ORIGINAL ARTICLE

Clinical efficacy of levonorgestrel and norethisterone for the treatment of chronic abnormal uterine bleeding

Muhammad Nadeem Ashraf,[1] Agha Habib-ur-Rehman,[2] Zahid Shehzad,[3] Shakir DakheelAllah AlSharari,[4] Ghulam Murtaza[5]

Abstract

Objective: To compare the clinical efficacy of levonorgestrel intrauterine system with oral norethisterone for the treatment of idiopathic chronic abnormal uterine bleeding.

Methods: This cross-sectional study was conducted at Bahawal Victoria Hospital, Jubilee Female Hospital, Civil Hospital and private clinics of consultant gynaecologists in Bahawalpur, Pakistan, from March to August 2014, and comprised patients presenting with abnormal uterine bleeding. The patients were equally and randomly divided into two groups, i.e. intrauterine levonorgestrel administered (group A) and norethisterone administered (group B). Mean age, duration of the disease and parity were determined using a predesigned questionnaire. The primary outcomes of the treatments, i.e. reduction in menstrual blood loss assessed by the pictorial blood assessment chart score, were recorded before the initiation of therapy, at 3 months and at 6months of the study. SPSS 16 was used for data analysis.

Results: There were 76 subjects; 38(50%) in each group. In group A, the mean age and mean duration of the disease was 34.16±6.327 years and 6.18±2.415 years compared to 34.21±3.595 years and 6.21±2.418 years in group B. The reduction in menstrual blood loss did not differ significantly between the groups after 3 months (p= 0.321). However, levonorgestrel intrauterine system was found more effective in reducing menstrual blood loss in 36(94.73%) patients, compared to norethisterone-treated patients 28(73.68%) after 6 months of the treatment (p=0.041). The response of both the treatments was found independent of patient's age, parity and chronicity of the disease.

Conclusion: The levonorgestrel intrauterine system was better than norethisterone with marked clinical benefit of profound reduction in menstrual blood loss.

Keywords: Uterine bleeding, Abnormal, Chronic, Levonorgestrelintrauterine system, Norethisterone, Pictorial blood assessment chart. (JPMA 67: 1331; 2017)

Introduction

Abnormal uterine bleeding (AUB) is a systemic disorder characterised by abnormal uterine bleeding in the absence of pregnancy and without evident genital tract pathology.[1] About 30% of women worldwide suffer from heavy menstrual bleeding (HMB) at some point during their reproductive age.[2-4] HMB can be characterised as a drop in haemoglobin and number of pads or tampons used per day.[5] Thus, AUB significantly affects the patient's quality of life, productivity and sexual life, and overall healthcare cost.[6-8] Menorrhagia or chronic AUB, as defined recently by the PALM-COEIN nomenclature system which stands for polyp; adenomyosis; leiomyoma; malignancy and hyperplasia; coagulopathy; ovulatory dysfunction; endometrial; iatrogenic; and not yet classified, and which is characterised by abnormal bleeding for at least 4 out of 6 months, expressed as increased regularity, volume, and/or timing.[2] Menorrhagia is the most conjoint indicator of AUB, eventually distressing 50-60% women with this ailment.[1] Thus, it has been perceived in clinical practices that the volume of blood loss is greater than 80ml / cycle in 40% of these patients.[9] Diverse contrivances anticipated in the pathogenesis of AUB comprise changes in endometrial prostaglandins and endometrial fibrinolytic action.[10]

Pictorial blood assessment chart (PBAC) is commonly used for the assessment of menstrual blood loss (MBL).[11] Alkaline haematin is an alternate method for the measurement of blood loss.[12] Medical treatments for AUB include antiprostaglandins, antifibrinolytics, and hormonal therapies, that is, combined oral contraceptive pills and progestogen, danazol and gonadotropin

[1,2]Faculty of Pharmacy and Alternative Medicine, [2,3]Sir Sadiq Muhammad Khan Abbasi Postgraduate Medical College, The Islamia University of Bahawalpur, Bahawalpur, [3]Bahawal Victoria Hospital, Bahawalpur, Pakistan, [4]Department of Pharmacology, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia, and Department of Pharmacology and Toxicology, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA, USA, [5]Department of Pharmacy, COMSATS Institute of Information Technology, Abbottabad, Pakistan.

