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Norethisterone Versus Levonorgestrel Intrauterine System in Heavy Menstrual Bleeding: Randomised Open Labelled Clinical Trial

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KEYWORDS

Norethisterone, LNG-IUS, Heavy Menstrual Bleeding and Endometrial Ablation

ABSTRACT:

Introduction: Within the United States, any abnormal pattern of bleeding from a wide range of causes, such as anovulation, pregnancy, uterine disease, and coagulopathies, is referred to as "ABNORMAL UTERINE BLEEDING" (AUB). Any departure from the typical menstrual pattern in terms of regularity, frequency, volume, or length of flow is what is meant by this definition.

Aims: To evaluate the effectiveness of LNG-IUS versus norethisterone in treating severe menstrual bleeding in terms of: Menstrual cycle time on average and PBAC/PABC score

Materials and method: The present study Randomised open labelled clinical trial. This Study was conducted from March 2017 – February 2018 at Dept. of bstetrics and gynecology in EDEN hospital in Medical college and hospital, Kolkata. Total 66 patients were included in this study.

Result: The mean haemoglobin concentration in group N was 9.40 % which increased to 9.41% after three months of treatment. The increase in mean haemoglobin concentration was only 0.1%. The p-value thus obtained was 2.028×10-21 (<0.05) which is statistically significant. The mean haemoglobin concentration in Group L was 9.21% before treatment was initiated, which increased to 9.45% after three months of insertion of LNG-IUS. The increase in mean haemoglobin concentration was 2.53%.

Conclusion: In addition to its clinical costs, heavy menstrual bleeding has significant social and economic repercussions. LNG-IUS and tablet norethisterone are secure and efficient ways to manage HMB. We find that while both LNG-IUS and Norethisterone are useful in treating excessive menstrual bleeding, LNG-IUS is more successful in reducing the incidence of hysterectomy and improving dysmenorrhea, as well as improving endometrial thickness, average menstrual cycle duration, and PABC score.

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Introduction

Heavy menstrual bleeding is a common disabling illness with large direct and indirect expenses, making it a significant clinical issue.Within the United States, any abnormal pattern of bleeding from a wide range of causes, such as anovulation, pregnancy, uterine disease, and coagulopathies, is referred to as "ABNORMAL UTERINE BLEEDING" (AUB). Any departure from the typical menstrual pattern in terms of regularity, frequency, volume, or length of flow is what is meant by this definition. This includes menorrhagia during adolescence, post-coital bleeding, and bleeding in the perimenopausal age group.

"MENORRHAGIA" is the medical name for cyclical bleeding that affects a woman's physical, mental, and social aspects of life and occurs at regular intervals but is excessive in amount and/or duration. It is defined as extra-long or heavy menstruation that lasts more than seven days or results in more than 80 milliliters of blood loss [1]. The term "HEAVY MENSTRUAL BLEEDING" (HMB) has lately superseded this one.These phrases are frequently used synonymously. However, DUB is the reason for severe menstrual bleeding in 50% of instances. According to reports, between menarche and menopause, 9–14% of women experience AUB. 10% to 30% of women in reproductive age and 50% of women going through perimenopause are affected. The conservatively projected yearly direct and indirect economic expenses of AUB were estimated to be at $1 billion and $12 billion, respectively, in a study done by Liu Z et al. in May 2007 [2]. Thus HMB is not just a clinical burden, but also a huge social and even an economic burden.

The PALM-COEIN classification of causes of abnormal uterine bleeding (AUB) and the FIGO systems' nomenclature and symptoms of AUB in the reproductive years are intended to support research, education, and the delivery of the best possible clinical treatment to impacted women. Experts in bench, translational, and clinical research from six continents have worked together to develop these platforms, with assistance from a variety of representatives from pertinent medical societies, journals, and regulatory authorities [3]. Nonetheless, there are still some contentious issues. The management of adenomyosis and leiomyoma types and subtypes, as well as the comprehension of their influence on clinical reproductive outcomes, continue to be areas of controversy. In reality, Sancı Met al. found that the traditional nomenclature for AUB was inadequate and perplexing when it came to the etiologic diseases among women of reproductive age who were not pregnant, based on their study involving 471 women conducted in June 2016. The PALM-COEIN approach for AUB classification was widely used, which improved communication with patients by defining the populations that should be assessed in clinical trials and enabling more relevant exchanges between doctors and investigators[4]

Untreated heavy menstrual flow can negatively affect a woman's everyday activities and lead to catastrophic repercussions. If left untreated, heavy monthly bleeding can sometimes be fatal and worsen or induce anemia. In a country like India, dietary deficiencies and parasite infections can exacerbate the severity of anaemia, which in turn can lead to excessive menstrual bleeding. The treating physician faces numerous obstacles when it comes to managing severe menstrual bleeding. Currently, there are two main categories of available treatments for severe menstrual bleeding: surgical and medicinal. Dilatation and curettage, endometrial ablation or resection, myomectomy, and hysterectomy are the principal surgical methods.

