LEVONORGESTREL RELEASING INTRAUTERINE SYSTEM VERSUS THERMAL BALLOON ABLATION FOR HEAVY MENSTRUAL BLEEDING; A PROSPECTIVE RANDOMIZED TRIAL.

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ABSTRACT

Objective : To compare the levonorgestrel intrauterine system (LNG-IUS) and thermal balloon ablation for the treatment of heavy menstrual bleeding.

Design : Prospective randomized trial.

Setting : Department of Obstetrics & Gynecology, Jahra Hospital, south of Kuwait (between august 2005 to December 2007).

Methods : Women with heavy menstrual bleeding were randomized to treatment with the LNG-IUS or thermal balloon ablation and followed

up by a postal and telephone questionnaire. Menstrual loss measured by a pictorial bleeding assessment chart (PBAC) at 3, 6, 12 and 24 months. Treatment success, side effects and treatment failures were recorded.

Results : Both the treatments had a significant reduction in PBAC scores. At 12 and 24 months, median PBAC scores were significantly lower in women treated with the LNG-IUS compared with women treated by thermal balloon ablation (15.5 versus 55.0 at 12 months [$P = 0.002$]; 14.0 versus 51.3 [$P = 0.002$] at 24 months). At 24 months, seven (29.1%) women still using the LNG-

IUS had amenorrhea compared with one (4.2%) woman successfully treated by thermal balloon ablation ($P = 0.036$). Treatment failed in 6 (20%) women using the LNG-IUS and in 5 (17.2%) women treated with thermal balloon ablation.

Conclusions : At 12 and 24 months of follow up, women with heavy menstrual bleeding treated with the LNG-IUS have significantly lower PBAC scores and higher amenorrhea rates than thermal balloon ablation.

INTRODUCTION

Menorrhagia is a common symptom accounting for 20% of all gynecological attendances to general practitioners. A substantial proportion of women are refractory to conservative Treatment⁽¹⁾ Endometrial destruction for the treatment of dysfunctional uterine bleeding was introduced in 1988 and was heralded as a procedure with lower morbidity and mortality (2) Satisfaction rates after endometrial ablation are high but the probability of receiving further surgery is approximately 40% (3) The levonorgestrel intrauterine system (LNG-IUS). The

LNG-IUS is an intrauterine device that releases 20 micrograms of levonorgestrel every 24 hours over 5 years. It was developed in Finland during the 1980s and licensed for contraception in 1990. Worldwide, the number of current LNG-IUS users is more than 4 million, (4) and the US food and drug administration approved the LNG-IUS for use as a contraceptive in 2001. (LNG-IUS) was originally used to avoid the menstrual dysfunction associated with the intrauterine contraceptive devices (IUCD). However, it has significant effects on menstrual loss⁽⁵⁾ and may be used as an alternative to surgery (6,7).

Thermal balloon ablation was first described by Neuwirth et al.,⁽⁸⁾ and the first clinical trials of a balloon ablation device were reported in 1994. (9) Both balloon ablation and other global ablation therapies have been compared in randomized trials with hysteroscopic resection or ablation, (10-13) and very similar treatment results have been reported. It is likely that these newer ablation therapies will largely replace operative hysteroscopy for women seeking a surgical treatment for their menorrhagia. Much

less data are available comparing these devices with what is probably the most likely to be used alternative treatment. The aim of this study was to compare a thermal balloon endometrial ablation device with the LNG-IUS in a prospective randomized trial.

METHODS

Women were recruited from august 2005 to December 2007 at Department of Obstetrics & Gynecology, Jahra Hospital, south of Kuwait an invitation letter being sent to women who appeared to meet our inclusion criteria. Women were eligible for entry if they had self-described heavy menstrual bleeding, had completed their family, were 25-50 years old at initial assessment and had a regular cycle, with discrete episodes of menstruation occurring every 3-6 weeks. Exclusion criteria were ultrasound abnormalities (submucousal fibroids, intramural fibroids greater than 3 cm in diameter, large subserosal fibroids, endometrial polyps); laboratory abnormalities (follicle-stimulating hormone level [FSH] higher than 30 iu/l, adverse endometrial histology) and hysteroscopic abnormalities (submucousal fibroids, endometrial polyps),