Correspondence: Muhammad Nadeem Ashraf.

Email: nadeem.ashraf@iub.edu.pk

releasing hormone analogues.[13,14] On the other hand, the surgical treatments include hysterectomy and endometrial ablation, but these are suitable only for those who have no wish to conceive in future.[15] Current management practices of chronic AUB in the Bahawalpur region include surgical intervention, that is, hysterectomy, and conservative medical treatments including nonsteroidal anti-inflammatory drugs(NSAIDs), progesterone, norethisterone, dyhydrogesterone combined oral contraceptive pills.[16] Pakistan is a developing country and in our clinical set-ups a majority of the patients belong to low socio-economic background. Socio-economic factor plays a major role in the selection of a particular type of treatment of AUB.[16,17] Oral norethisterone is cost-effective, and has an effective role in the reduction of blood loss associated with AUB, however, the incidence of adverse effects appears to be higher than levonorgestrel in recommended doses.[18-22] Moreover, its frequent dosing (3 times/day) and for a prolonged period of time may cause serious compliance issues and, therefore, higher treatment costs.[16] Local progestogens, delivered by levonorgestrel intrauterine system (Mirena®) have been proven an effective treatment of AUB in recent years.[18,19,23-27] In addition, the local administration (intrauterine) of levonorgestrel produces minor systemic hormonal effects and is, therefore, better tolerated than orally administered levonorgestrel.[26-28] The intrauterine levonorgestrel (LNG-IUS) is effective for up to five years after insertion, allowing for reversible, long-term and cost-effective treatment without compliance issues.[19,25-27,29]

The current study was planned to find more effective and safer treatment of AUB. It was also determined whether the treatment outcomes had any association with patient's age, parity and chronicity of the disease.

Patients and Methods

This cross-sectional, prospective, randomised, multicentre clinical study was conducted at the gynaecology units of Bahawal Victoria Hospital (BVH), Jubilee Female Hospital, Civil Hospital and private clinics of consultant gynaecologists in Bahawalpur, Pakistan, from March to August 2014. Approval for the study was obtained from the ethics committee of Post Graduate Medical College (PGMC) as well as the Board of Advanced Studies and Research (BASR), the Islamia University of Bahawalpur. This study was conducted in accordance with good clinical practices (GCP)[30] and Helsinki's guidelines for human use in laboratory work.[31]

Patients fulfilling the inclusion criteria and willing to participate in the study were included. Those who were grand multi para and aged 40-45 years required hysterectomy because of heavy bleeding (Figure-1). The remaining patients were randomly allocated by lottery method into two equal groups; A and B. The purpose, procedure, and risks/benefits of the study were explained to the patients, and written informed consent was taken.

Literacy status of the patients ranged from illiterate to higher postgraduate status. The illiterate patients were educated to calculate their scores according to the size of 1 rupee coin blood stained pad (score 1) or size of 5 rupee coin (score 5)as shown in the PBAC scoring chart.[11]

Those included were patients with dysfunctional uterine bleeding measuring PBAC score >100 for 2 consecutive cycles; uterus size less than 10 cm on ultrasonography; negative cervical cytology on Pap smear; and patients aged 18-45 years.

Those excluded were patients who had contraindications for levonorgestrel intrauterine system and norethisterone use; pregnancy; post-menopausal bleeding; uterine neoplastic disease; patients with concomitant use of medications that could influence the study objectives including sex steroids, any treatment for menorrhagia (including tranexamic acid and NSAIDs); patients who had intramural or subserous fibroids of mean diameter $\geq$ 4cm or submucous fibroids, adenomyosis, or endometrial abnormalities; and those with coagulation disorders, liver disease or pelvic inflammatory disease.

Individual study period was 6 months. Each selected patient of either group was advised to visit hospital/clinic at the end of each month, and was evaluated for the control of AUB as the result of the treatment given. Monthly PBAC scoring was also reviewed. However, 3-month and 6-month post-treatment PBAC scoring was taken into account for comparison.

