads used/cycle

Out of 55 women in group A, 10 (18%) women used/cycle 20 or less sanitary pads per menstrual period, 25 (45%) women used/cycle between 21 and 25 sanitary pads per menstrual period, while remaining 20 (37%) women used/ cycle more than 25 sanitary pads per menstrual period. On the other hand, out of 55 women in group B, 11 (20%) women used/cycle 20 or less sanitary pads per menstrual period, 15 (27%) women used/cycle between 21 and 25 sanitary pads per menstrual period, while remaining 29 (53%) women used/ cycle more than 25 sanitary pads per menstrual period. The distribution of sanitary pads used at baseline of all the enrolled women in two study groups is shown in Table No:02.

Total blood lost

Out of 55 women in group A, 10 (18%) women reported up to 100 ml blood lost per menstrual period, 25 (45%) women reported between 110 ml and 150 ml blood lost per menstrual period, while remaining 20 (37%) women reported more than 150 ml blood lost per menstrual period. On the other hand, out of 55 women in group B, 11 (20%) women reported up to 100 ml blood lost per menstrual period, 15 (27%) women reported between 110 ml and 150 ml blood lost per menstrual period, while remaining 29 (53%) women reported more than 150 ml blood lost per menstrual period. The distribution of blood lost at baseline of all the enrolled women in two study groups is shown in Table No:02.

Hemoglobin level

Out of 55 women in group A, 10 (18%) women had hemoglobin level less than 9 g/dl, 36 (66%) women had hemoglobin level between 9 and 11 g/dl, while remaining 9 (16%) women had more than 11 g/dl. On the other hand, out of 55 women in group B, 13 (24%) women had hemoglobin level less than 9 g/dl, 41 (74%) women had hemoglobin level between 9 and 11 g/dl, while remaining 1 (2%) woman had more than 11 g/dl. The distribution of hemoglobin level at baseline of all the enrolled women in two study groups is shown in Table No:02.

End treatment data (at 6 months)

Total number of sanitary pads used/cycle

Out of 55 women in group A, 33 (60%) women used/cycle 20 or less sanitary pads per menstrual period, 7 (13%) women used/cycle between 21 and 25 sanitary pads per menstrual period, while remaining 15 (27%) women used/ cycle more than 25 sanitary pads per menstrual period. On the other hand, out of 55 women in group B, 17 (31%) women used/cycle 20 or less sanitary pads per menstrual period, 16 (29%) women used/cycle between 21 and 25 sanitary pads per menstrual period, while remaining 22 (40%) women used/ cycle more than 25 sanitary pads per menstrual period. The distribution of sanitary pads used/ cycle at end of treatment of all the enrolled women in two study groups is shown in Table No:03.

Total blood lost

Out of 55 women in group A, 43 (78%) women reported up to 100 ml blood lost per menstrual period, 11 (20%) women reported between 110 ml and 150 ml blood lost per menstrual period, while remaining 1 (2%) woman reported more than 150 ml blood lost per menstrual period. On the other hand, out of 55 women in group B, 17 (31%) women reported up to 100 ml blood lost per menstrual period, 33 (60%) women reported be-

tween 110 ml and 150 ml blood lost per menstrual period, while remaining 5 (9%) women reported more than 150 ml blood lost per menstrual period. The distribution of blood lost at end of treatment of all the enrolled women in two study groups is shown in Table No:03.

Hemoglobin level

Out of 55 women in group A, 2 (4%) women had hemoglobin level less than 9 g/dl, 37 (67%) women had hemoglobin level between 9 and 11 g/dl, while remaining 16 (29%) women had more than 11 g/dl. On the other hand, out of 55 women in group B, 4 (7%) women had hemoglobin level less than 9 g/dl, 47 (85%) women had hemoglobin level between 9 and 11 g/dl, while remaining 4 (8%) women had more than 11 g/dl. The distribution of hemoglobin level at end of treatment of all the enrolled women in two study groups is shown in Table No:03.

Comparison between two study groups

Comparison between two study groups regarding the mean differences in total number of sanitary pads used/ cycle, total blood loss and hemoglobin level at baseline and at end of treatment is given below. Mean difference in total number of sanitary pads used/cycle at baseline and end of treatment The mean (SD) difference from baseline to end of treatment in the total number of sanitary pads used/ cycle in women enrolled in group A was 8.85 (±6.0) pads while the mean (SD) difference in the total number of sanitary pads used/ cycle in women enrolled in group B was 1.84 (±5.2) pads. These differences were statistically significant ($p<0.0001$).

Mean difference in total blood loss at baseline and end of treatment The mean (SD) difference from baseline to end of treatment in the total blood lost in women enrolled in group A was 44.3 (±29.9) ml while the mean (SD) difference in the total blood lost in women enrolled in group B was 9.18 (±26.4) ml. These differences were statistically significant ($p<0.0001$).