incidental adnexal abnormality on ultrasound, severe intermenstrual bleeding, severe dysmenorrhea, severe pre menstrual pain, chronic pelvic pain, medical contraindications to either study treatment, previous endometrial ablation or resection, uninvestigated postcoital bleeding and untreated abnormal cervical cytology. Women giving a written informed consent were randomized to either LNG-IUS or thermal balloon ablation. Computer generated, randomization in blocks of 20 had been prepared prior to the commencement of the study and placed in consecutively numbered opaque envelopes. Treatments were performed in an outpatient setting during the first 10 days of the participant's menstrual cycle. Local anesthetic (1 ml of 1% lignocaine and adrenaline 1 in 200 000) was injected into each quadrant of the cervix, the cervix was dilated if required and uterine cavity length measured with a uterine sound. All women underwent a diagnostic hysteroscopy using a 4-mm hysteroscope, with 0.9% saline solution to distend the uterine cavity prior to the insertion of either the LNG-IUS or the thermal balloon ablation. Women who could not tolerate

hysteroscopy or treatment under local anesthetic were rescheduled to have their hysteroscopy or treatment under a general anesthetic on the next available theatre list. The LNG-IUS (Mirena; Schering Co., Turku, Finland) (Figure 1) was inserted as per manufacturer's instructions. All women being treated with thermal balloon ablation also had intravenous access established, and 1-3 mg midazolam (Hypnovel; Roche Products (NZ) Ltd, Auckland, New Zealand) were administered. Women were given diclofenac 50 mg (Voltaren EC; Novartis Pharmaceuticals, Auckland, New Zealand) 1 hour before treatment. Thermal balloon ablation was undertaken using the Thermachoice device (Gynecare Inc., Menlo Park, CA, USA) (Figure 2) as per manufacturer's instructions. The objective of the study was to compare the efficacy of LNG-IUS and thermal balloon ablation for the management of heavy menstrual bleeding. The primary outcomes assessed were In order to quantify menstrual blood loss, women were asked to complete a pictorial blood loss assessment chart (PBAC) as devised previously (Higham et al., 1990). (14) This method does not

yield an exact flow volume in milliliters; a score is calculated taking into account the degree to which each item of sanitary protection is soiled with blood, as well as the total number of pads or tampons used. A monthly score >100 on this chart, which is equivalent to a uterine blood loss >80 ml as measured by the alkaline haematin method, is defined as menorrhagia. Hemoglobin and FSH levels were also measured at pre-treatment, 3, 12 and 24 months. Standardized sanitary products were issued for use during completion of PBAC questionnaires in order to allow for comparisons of the PBAC score to be made. Women had direct access to the research nurse throughout the study, and if necessary, alternative management options were discussed, selected and arranged. A treatment failure was deemed to have occurred whenever a major change in treatment was completed. For the LNG-IUS, this was confirmed expulsion, completed removal or the initiation of alternative therapy. For thermal balloon ablation, this was the initiation of medication or the completion of alternative surgery, such as hysterectomy. Treatments were oth-

erwise described as 'non failed'. Chi-square test, t test and Wilcoxon test were used for statistical analysis. This was based on a review of earlier studies of the LNG-IUS and other ablation therapies, which suggested that this was likely to represent a clinically meaningful difference for women who believed that they had problematic menstrual bleeding

RESULTS

Between July 2005 and December 2007, 94 women were assessed in the gynecology clinic in department of obstetrics & gynecology. Jahra Hospital, south of Kuwait 15 women were excluded because they did not have heavy menstrual bleeding, 12 women had ultrasound abnormalities (7 women-submucous fibroids, 3 women-endometrial polyp, 2 women-adnexial mass) or had laboratory abnormality (two women -FSH level higher than 30 IU/L). 65 women were randomized, but six women were excluded after randomization when a hystroscopic abnormality (submucous fibroid) was found, 59 women were included in the trial, 30 women were treated with the LNG-IUS, and 29 women were treated by thermal balloon ablation.

One woman randomized to the thermal balloon ablation group was treated under general anesthesia after not tolerating the initial part of the balloon ablation procedure. All the initial hysteroscopy procedures and other treatments were undertaken in an outpatient clinic setting. There were no significant differences in patient characteristics following randomization (Table 1). Pre-treatment FSH and hemoglobin levels were also similar in the LNG-IUS and thermal balloon ablation groups, FSH, 7.2(1.1) versus 7.0 (3.1) IU/L; hemoglobin, 10.2(0.7) versus 10.4 (0.6) g/l. objectively measured menstrual blood loss assessed by PBAC score was significantly reduced in both the treatment groups compared with pre-treatment scores. At 3 and 6 months, there were no significant differences in PBAC scores between the two groups. At 12 and 24 months, PBAC scores were significantly lower in women treated with the LNG-IUS compared with women treated with thermal balloon ablation (Table 2). A similar trend was seen in amenorrhea rates, although these results only became significant at 24 months of follow up, with 7 (29.1%) of the success-