Materials And Methods

Study Design: Randomised open labelled clinical trial.

Study Area: The Discussed Study Titled**: "Norethisterone Versus Levonorgestrelintrauterine System In Heavy Menstrual Bleeding: Randomised Open Labelled Clinical Trial"** was carried out in the department of obstetrics and gynecology in EDEN hospital in Medical college and hospital, Kolkata after approval from the hospital ethics committee.

Period Of Study: March 2017 – February 2018

Study Population: The patients with chief complaint of heavy menstrual bleeding who attended the out patient's department (OPD) of Eden hospital in medical college Kolkata were selected for this study based on the following eligibility criteria:

Inclusion criteria:

a. Women of reproductive age group.

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b. Aged between 18-45 years,
c. BMI <25
d. With normal pelvic examination.
e. Negative cervical cytology.
f. Menstrual blood loss> or = 80 ml.
g. Bleeding more than normal cycle or > or =7days
h. Passage of clots more than 1cm
i. PABC score of >100 for at least one cycle
j. Signs of anaemia

Exclusion criteria:

a. Pregnant women
b. Women < 18 years or > 45 years
c. Post menopausal bleeding PV
d. Patients who had intramural or subserous fibroids of mean diameter > 4cm or submucous fibroids, adenomyosis, or endometrial abnormalities
e. Known cases of Endometrial and cervical cancer
f. Women treated with steroid hormones or anticoagulants in last 3 months.
g. Women who used injectable hormones for contraception in the last 12 months.
h. Women with hypothyroidism or hyperprolactinemia
i. Women with pelvic inflammatory disease (PID)
j. Women with liver or vascular disease or women who are immunocompromised
k. Patients treated with other drugs like NSAIDS or Tranexamic acid
l. Women with haemoglobin <7 gm% who need additional haematinic or blood transfusion
m. Patients who had contraindications for levonorgestrel-intrauterine system and Norethisterone use

SAMPLE SIZE: By using Irvine et al (1998) comparative study that reported that LNG-IUS was effective in reducing menstrual blood loss by 94% compared to 87 by oral Norethisterone.[5]
The estimated sample size: 66

SAMPLE DESIGN: Based on lottery method, the 66 patients were randomly allocated in two groups, each consisting of 33 patients.

Result

Table 1: Distribution according to duration of symptoms and menstrual cycle, PBAC scores, endometrial thickness, and haemoglobin concentration

Parameter	Group N	Group L	p-value
Duration of symptoms (in months)	5.38 ± 0.36	4.76 ± 0.25	0.29
Duration of menstrual cycle	2.03 ± 0.21	2.24 ± 0.22	0.3
PABC score	442 ± 9.62	419.85 ± 10.5	0.4
Endometrial thickness (in mm.)	11.7 ± 0.28	11.6 ± 0.24	0.42
Haemoglobin concentration % (g/dl)	9.4 ± 0.18	9.21 ± 0.15	0.99

Table 2: Distribution of mean PABC score, endometrial thickness and mean haemoglobin concentration before and after treatment with Norethisterone (Group N) and LNG-IUS (Group L)

Parameter		Group N	Group L
PABC score	Before treatment	442.7	419.85
	After treatment (3 months)	297.76	139.67
	p-value	0.04	0.00008
Endometrial thickness (in	Before treatment	11.7	11.06

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mm.)	After treatment (3 months)	8.8	6.97
	p-value	0.001	0.0000001
Mean haemoglobin concentration (in %)	Before treatment	9.41	9.21
	After treatment (3 months)	9.41	9.45
	p-value	~ 0	~ 0

Table 3: Distribution of average duration of menstrual cycle (in days), hysterectomy rates and Dysmenorrhea rates with Norethisterone (Group N) and LNG-IUS (Group L)

Parameter		**Group N**	**Group L**
Average duration of menstrual cycle (in days)	efore treatment	.27	.94
	fter treatment (3 months)	.15	.79
hysterectomy rates	Number of women underwent hysterectomy	19	5
	Percentage of women underwent hysterectomy	57.57%	15.15%
dysmenorrhea	Before treatment	19	5
	After treatment	57.57%	15.15%
	Percentage of absence	85.71%	93.75%

