LEVONORGESTREL-RELEASING INTRAUTERINE SYSTEM AS AN ALTERNATIVE THERAPY IN ABNORMAL UTERINE BLEEDING

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ABSTRACT

BACKGROUND

Abnormal uterine bleeding is one of the most frequent reasons for gynaecological consultation, occurring in approximately 30% of women of reproductive age. Menorrhagia by definition implies a menstrual blood loss equal to or greater than 80 mL. Many women seek consultation for bleeding episodes of less than this amount because of the stress associated with it. Most frequently used medications are combinations of prostaglandin synthetase inhibitors and antifibrinolytic drugs, nonsteroidal anti-inflammatory drugs, oral progesterone like Norethisterone or medroxyprogesterone acetate and combined oral contraceptives. The usual treatment for women with menorrhagia not desiring further pregnancies and those not responding to medical managements is either hysterectomy or endometrial ablation. Endometrial ablation less commonly performed due to low success rate. Levonorgestrel intrauterine system (LNG-IUS) is a new modality in the treatment of AUB.

The objective of this study is to evaluate the use of Levonorgestrel intrauterine system as a treatment for women with menorrhagia.

MATERIALS AND METHODS

This is a prospective interventional comparative study conducted on women with abnormal uterine bleeding. The duration of study was from March 2012 to October 2013. The respondents include those outpatients attending Gynaecology Department of Government Medical College, Kottayam with menorrhagia. The samples size was 50 of which 25 were in experimental groups and remaining 25 in control group. Experimental group were given LNG IUS for menorrhagia and the remaining 25 patients were given oral progestins for heavy menstrual bleeding. In order to make a comparison of the impact of the two different kinds of interventions, the Hb level as well as the amount of blood loss were systematically estimated at frequent intervals. Accordingly, these measurements were carried for the said both groups at the commencement of research study and thereafter at an interval of 1 month, 3 months and 6 months.

RESULTS

There is a statistical improvement in the Hb level from the 3rd month of insertion of LNG-IUS ($p > 0.005$). At the commencement of study, the mean score of Hb among experimental group was 10.52 g% as against 10.16 g% among the control group. While at 1 month, it was found to be 10.98 g% as against 10.34 g% among the control group. At the third month, it was 11.53 g% as against 10.58 g% and at 6 months, it was 11.76 g% as against 10.87 g%. The amount of blood loss was also found to be decreased in the IUS group. The mean amount of blood loss at the commencement of the study in the experimental group and control group were 117 mL as against 114.4 mL, while at 1 month it was 100.8 mL as against 102.24 mL in control group. After 3 months, the blood loss was 78.2 mL as against 93 mL in control group. At 6 months, it was 62.27 mL as against 83.08 mL.

CONCLUSION

The use of Levonorgestrel releasing intrauterine system (LNG IUS) is found to be effective in controlling menstrual blood loss and thus achieving higher Hb levels.

KEYWORDS

Abnormal Uterine Bleeding, Levonorgestrel Intrauterine Device, Progestins.

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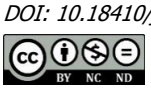

BACKGROUND

Abnormal uterine bleeding is one of the most frequent reasons for gynaecological referrals, occurring in approximately 30% of women of reproductive age. Menorrhagia is a menstrual blood loss equal to or greater than 80 mL.[1] Many women seek consultation for bleeding episodes of less than this amount because of the stress associated with it.[2]

There are different modalities for the treatment of menorrhagia ranging from medical therapy to surgical

treatment. The medical management includes hormonal and non-hormonal treatment with NSAID and antifibrinolytics.

The most commonly prescribed hormonal methods include-

a. Oral Contraceptive Pill

It can be started at any time. It is a very potent and cheap modality of treatment. It reduces blood loss by 50%. However, there are certain contraindications to its use like previous thromboembolic event or stroke, history of oestrogen-dependent tumour, active liver disease, pregnancy, hypertriglyceridaemia and women older than 35 years and who smoke >15 cigarettes per day.

b. Progestin Therapy

The most commonly used progestin is medroxyprogesterone.[3] But if the woman experiences PMS-like side effects, micronised progesterone, norethindrone, dydrogesterone may be considered. Progestin therapy is administered as either continuous or cyclical. In the cyclical regimen, start medroxyprogesterone 10 mg daily for 14 days from 16th day of cycle. If bleeding occurs before completing the 14-day course, the patient can double the dose (20 mg). Continuous progestins may be indicated if the goal is to achieve amenorrhea (e.g., busy professional or athlete, intractable menstrual migraine, catamenial seizures, severe mental retardation). There are different options like-
Oral Progestin- medroxyprogesterone (Provera) 10 to 20 mg daily, depomedroxyprogesterone (Depo-Provera) 150 mg IM every 13 weeks and Levonorgestrel IUD (Mirena).[4,5,6]