Mean difference in hemoglobin level at baseline and end of treatmentThe mean (SD) difference from baseline to end of treatment in the hemoglobin level in women enrolled in group A was 0.68 (±0.71) g/dl, while the mean (SD) difference in the hemoglobin level in women enrolled in group B was 0.40 (±0.52) g/dl. These differences were statistically significant ($p=0.018$).

Comparison of subjective feeling between two study groups

Out of 55 women in group A, 38 (69%) showed satisfaction with treatment, while remaining 17 (31%) showed no satisfaction with treatment. On the other hand, out of 55 women in group B, 24 (44%) showed satisfaction with treatment, while remaining 31 (56%) showed no satis-

TABLE 1: AGE DISTRIBUTION OF ALL ENROLLED WOMEN (n=110)

Age (in years)	Group A	Group B
Mean	41.1	41.0
Standard deviation	±3.3	±3.5
Median	42.0	42.0
Range (min - max)	(34 – 47)	(30 – 45)

TABLE 2: BASELINE DATA

Number of sanitary pads used/ cycle	Group A	Group B
Mean	27.8	25.9
Standard deviation	±6.5	±5.3
Median	28.0	26.0
Range (min - max)	(16 – 40)	(19 – 40)
Blood lost (ml)		
Mean	139.2	129.5
Standard deviation	±32.5	±26.6
Median	140.0	130.0
Range (min - max)	(80 – 200)	(90 – 200)
Hb (mg/dl)		
Mean	10.1	9.5
Standard deviation	±1.1	±0.74
Median	10.1	9.8
Range (min - max)	(7.8 – 13.0)	(7.8 – 11.1)

TABLE 3: END TREATMENT DATA

Number of sanitary pads used/ cycle	Group A	Group B
Mean	19.0	24.1
Standard deviation	±5.0	±5.5
Median	18.0	24.0
Range (min - max)	(10 – 33)	(15 – 40)
Blood lost (ml)		
Mean	94.9	120.3
Standard deviation	±24.8	±27.6
Median	90.0	120.0
Range (min - max)	(50 – 165)	(75 – 200)
Hb (mg/dl)		
Mean	10.8	9.9
Standard deviation	±1.0	±0.71
Median	10.6	10.1
Range (min - max)	(8.7 – 13.6)	(8.1 – 12.6)

faction with treatment. This difference was statistically significant (p=0.007).

DISCUSSION

Heavy menstrual bleeding, defined objectively as blood loss 80 mL or more per menstrual cycle, is an important cause of iron-deficiency anemia and adversely affects health-related quality of life[10]. Although hysterectomy or endometrial ablation provides effective surgical options for heavy menstrual bleeding, both approaches are associated with perioperative and long-term surgical risks[11,13]. Algorithms for heavy menstrual bleeding emphasize the use of medical treatment before resorting to surgical options[10]. There are a number of treatments available for HMB such as Norethisterone, levonorgestrel releasing Intra Uterine Device, endometrial ablation and hysterectomy, but since none of them is proved to be superior to the others, and as all treatments have their advantages and disadvantages, counselling of patient with HMB is recommended to enable her to choose the treatment options best suiting her condition[14]. A lot of studies have shown Levonorgestrel releasing Intra Uterine Device to be effective for treating HMB and thus resulting in improved patient satisfaction[15].

The aim of the current study was to compare levonorgestrel intrauterine system and norethisterone in idiopathic heavy menstrual bleeding. During the study period of 8 months, a total of 110 women with idiopathic heavy menstrual bleeding (55 in each study arm) presented at the Department of Gynaecology and Obstetrics, Fauji Foundation Hospital, Rawalpindi were enrolled. The mean (SD) age of women enrolled in levonorgestrel intrauterine system group was 41.1 (± 3.3) years and it was 41.0 (± 3.5) years in norethisterone group. In levonorgestrel intrauterine system group, 21 (38%) women were less than 40 years of age, while in norethisterone group 16 (30%) women were less than 40 years of age. In levonorgestrel intrauterine system group 54 (98%) women were multigravida whereas in norethisterone group all 55 (100%) women were multigravida. The comparison of mean difference in various parameters from baseline to end of treatment between two study groups showed that women in levonorgestrel intrauterine system group had significantly less mean number of sanitary pads used/ cycle (p<0.0001), significantly lower mean blood loss (p<0.0001) and significantly mean higher hemoglobin level (p=0.018) compared to women in norethisterone group. Similarly, a significantly higher number of women in levonorgestrel intrauterine system group showed satisfaction with treatment than women in norethisterone group (p=0.007) at the end of treatment (after 6 months). Our results are comparable with other studies around the world.