The LNG-IUS (Mirena®) insertion was performed by senior gynaecologists in group A patients, while in group B, norethisterone containing tablet was given orally at a dose of 5mg three times daily for 5-26 days of cycle over consecutive cycles. Prophylactically, injectable single dose of antibiotic was given to the patients included in group A. LNG-IUS was inserted by using aseptic measures during the last four days of menstrual bleeding.

Patients were put in lithotomy position, and pelvic examination was done after emptying the bladder. The size of the uterus was confirmed with uterine sound. Then, the posterior vaginal wall was retracted with Sim's speculum, anterior cervical lip was held with Vulsellum, and Mirena® was inserted into uterine cavity. Length of

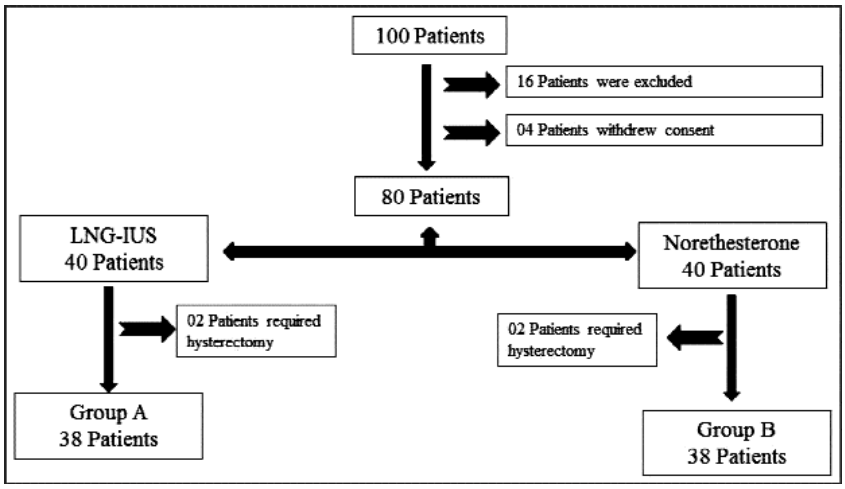
the thread was shortened subsequently. Post-insertion oral analgesic and antibiotic were administered to these patients. MBL was measured by PBAC; the charts were given to all the patients and they were explained how to use it.

Each patient was followed for the assessment of PBAC score after 3 and 6 months after the initiation of either treatment. The data was recorded on a specially designed proforma which contained two parts. Part 1 included the patient's bio-data while part 2 contained the study variables, i.e. parity, duration of the disease, PBAC score, etc.

Data was analysed using SPSS16. Data was presented as mean ± standard error of the mean (SEM). Baseline characteristics like age, parity, chronicity of the disease were determined through mean and percentage, and significance level for these factors were determined via Student's t-test. Chi-square test was applied to compare the efficacy of both groups. Average PBAC scores were analysed by t-test for groups comparison, and analysis of variance (ANOVA) with posthoc Tukey's test for multiple comparisons. Differences were considered to be significant at $P<0.05$.

Results

Of the 80 patients selected initially, 4(5%) required



AUB: Abnormal uterine bleeding.
LNG-IUS: Levonorgestrelintrauterine system.

Figure-1: Flowchart diagram of the study population of patients with AUB treated either with the LNG-IUS (n=38) or with norethisterone (n=38).

Table-1: Baseline characteristics of the patients with AUB treated with the LNG-IUS (n=38) or Norethisterone (n=38).

Sr #	Characteristics			LNG-IUS	Norethisterone	P
1	Mean Age (years)			34.16 ± 6.327	34.21 ± 3.595	0.09
2	Parity (n)			2.43±0.24	2.47±0.21	0.95
3	Mean Duration of Disease (years)			6.18 ± 2.415	6.21 ± 2.418	0.63
4	Mean Baseline PBAC (ml)			316.76±04.755	341.18±04.283	0.82
5	Parity (n)		Multi Para	11	14	---
			Grand Multipara	27	24	
6	Number of patient recovered (n)		Yes	36	28	0.03
			No	2	10	
7 (a)	Age Stratification		Yes	31	26	0.99
	(30-40 years)		No	02	10	
7 (b)	Age Stratification		Yes	05	02	0.99
	(41-48 years)		No	00	00	
8	Stratification for Parity (n)	Multi Para	Yes	10	08	0.50
			No	01	06	
		Grand Para	Yes	26	20	0.12
			No	01	04	
9	Stratification for chronicity of the disease (years) (n)	3-6	Yes	21	13	0.99
			No	01	05	
		7-10	Yes	15	15	0.13
			No	01	02	

LNG-IUS: Levonorgestrelintrauterine system
AUB: Abnormal uterine bleeding
PBAC: Pictorial blood assessment chart.