Mirena- Mirena (Levonorgestrel-releasing intrauterine system) consists of a T-shaped polyethylene frame (T-body) with a steroid reservoir (hormone elastomer core) around the vertical stem. The reservoir consists of a white or almost white cylinder, made of a mixture of levonorgestrel and silicone (polydimethylsiloxane), containing a total of 52 mg levonorgestrel. The reservoir is covered by a semi-opaque silicone (polydimethylsiloxane) membrane. The T-body is 32 mm in both the horizontal and vertical directions. The polyethylene of the T-body is compounded with barium sulfate, which makes it radiopaque. A monofilament brown polyethylene removal thread is attached to a loop at the end of the vertical stem of the T-body. LNG-IUS is a small T-shaped intrauterine system (IUS) which after insertion releases the hormone levonorgestrel into the uterus. LNG-IUS contains a total amount of 52 mg levonorgestrel with an initial release rate of 20 microgram per 24 hours.

Levonorgestrel is a progestogen with anti-oestrogenic activity. Levonorgestrel can also be administered into the uterine cavity as an intrauterine delivery system. This allows a very low daily dosage, as the hormone is released directly into the target organ. It is a potent progestin of the 19-nortestosterone class which possesses characteristic gestagenic properties such as endometrial transformation (development of a secretory endometrium), antigonadotropic action and antioestrogenic effects. LNG-IUS has mainly local progestogenic effects in the uterine cavity. The high levonorgestrel concentrations in the endometrium down-regulate endometrial oestrogen and progesterone receptors, making the endometrium insensitive to the circulating estradiol and a strong antiproliferative effect is seen. Morphological changes of the endometrium and a weak local foreign body reaction, due to the presence of an intrauterine device are observed during use of LNG-IUS. Thickening of the cervical mucus prevents passage of the sperm through the cervical canal. Ovulation is inhibited in some women.

The menstrual pattern is a result of the direct action of levonorgestrel on the endometrium and does not reflect the ovarian cycle. Bleeding patterns may vary from regular scanty menstruation in some women to oligo/amenorrhea in others. Amenorrhea is due to the local effect of levonorgestrel on the endometrium, which under strong local suppression does not proliferate in response to oestrogen.

Worldwide, intrauterine devices (IUDs) are the most widely used and effective reversible contraceptive method and are safe, extremely "low maintenance" contraceptives. They are second only to female sterilisation as the most prevalent method of family planning worldwide (13.6% vs 20.5%). There is currently a wide variety of IUDs available worldwide; some are inert, some are copper containing, and some are medicated with Levonorgestrel.[7]

The LNG-IUS provides highly effective contraception for up to five years, with potential for approval for up to seven years in the near future.[8] The mechanisms of action of the LNG-IUS are similar to that of Levonorgestrel implants or Levonorgestrel-containing mini-pills; although it accomplishes these effects with much lower peak serum levels than other progestin-containing contraceptives (0.1-0.4 ng/mL vs. 1.7-15.2 ng/mL with combined and progestin-only oral contraceptives, respectively, and 5.4 ng/mL for combined vaginal preparations).[9] Levonorgestrel, a highly potent second generation progestin, thickens cervical mucus and suppresses endometrial proliferation (preventing decidualisation of the stroma). This creates a hostile environment for sperm survival, inhibiting motility and capacitation with the net effect combining to prevent fertilisation. The LNG-IUS also produces endometrial thinning with fragile superficial vessels which, in the unlikely event of fertilisation, may prevent implantation. As a result of these various contraceptive actions, the efficacy rate of the LNG-IUS is high, with only 0.1% of women experiencing an unintended pregnancy within the first year of typical use.

Dosage and Administration

LNG-IUS is inserted into the uterine cavity. One administration is effective for five years. The in vivo dissolution rate is approximately 20 microgram/24 hours initially and is reduced to 10 microgram/24 hours after five years. The mean dissolution rate of Levonorgestrel is about 14 microgram/24 hours over the time up to five years. LNG-IUS, when inserted according to the insertion instructions, has a failure rate of approximately 0.2% at 1 year and a cumulative failure rate of approximately 0.7 % at 5 years.

Insertion and Removal/Replacement

Before insertion, the woman must be informed of the efficacy, risks and side effects of LNG-IUS In particular, the woman should be informed about the expected differences in bleeding pattern, amenorrhea and hormonal effects. Studies have suggested that good counselling is likely to reduce unnecessary removals of LNG-IUS.