Naqaish and colleagues from Pakistan carried out a study to compare patient satisfaction for Levonorgestrel intra uterine system (LNG-IUS) and Norethisterone for the treatment of HMB. This descriptive case series study was conducted at the Department Obstetrics and Gynaecology, Shifa International Hospital, Islamabad between September, 2011 and September, 2012. The investigators enrolled 119 women with HMB through consecutive sampling technique. Treatment outcome was in terms of patient satisfaction scale, and decrease in bleeding after6 months. The mean (SD) age of the patients was 41.03 (±4.415) year ranging from 28–60 years. The mean (SD) parity of women in the study was 3.22 (±1.188) with a range of 1–7. The investigators found that the satisfaction level was significantly (p<0.05) greater (90% versus 20%) in Group A (levonorgesterol-releasing intrauterine system) as compared with Group B (Norethisterone). Similarly, the blood loss was significantly (p<0.05)decreased in Group A (98%) as compared with Group B (80%). The preference of continuing the method as well as recommendation to a friend was significantly greater in Group A as compared to Group B. Hence, the authors concluded that the levonorgesterol-releasing intrauterine system (LNG-IUS) is a better choices compared to Norethisterone, for treatment of HMB with 90% patients highly satisfied[8].

Kaunitz et al from USA carried out a study to compare the effects of the levonorgestrel-releasing intrauterine system (LNG-IUS)with cyclic oral medroxyprogesterone acetate (MPA)on hemoglobin and serum ferritin levels in women with heavy menstrual bleeding (HMB). This was a multicenter, randomized study assessing the efficacy of the LNG-IUS and oral MPA(10mg/dayfor10days) in women with confirmed HMB over 6 cycles of treatment. A total of 165 women were randomized (82 LNG-IUS/83 MPA) in the study. The investigators found increases in median hemoglobin levels from baseline to Cycle 6 (7.5%vs.1.9%;p=0.001) andmedianserumferritinlevels(68.8%vs.14.3%;p=0.001)were greater in the LNG-IUS group than in the oral MPA group. Hence, the authors concluded that women treated with the LNG-IUS had greater increases in median hemoglobin and serum ferritin levels,and higher rates of subjective improvement than women treated with oral MPA[9].

Yet another study by Kaunitz and coworkers from USA conducted a study to compare the efficacy and safety of the levonorgestrel-releasing intrauterine system and oral medroxyprogesterone acetate in the treatment of idiopathic heavy menstrual bleeding.In this multicenter, randomized, controlled study, women aged 18 years or older with heavy menstrual bleeding(menstrualblood loss 80 mL or more per cycle) were randomly assigned to six cycles of treatment with either levonorgestrel-releasing intrauterine system or oral medroxyprogesterone acetate (10 mg daily for 10 days beginning on day 16 of each cycle). The primary efficacy variables were the absolute change in menstrual blood loss from baseline to end of study and the proportion of women with successful treatment (defined as menstrual blood loss less than 80 mL and a 50% or greater reduction in menstrual blood loss from baseline). The investigators found that of 807 women screened, 165 were randomly assigned to treatment (levonorgestrel-releasing intrauterine system n=82, oral medroxyprogesterone acetate n=83). At the end of the study,

the absolute reduction in median menstrual blood loss was significantly greater in the levonorgestrel-releasing intrauterine system group (-128.8 mL, range -393.6 to +1242.2 mL) than in the medroxyprogesterone acetate arm (-17.8 mL, range -271.5 to +78.6 mL, P <0.001), and the proportion of women with successful treatment was significantly higher for the levonorgestrel-releasing intrauterine system (84.8%) than for medroxyprogesterone acetate (22.2%, P <0.001). Therefore, the authors concluded that in women with idiopathicheavy menstrual bleeding, the levonorgestrel-releasing intrauterine system reduces menstrual blood loss more effectively and has a higher likelihood of treatment success than oral medroxyprogesterone acetate[3].

A study by Shaaban and coworkers from Egypt was conducted to compare the efficacy of a levonorgestrelreleasing intrauterine system (LNG-IUS) and a low-dose combined oral contraceptive (COC) in reducing adenomyosis-related pain and bleeding. A randomized clinical trial included 62 participants complaining of pain and bleeding that was associated with adenomyosis. Participants were randomly assigned to either LNG-IUS or COC treatment. The outcomes included the improvement of pain using a visual analogue scale, menstrual blood loss using a menstrual diary and estimated uterine volume by ultrasound for 6 months oftreatment. The authors also compared uterine arteries and intra myometrial Doppler indices before and 6 months after treatment with both LNG-IUSand COCs. The investigators found that both treatments significantly reduced pain after 6 months of use; however, the reduction was greater in the LNG-IUS group (from6.23±0.67 to 1.68±1.25) compared with the COCs group (from 6.55±0.68 to 3.90±0.54). Both treatment arms significantly decreased the number of bleeding days, uterine volume and Doppler blood flow in the uterus from before to after treatment. These effects were more significant in the LNG-IUS arm compared with the COC arm. The authors concluded that both LNG-IUS and COCs decreased the pain and menstrual bleeding that is associated with adenomyosis. However, LNG-IUS is more effective than the COCs in reducing pain and menstrual blood loss. This effect may be secondary to the decrease in uterine volume and the increase in blood flow resistance[16].