The average duration of symptoms (in months) in group N was 5.38 ±0.36 and the standard deviation was 2.09. In group L it was 4.76 ± 0.25, and the standard deviation was 1.46. The p- value obtained was 0.29(>0.05), which revealed that there was no statistically significant difference between the two groups.Moreover, the average duration of menstrual cycle among group N is 8.27 ± 0.29. The standard deviation obtained is 1.64. In group L the average duration of menstrual cycle was calculated to be as8.94 ± 0.34. The standard deviation in group L was 1.94. The p-value obtained was 0.26 (>0.05). The mean PBAC score of group N was calculated to be 442.70 ± 9.62, and the standard deviation obtained was 55.26. In group L the mean PBAC score calculated was 419.85 ± 10.50, and the standard deviation thus obtained was 60.34. The p value was 0.40 (>0.05) which revealed the difference in data in both the groups was statistically not significant. Moreover, the mean endometrial thickness (in mm.) in both groups: group N, groups respectively was, 11.70 ± 0.28 and 11.06 ± 0.24. The standard deviation obtained in group N was 1.60 and in group L was 1.36.The p value obtained was 0.42(>0.05). There has been a decrease in PABC scores in both the groups. The score before treatment in Group N was 442.70 and after treatment it was 297.76. The decrease in PABC score in Group N was 32.74%.The p-value obtained is 0.040 (<0.05) therefore it is statistically significant. In Group L the score before the commencement of treatment was 419.85, and it decreased to 139.67. The decrease in PABC score in group L was 66.70%. The p-value calculated is 0.000080(<0.05). The mean endometrial thickness in Group N was 11.70 mm which reduced to 8.80mm.after three months of treatment. The reduction in endometrial thickness thus calculated was24.79%.p-value obtained was 0.001(<0.05).

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The mean haemoglobin concentration in group N was 9.40 % which increased to 9.41% after three months of treatment. The increase in mean haemoglobin concentration was only 0.1%. The p-value thus obtained was 2.028×10-21 (<0.05) which is statistically significant. The mean haemoglobin concentration in Group L was 9.21% before treatment was initiated, which increased to 9.45% after three months of insertion of LNG-IUS. The increase in mean haemoglobin concentration was 2.53%.The p-value obtained was 2.63×10-20 (<0.05), which is definitely statistically significant. that the duration of menstrual cycle decreased in both the groups. In Group N, it decreased from 8.27 days to 6.15 days. The decrease was 25.63%. In Group L the duration before treatment was 8.94 days which decreased to 5.79 day. The decrease was 35.23%. In Group N, out of the 33 women, 19 of them underwent hysterectomy at the end of three months of treatment. The hysterectomy rate in Group N was 57.57%. In Group L, among the 33 women only 5 of them underwent hysterectomy at the end of three months of insertion of LNG-IUS. The hysterectomy rate in Group L was 15.15%. there was a significant reduction of dysmenorrhoea in both the groups. But the reduction in group L was 93.75%which is more than the reduction in group N which was 85.71%.

Discussion

According to the criterion of heavy menstrual bleeding, the average length of the menstrual cycle for both groups was greater than seven days. Group N experienced an average symptom duration (mean ± SEM) of 5.38±0.36 months and an average menstrual cycle duration (mean ± SEM) of 8.27±0.29 days. In group L, the average menstrual cycle duration (mean ± SEM) in days was 8.94 ± 0.34 and the average symptom duration (mean ± SEM) in months was 4.76 ± 0.25.The average length of the menstrual cycle and the average duration of symptoms yielded p values of 0.26 and 0.29, respectively. On the initial visit, the PBAC score was determined. From day 1 to day 21 of the menstrual cycle, Group N received three daily tablets containing 5 mg of norethisterone, with a seven-day interval in between. For a duration of three months, they were instructed to take the medication on a regular and cyclical basis. Levonorgestrel-intauterine systems were implanted in Group L patients. The PBAC score was then determined for every month. Group N's mean PBAC score was determined to be 442.70 ± 9.62. The calculated mean PBAC score for group L was 419.85 ± 10.50. The statistical insignificance of the difference un data between the two groups was indicated by the p value of 0.40 (>0.05). The average hemoglobin concentration in percentage terms for the N and L groups are 9.40 ± 0.18 and 9.21 ± 0.15, respectively. The statistical insignificance of the difference un data between the two groups was indicated by the p value of 0.99 (>0.05).