A physical examination, including pelvic and breast examinations, and a cervical smear should be performed. Pregnancy, sexually transmitted diseases and endometrial pathology should be excluded, and genital infections have to be successfully treated.

The position of the uterus and the size of the uterine cavity should be determined. Fundal positioning of LNG-IUS is particularly important in order to ensure uniform exposure of the endometrium to the progestogen, prevent expulsion and maximise efficacy. The woman should be re-examined 4 to 12 weeks after insertion and once a year thereafter, or more frequently if clinically indicated. Because irregular bleeding/spotting is common during the first months of therapy, it is recommended to exclude endometrial pathology before insertion of LNG-IUS.

The intrauterine system should be removed after five years. If the user wishes to continue using the same method, a new intrauterine system can be inserted at the same time.[10,11]

The contraindications for its use includes pregnancy, pelvic inflammatory disease, cervicitis, cervical dysplasia, uterine or cervical malignancy, undiagnosed abnormal uterine bleeding, congenital or acquired uterine anomaly, and acute liver disease or liver tumour.

Objective of Study

1. To determine the impact of LNG-IUS in excessive uterine bleeding.
2. To measure the menstrual blood loss.

MATERIALS AND METHODS

The study was conducted in the Department of Obstetrics & Gynaecology, Govt. Medical College, Kottayam from March 2012 to October 2013. It was a Prospective Interventional Comparative study with an experimental group – having women who were using LNG-IUS and a control group where women received oral progestins.

Inclusion Criteria

- Women aged 33-49 yrs. on treatment for excessive uterine bleeding.
- Uterine fibroids <12 weeks size.
- Endometriosis.
- Adenomyosis.

Exclusion Criteria

- Women with submucous fibroid.
- History or current clinical evidence or suspicion of malignancy.
- Active liver disease.
- Adnexal tumour or cysts.
- Pelvic inflammatory disease within the previous 12 months.

50 women satisfying all inclusion criteria were selected from Gynaecology Op after getting written informed consent. They were assorted into experimental and control group. A detailed history and examination was done. Those in the experimental group with menorrhagia were advised LNG-IUS while those in the control group received oral progestins for abnormal uterine bleeding.

Patients were followed up in OP for 1 year with Hb g% and assessment of blood loss in each period during 1, 3 & 6 months after insertion.

The data were collected with a proforma filled by the subjects. Blood loss assessment was done using pictorial blood loss assessment chart.

The data was analysed using Student's t test and ANOVA for mean blood loss.

RESULTS

	Group	N	Mean	Std. Deviation	t	p Value
Hb at the Time of Insertion	Women Who are Using LNG-IUS	25	10.528	1.1271	1.34	0.186
	Those who Receive Oral	25	10.160	0.7805		
Hb at 1 Month	Women Who are Using LNG-IUS	25	10.984	0.9957	2.54	0.014
	Those who receive Oral	25	10.340	0.7848		
Hb at 3 Months	Women Who are Using LNG-IUS	24	11.533	1.0399	3.58	0.01
	Those who Receive Oral	25	10.584	0.8009		
Hb at 6 Months	Women Who are Using LNG-IUS	24	11.76	1.067	3.28	0.02
	Those who Receive Oral	25	10.87	0.822		

Table 1. Data and Result of Test of Significance Difference between Experimental Group and Control Group in Hb

	Group	N	Mean	Std. Deviation	t	P Value
Blood Loss at the time of Insertion/mL	Women Who are Using LNG-IUS	25	117.00	24.238	0.962	0.341
	Those Who Receive Oral Progestins	25	111.40	16.106		
Blood Loss at 1 Month/mL	Women Who are Using LNG-IUS	25	100.80	17.776	0.363	0.719
	Those Who Receive Oral Progestins	25	102.24	8.852		
Blood Loss at 3 Months/mL	Women Who are Using LNG-IUS	25	78.20	20.253	3.27	0.002
	Those Who Receive Oral Progestins	25	93.00	10.000		
Blood Loss at 6 Months/mL	Women Who are Using LNG-IUS	25	62.327	24.286	3.64	0.001
	Those Who Receive Oral Oral Progestins	25	83.08	14.068		

Table 2. Date and Result of Test of Significance Difference between Experimental Group and Control Group in Blood Loss

DISCUSSION

At the commencement of study, the mean score of Hb among experimental group was 10.52 g% as against 10.16 g% among the control group. While at 1 month mean score of Hb level among experimental group was found to be 10.98 g% as against 10.34 g% among the control group. At the third month, the mean score of Hb level among experimental group was found to be 11.53 g% as against 10.58 g%. At 6 months, the mean Hb level among the experimental group was found to be 11.76 g% as against 10.87 g% among the control group.