Table-2: Pictorial Blood Assessment Chart and Scoring System for Assessment of Menstrual Blood Loss.

How to use the PBAC scoring system:

- During the course of your period record use of tampons and sanitary towels.
- Record clots by indicating whether they are the size of a 1p or 50p coin.
- Record any incidences of flooding.

Scores:

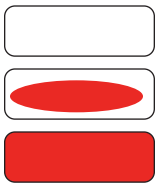
- A lightly stained towel (pic 1) will score 1 point, a moderately stained towel (pic 2) 5 points, a towel which is saturated with blood (pic 3) will score 20 points.
- A lightly stained tampon (pic 4) will score 1 point, a moderately stained tampon (pic 5) 5 points and a tampon that is fully saturated (pic 6) will score 10 points
- A clot the size of 1p scores 1 point, a 50p sized clot scores 5 points and flooding also scores 5 points

Results

Once period have finished, total up scores. A score of 100 or greater may indicate heavy periods.

NAME: SCORE: DAY START:

	Day							
TOWEL	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**



CLOTS/ FLOODING

TAMPON	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**

CLOTS/ FLOODING

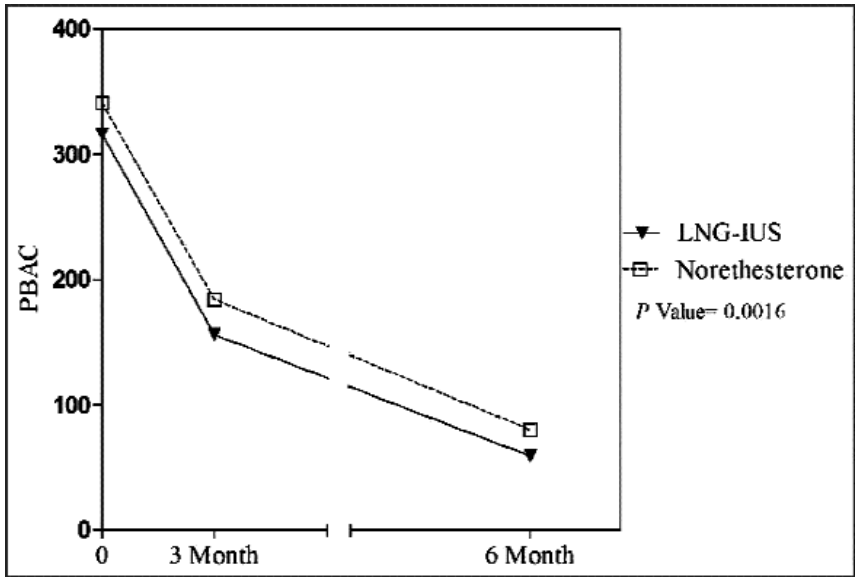
1PENNY=1 RUPEE=17.2mm,5 penny=5 Rupee coin=19.2 mm(11)
PBAC: Pictorial blood assessment chart.

Table-3: Mean PBAC Score assessment between the studied groups.

Treatments Given	Baseline mean PBAC score	P value	After 3 months	P value	After 6 months	P value
LNG-IUS	316.76	P=0.38	155	P=0.32	59.45	P = 0.04
Norethisterone	341.18		184		80.87	