Jensen et al conducted pooled analysis of randomized controlled trials to characterize the changes in bleeding pattern over time in women receiving the levonorgestrel releasing intrauterine system (LNG-IUS) for heavy menstrual bleeding (HMB). The investigators conducted post hoc pooled analysis of the impact of the LNG-IUS on bleeding patterns in four comparator studies of medical and surgical treatment options for HMB. The investigators enrolled women aged ≥ 18 years with HMB without organic pathology. The change in the number of bleeding and spotting (B/S) days and bleeding patterns was assessed over the duration of the studies pooled. A total of 163 women received the LNG-IUS in randomized trials. Relative to pretreatment baseline, there was a transient increase in the mean number of bleeding days in the first month of treatment, which returned to baseline by the second month and declined thereafter. Although the number of spotting days also increased during the first month of treatment, these declined with continued use but remained elevated relative to baseline during the first year of treatment. Hence, the authors concluded that in women with HMB, the LNG-IUS is associated with an initial increase in number of B/S days that improve over time[17].

Since HMB is a subjective finding, its treatment regimens should address specific aspects of the menstrual cycle that seem to be abnormal, such as cycle length or quantity of bleeding[18]. The guidelines from the National Institute for Health and the Clinical Excellence[10] recommend the use of LNG-IUS in women with benign HMB. If bleeding was not controlled with medical management, endometrial destruction was recommended to resolve symptoms. The surgical options include conservative surgery and hysterectomy. However, LNG-IUS has been shown to provide a non-surgical alternative, which is reversible and spares fertility[19].

Evaluation of the efficacy of therapies for HMB has evolved from a focus merely on quantity of bleeding to one focused on patient-based outcomes as well especially, measures of quality of life (QOL). Clinical guidelines(20) recommend the use of patient-based outcome measures because these measures capture the effect of heavy bleeding on women's psychological and physical well-being. Comparative studies have established the superiority of the levonorgestrel-IUS over other treatments in reducing blood loss in women with HMB[9].

Rationalized meta-analyses, including the results of nine randomized trials (involving a total of 783 women) of LNG-IUS as compared with non-hormonal and hormonal treatments, showed that the LNG-IUS resulted in a greater reduction in menstrual-blood loss at 3-12 months of follow-up[21]. Nevertheless, it was unclear whether these short-term benefits endure, particularly since the discontinuation rate of LNG-IUS are as high as 28% at 2 years[22], and the effects of this therapy on bleeding-related QOL were unknown. Recently, results of the effectiveness and cost-effectiveness of levonorgestrel-containing intrauterine system in primary care against standard treatment for menorrhagia (ECLIPSE) trial[2] were published in The New England Journal of Medicine (NEJM). ECLIPSE was a pragmatic, multicenter, randomized trial that compared the clinical effectiveness of the LNG-IUS with that of usual medical treatment (tranexamic acid, mefenamic acid, combined estrogen–progestogen, or progesterone alone) in the primary care setting. The trial has added strong evidence that LNG-IUS improves QOL more than the usual medical treatments do for this condition[18].

Furthermore, the Systematic Review Group of the Society of Gynecologic Surgeons recently conducted a systematic review with the goal of producing an evidence-based guideline on nonsurgical treatment decision-making for abnormal uterine bleeding presumed secondary to ovulatory dysfunction and to endo-

metrial dysfunction. It was published in the Green Journal (Obstetrics and Gynecology)[23] reaching a conclusion that for the reduction in mean blood loss in women with HMB presumed secondary to abnormal uterine bleeding presumed secondary to endometrial dysfunction, use of the LNG-IUS is recommended over OCPs, luteal-phase progestin's, and NSAIDs[18].

Hence, several studies as mentioned above, similar to our study findings revealed that levonorgesterol-releasing intrauterine system has higher efficacy compared to other medical treatment such as norethisterone for the management of HMB.

CONCLUSION

In conclusion, our study shows that women who were given levonorgestrel releasing intrauterine system showed a significantly lower use of sanitary pads, significant low volume of blood loss, significant improvement in hemoglobin levels and a significantly higher percentage of them showed satisfaction with the treatment after 6 months of treatment compared to women who were given norethisterone treatment for the management of HMB in our clinical setting. However, there is a need to conduct more studies using large sample size with multiple study sites in Pakistan to validate these results.

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