After three months, the PABC score of the patients in group N dropped to 297.70 from an initial 442.70. The score was decreased by 32.74%. The resultant p-value was 0.040. After three months, the patients in group L's PABC score dropped from 419.85 to 139.67. The score was decreased by 66.67%.

These results were consistent with a study by Irvine et al., which found that the levonorgestrel intrauterine system reduced menstrual blood loss by 94% (median reduction 103 ml; range 70 to 733 ml) and oral norethisterone by 87% (median reduction 95 ml; range 56 to 212 ml) when menstrual blood loss at three months was expressed as a percentage of the control. [5] Similar outcomes were found in a different trial conducted in March 2016 by Kiseli M et al. Patients treated with Norethisterone tablets experienced a reduction in menstrual blood loss of 53.1%, but patients treated with LNG-IUS experienced a higher reduction of around 85.8%.[6]

After three months of treatment, the mean endometrial thickness in group N decreased to 8.80 mm from 11.70 mm. Thus determined, the endometrial thickness was reduced by 24.79%. The obtained p-value of 0.001 (<0.05) indicates statistical significance. After three months of treatment, the mean endometrial thickness in group L decreased to 6.97 mm from 11.06 mm. 36.89% was the calculated reduction in endometrial thickness. A statistically significant p value of 1.89×10-7 (<0.05) was discovered.

There was barely a 0.1% rise in the mean hemoglobin concentration. Thus, a statistically significant p value of 2.028×10 -21(<0.05) was achieved. Before therapy began, group L's mean hemoglobin concentration was 9.21%; three months after the LNG-IUS was inserted,

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that number rose to 9.45%. There was a 2.53% rise in the average hemoglobin concentration.

The average menstrual cycle duration dropped considerably in both groups. It dropped from 8.27 days to 6.15 days in group N. There was a 25.63% drop. Before treatment, group L's duration was 8.94 days; this dropped to 5.79 days. Rees Met al.'s 2000 investigation produced findings that were comparable to these. The levonorgestrel-releasing intrauterine device (LNG IUS) was found to be significantly more effective in that trial when compared to oral cyclical norethisterone (NET), which was delivered on days 5–26. [7]

Of the sixty-six women who were chosen, twenty-four did not respond well enough to treatment and were scheduled for hysterectomy after three months. Nineteen of the thirty-three women in group N had hysterectomy after three months of treatment. In group N, the hysterectomy rate was 57.57%. Out of the 33 women in group L, only 5 had a hysterectomy after three months of LNG-IUS insertion. In group L, the hysterectomy rate was 15.15 percent.

In their investigation, Lähteenmäki P et al. discovered comparable outcomes. They came to the conclusion that before undergoing a hysterectomy or other invasive procedure, the levonorgestrel intrauterine system is a good conservative option to a hysterectomy in the treatment of menorrhagia. [8]

Dysmenorrhea is menstrual pain severe enough to interfere with a woman's life. It is among the most typical signs and symptoms of excessive menstrual flow. Before starting treatment, 33 of the 66 women who were chosen for the trial also experienced dysmenorrhea. Of the 33 women in group N, 14 experienced dysmenorrhea. Of the 33 women in group L, about 16 experienced dysmenorrhea. Group L experienced a drop of 93.75%, greater than the 85.71% reduction experienced by group N.

Comparable outcomes were seen in a 2013 trial by Janeshgupta et al., which discovered that levonorgestrel-IUS was superior to standard medical treatment in lowering the negative effects of excessive monthly bleeding on quality of life in women with menorrhagia who presented to primary care physicians. (Sponsored by the ECLIPSE Controlled-Trials program of the National Institute of Health Research Health Technology Assessment Program.) [9]

Conclusion

We conclude that heavy menstrual bleeding is not just a clinical burden but also a huge economic and social burden. LNG-IUS and tablet norethisterone are secure and efficient ways to manage HMB. This study found that the reduction of excessive menstrual bleeding was achieved by both LNG-IUS and Norethisterone, as demonstrated by the decrease in endometrial thickness, the average length of the menstrual cycle, and the PABC score. However, LNF-IUS reduced menstrual blood loss more than norethisterone did. The hemoglobin percent improved just slightly. Hence, both LNG-IUS and Norethisterone are useful in treating excessive menstrual bleeding; however, LNG-IUS is more effective in reducing the incidence of hysterectomny and improving dysmenorrhea, as well as improving endometrial thickness, average menstrual cycle duration, and PABC score.

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