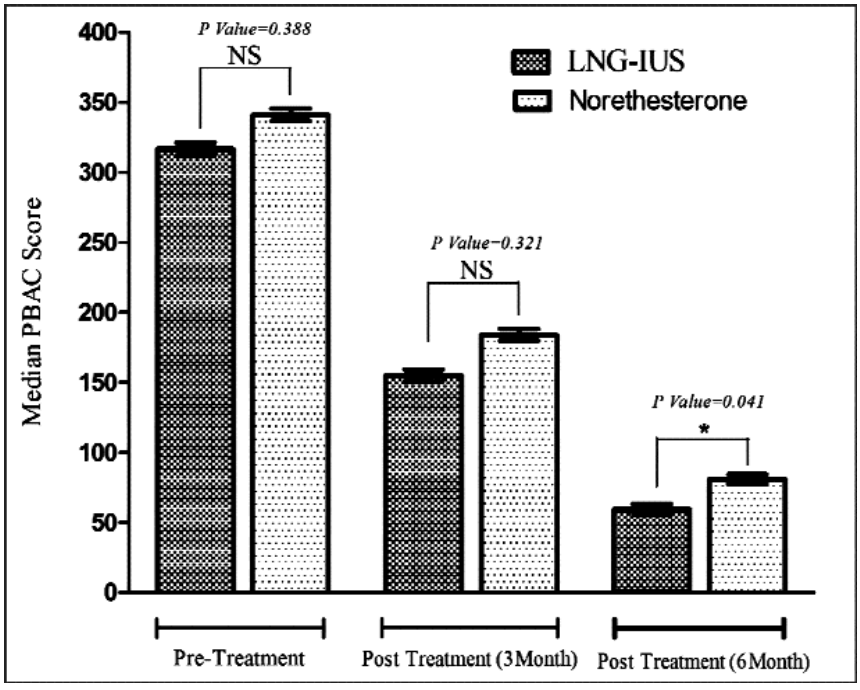
The data shown are Means±SEM.
LNG-IUS: Levonorgestrelintrauterine system
PBAC: Pictorial blood assessment chart
SEM: Standard error of mean.

hysterectomy because of heavy bleeding, therefore, the number of participants was 76(95%). They were divided into two groups having 38(50%) members each. The mean age and mean duration of the disease for group A was 34.16±6.327 years and 6.18±2.415 years, respectively, compared to 34.21±3.595 years and 6.21±2.418 years, respectively, in group B. Hence, both of these baseline factors were comparable between the groups. In group A, 11(28.95%) patients were multipara and 27(71.05%) were grand multipara. In group B, 14(36.84%) patients were multipara and 24(63.16%) were grand multipara. Both the groups were further



LNG-IUS significantly lowered the PBAC score during the course of the treatment period as compared to norethisterone (*P< 0.05).
LNG-IUS: Levonorgestrelintrauterine system. MBL: Menstrual blood loss.
PBAC: Pictorial blood assessment chart.

Figure-2: Median change in MBL over 6 months of the treatment period with the LNG-IUS and norethisterone.



The data has shown as mean ± SEM values of both treatment groups at pretreatment, Post Treatment (3 Months) and Post Treatment (6 Months) intervals.
LNG-IUS: Levonorgestrelintrauterine system. SEM: Standard error of mean.
PBAC: Pictorial blood assessment chart. NS: Not significant.

Figure-3: Graphical representation of the assessment of mean PBAC scores of LNG-IUS and norethisterone at different treatment intervals.

stratified for age, parity and duration of the disease (chronicity) in order to evaluate any association of these parameters with the outcomes of the treatments (Table-1).

The response of the treatments was measured as PBAC score (Table-2). Group A exhibited median PBAC score of 155±3.256 and 59.45±2.92 after 3 and6 months of the treatment, respectively. Group B showed median PBAC score of 184±2.29 and 80.87±2.21 after 3 and 6 months of the treatment, respectively. The median PBAC score did not differ significantly at 3 months post-treatment between the groups ($p>0.05$, $F=1.45$). However, group A showed significantly higher response (reduction in MBL) as compared to group B after 6 months of the treatment ($p<0.05$, $F=4.30$) (Table-3) (Figures-2, 3).

These findings also correspond to the number of patients recovered in both groups, i.e. LNG-IUS reduced MBL in 36(94.73%) patients while norethisterone reduced MBL in 28(73%) patients after 6 months of the treatment ($p<0.05$) (Figure-4).