The obtained 't' value and p values of each observation, it is clear that in case of Hb at the time of insertion the obtained 't' value is 1.34 which is less than the statistical value 1.96 at 0.05 level of significance ($p>0.05$). This means that there exists no significant difference between the experimental group and control group.

But in the case of Hb at 1 month, the obtained 't' value is 2.54 which is greater than the table value 1.96 at 0.05 level of significance ($p <0.05$). This shows that there exists a significant difference between the experimental group and control group in their Hb at one month of observation.

The obtained 't' value is 3.58 which is greater than the table value 1.96 at 0.05 level of significance ($p <0.05$), meaning that there exists a significant difference between the experimental group and control group in their Hb at 3 months' observation.

The obtained 't' value is 3.28 which is greater than the table value 1.96 at 0.05 level of significance ($p <0.05$), which means there exists a significant difference between the experimental group and control group in their Hb 6 month observations.

In a previous study conducted in the Department of Obstetrics and Gynaecology at Khyber Teaching Hospital, Peshawar in Aug. 2005 to Aug. 2007. 32 patients with dysfunctional uterine bleeding were counselled, investigated and had LNG-IUS. 59% of the patients who had been advised hysterectomy backed out and were satisfied with LNG-IUS. 88% patients were relieved of menorrhagia and 100% improvement was seen in cases with polymenorrhagia. 50% of patients had an Hb of more than 11 g% after 3 months use.

A study conducted by Kerstin Andersson et al at East Hospital, Sweden in 1990, where they estimated the serum ferritin and haemoglobin concentration before and after LNG-IUS insertion. After 12 months, the mean serum ferritin concentration had increased significantly ($p<0.001$). Only those women who came for the 6 or 12 months followup were included in the investigation of ferritin level. The mean Hb concentration was significantly increased after 6 and 12 months ($p<0.01$).

The blood loss assessment done as part of the research by way of pictorial blood loss assessment chart. It was found that the mean amount of blood loss at the commencement of the study in the experimental group and control group were high (117 mL as against 114.4 mL) while at 1 month the mean loss in the experimental group was 100.80 mL as against 102.24 mL in control group. After 3 months, the mean blood loss among the experimental group was 78.2 mL as against 93 mL in control group. At 6 months, the mean loss in the experimental group was found to 62.27 mL as against 83.08 mL.

In case of blood loss at the time of insertion, the obtained 't' value 0.962 is less than the statistical value 1.96 at 0.05 level of significance ($p>0.05$), meaning that there exists no significant difference between the experimental group and control group.

At 1 month, the obtained 't' value is 0.363 which is less than the statistical value 1.96 at 0.05 level of significance ($p >0.05$) which means that there exists no significant difference between the experimental group and control group loss at 1 month of observation.

The obtained 't' value is 3.27, which the greater than the table value 1.96 at 0.05 level of significance ($p<0.05$) means there exists a significant difference between the experimental group and control group in their blood loss at 3 months of observation.

At 6 months, the obtained 't' value is 3.64 which is greater than the table value 1.96 at 0.05 level of significance ($p<0.05$), suggesting that there exists a significant difference between the experimental group and control group in their blood loss at 6 months of observation.

Studies conducted by Irvine et al as a randomised comparative parallel group study, found that in the control

group, the LNG-IUS reduced menstrual blood loss by 94% (median reduction 103 mL, range 70 to 733 mL) and oral progestins by 87% (median reduction 95 mL, range 56 to 212 mL). After three cycles of treatment, 76% of the women in the LNG-IUS group wished to continue with the treatment compared with only 22% of the progestin group.

CONCLUSION

This prospective interventional comparative study among 50 women with abnormal uterine bleeding conducted in the Department of Obstetrics and Gynaecology at Govt. Medical College, Kottayam from March 2012 - October 2013 showed that the use of Levonorgestrel releasing intrauterine system (LNG-IUS) is found to be effective in controlling menstrual blood loss and thus achieving the Hb level above 12 g%. The Hb levels at the time of insertion and after 12 months is 10.52 and 12.40 respectively. The blood loss at the time of insertion is 117 mL and 11 women became amenorrhoeic after LNG-IUS insertion and four women became oligomenorrhoeic. While evaluating the women with menorrhagia treated with LNG-IUS it was found that the median days of bleeding decreased from 7 days in first 3 months to 3 days during the sixth month and the mean menstrual blood loss reduced from 117 mL to 20-30 mL.

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