Further, there was no association found in patient's age and reduction in MBL after 6 months of the treatment in either group ($p>0.05$). Similarly, stratification for parity in group A showed 10(90.91%) and 26(96.3%) reduction in MBL, and in group B showed 8(57.14%) and 20(83.33%) ($p>0.05$) reduction in MBL in multiparas and grand multiparas, respectively. No association was found between parity and reduction in MBL after the treatments in both groups ($p>0.05$).

Moreover, stratification for the duration of the disease (chronicity) was done for the groups, and two subgroups were made, i.e. patients having chronicity of 3-6 years and 7-10 years. Group A exhibited reduction in MBL in 21(95.45%) and 15(93.75%) patients of 3-6 years and 7-10 years chronicity, respectively ($p >0.05$).

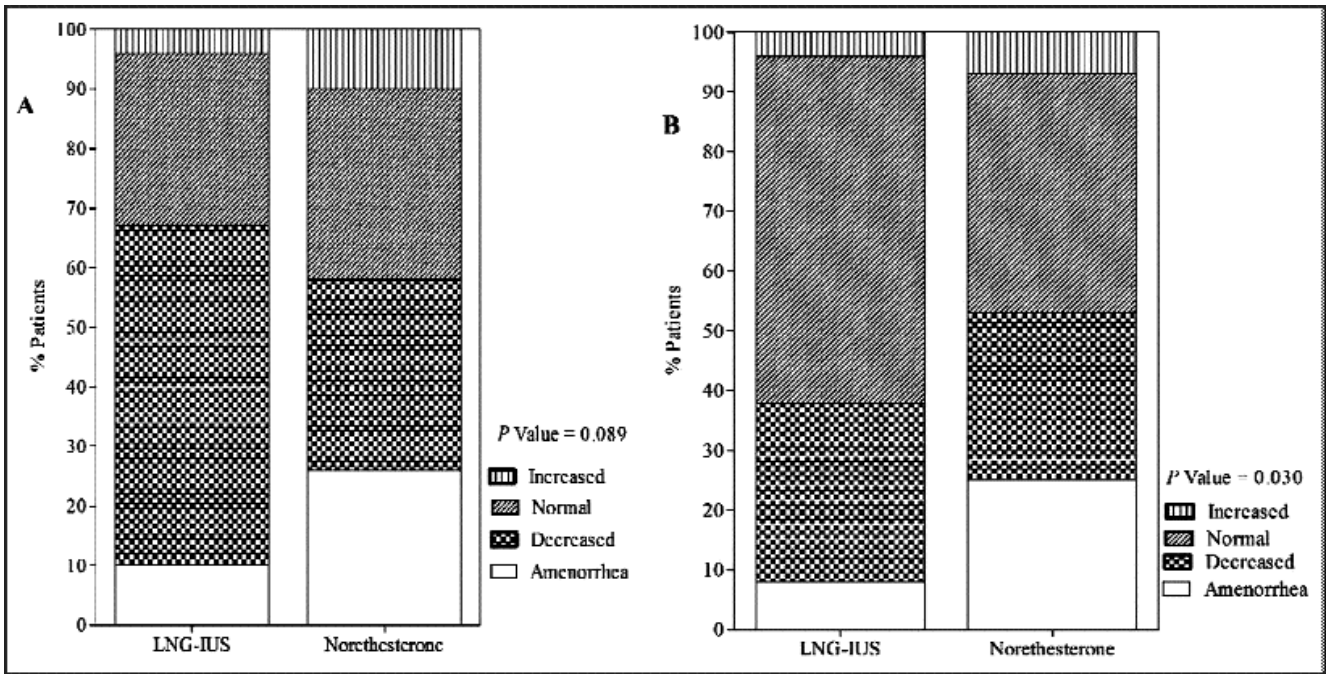


Figure-4: Evaluation of menstrual bleeding patterns in the third month (A) and sixth month (B) in patients with abnormal uterine bleeding treated with the LNG-IUS (n=38) or norethisterone (n=38). Comparison between the two groups was performed using the chi-square test. The treatment response (measured as number of patients cured) of LNG-IUS was significantly higher in group A patients than in norethisterone administered group B patients at the end of 6 months post-treatment (*P< 0.05).

Discussion

Menstrual disorders are among the major gynaecological problems. A large portion of the women population lives in rural areas in Asian countries like India and Pakistan. They usually have limited health care facilities available close to their residential proximities and have to move to big cities to get a proper treatment.[32] As for menstrual disorders like AUB are concerned, the patients not only have to undergo a number of investigational procedures, but they also have to be on the long waiting lists for months because of the burden on the hospital theatres. Substantial costs are incurred due to a long convalescence in both hospitals and at homes.[33] LNG-IUS was developed in Finland during 1980s and licensed for contraception in 1990. This intrauterine system releases 20µg of levonorgestrel every 24 hours over the period of five years. LNG-IUS has been used by more than 9 million women worldwide since its launch for the treatment of heavy menstrual bleeding, for contraception and as hormone replacement therapy component for progestogen.[34,35]

LNG-IUS and norethisterone (15mg) administered daily during 5th to 26th days of the menstrual cycle are considered first-line and second-line treatments, respectively. Injected long-acting progestogen acts as the third-line management technique for AUB.[36] Norethisterone prevents proliferation of the endometrium and also acts as a contraceptive at the dose of 15mg daily on 5-26th days of the cycle. The quality of life of women suffering from menorrhagia or heavy menstrual bleeding is impaired in many respects. Excessive bleeding and pain or both may impose severe constraints on their professional, social, and family activities.[37] Clinicians use both LNG-IUS and conservative medical therapy for the management of AUB in the local population of Bahawalpur and other parts of Pakistan.[16,17,38] The conservative medical treatment is the preferred mode of management mainly because of the associated low treatment cost.[16]

Here, we have demonstrated the clinical efficacy of LNG-IUS and norethisterone in terms of reduction in MBL in Bahawalpur, Pakistan. Interestingly, the PBAC score did not differ significantly between the groups after three months of the treatment. However, LNG-IUS treatment significantly reduced MBL in group A patients (94.73%) than in norethisterone treated group B (73%) at the end of the study period as measured by the PBAC score ($p< 0.05$). These findings are in accordance with many recently published studies where LNG-IUS had been proven more effective than conservative medical therapy, including norethisterone.[18,19,24,25] For instance, famous trial study 'Evaluation of COPD [chronic obstructive pulmonary disease] Longitudinally to Identify Predictive Surrogate End-

points'(ECLIPSE) depicted that LNG-IUS has greater clinical advantage over usual medical treatment in reducing heavy menstrual bleeding (HMB).[26] Similarly, LNG-IUS was shown to be cost-effective in both the short term and medium term, and also reduced the impact of HMB on women's quality of life.[25,26] Another study demonstrated superiority of LNG-IUS in reducing MBL, lower rate of discontinuation and treatment failure as compared to conventional medical treatment.[19] In another study conducted in Pakistan, Naqaish et al. reported 98% reduction in MBL by LNG-IUS in their design of experiments.[32] Furthermore, various other researchers from other parts of the world reported 80 - 82% reduction in heavy menstrual bleeding after treatment with LNG-IUS.[24,39,40]

Since, LNG-IUS needs one-time insertion in every 5 years, there are lesser risks of non-compliance involved, and more psychological satisfaction to patient that her reproductive tract is intact. Moreover, keeping in view the socio-economic background, LNG-IUS may be more cost-effective in terms of patient's time and convenience, lesser incidence of reported side effects, and will reduce burden of surgery (theatres) and post-operative care in case of surgical option of hysterectomy. Our findings combined with the previous findings favour the use of LNG-IUS over norethisterone in the prevailing scenario of our clinical set-ups.

Unlike previous studies, we also evaluated any possible association of age, parity, and chronicity of the disease to the treatments. We found no association of these factors to either of the treatment given. Hence, we may suggest that LNG-IUS may be a better choice for the treatment of chronic AUB with more pronounced clinical benefits, e.g. a better reduction in menstrual bleeding with the higher population of the patients responding to the treatment.

Conclusion

LNG-IUS may significantly reduce compliance issues associated with other treatments of idiopathic chronic AUB. However, its higher purchasing price may still limit its widespread use in the local population of Bahawalpur region, Pakistan.

Disclaimer: None.

Conflict of Interest: None.

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