fully treated women having amenorrhea on PBAC scores in the LNG-IUS group and 2 (8.3%) woman in the thermal balloon ablation group ($P = 0.036$). Treatment failures were assessed at 3, 6, 12 and 24 months. In the LNG-IUS group, the 6 treatment failures included the following: by 3 months, one LNG-IUS expelled and one removed because of pain; by 6 months, no further treatment failures; by 12 months, one woman with menorrhagia, two LNG-IUS removed because of troublesome, unscheduled bleeding and one further LNG-IUS expelled and by 24 months, In the thermal balloon ablation group, the 5 treatment failures included the following: at 3 months, no treatment fail-

ures; at 6 months, two women with menorrhagia; at 12 months, one women with menorrhagia and at 24 months, two women with menorrhagia. Among the 6 treatment failures in the LNG-IUS groups, two women had a thermal balloon ablation, one was prescribed the oral contraceptive pill, two underwent hysterectomy and one had no further treatment. Among the 5 treatment failures in the thermal balloon ablation group, two women were treated with the LNG-IUS and two underwent hysterectomy one had no further treatment. There were no serious complications in either treatment group.

Table (1): Baseline Characteristics of randomized women prior to treatment Values are given as mean (SD).

Characteristics	LNG-IUS (n=30)	TBA (n=29)
Age(y)	40.1(6.1)	41.0(4.2)
Duration of menstruation (days)	7.3(2.4)	7.0(2.8)
Length of cycle (days)	27.5 (3.7)	26.9 (3.5)
Number of daysof painful bleeding	3.7 (1.6)	4.0 (2.1)
Endometrial thickness at time of treatment	8.3(3.2)	8.1(2.1)
Cavity length (cm)	8.3(0.8)	7.9(0.7)
Haemoglobin (g/L)	10.2(0.7)	10.4 (0.6)
PBAC score	389 (119)	400(103)
Fsh (IU/L)	7.2(1.1)	7.0(3.1)

TBA: Thermal balloon ablation.

LNG-IUS: Levonorgestrel intrauterine system.

Table (2): Menstrual status at randomization and at 3-, 6-, 12- and 24-month follow-up periods (excluding treatment failures).

	LNG-IUS (n = 30)			TBA (n = 29)			P value
	N (%)	Mean (SD)	Median	N (%)	Mean (SD)	Median	
3 months Amenorrhea Total PBAC score	2(8.3)	135.0(188.5)	56.0	5(20.8)	236.8(436.5)	68.0	0.245 0.462
6 months Amenorrhea Total PBAC score	2(8.3)	80.2 (107.2)	36.0	1(4.2)	110.5(139.2)	50.5	0.743 0.090
12 months Amenorrhea Total PBAC score	5(20.8)	40.1 (77.3)	15.5	2(8.3)	93.4 (112.0)	55.0	0.264 0.002
24 months Amenorrhea Total PBAC score	7(29.1)	21.2 (28.8)	14.0	1(4.2)	74.6(85.1)	51.3	0.036 0.002

TBA: Thermal balloon ablation.

LNG-IUS: Levonorgestrel intrauterine system.

Fig. 1 : LNG-IUS (Mirena)

DISCUSSION

Both treatments compared in this study are well established for the management of menorrhagia, but there have been few direct comparisons of the two techniques, Soysal et al.⁽¹⁵⁾ randomized 72 women to treatment with either the LNG-IUS or the thermal balloon ablation with the Thermachoice device. At 12 months post-treatment, the reduction in PBAC scores was significantly greater in the thermal balloon ablation group compared with the LNG-IUS group (a reduction of 388.2 [SD 21]

Fig. 2 : Thermal balloon system .

versus 343 [SD 27]; $P < 0.001$). In another study, Barrington et al.¹⁶ compared the LNG-IUS with the Thermochoice device in 50 women using PBAC scores at pre-treatment and at 6 months post-treatment. At 6 months, PBAC scores were not significantly different in the two groups. Three of the 25 women treated with the LNG-IUS requested removal or hysterectomy, and 5 of the 25 women treated with thermal balloon ablation requested hysterectomy. No medical treatment or conservative surgery can rival hysterectomy in achieving 100%

cessation of bleeding; yet, randomized studies reporting on the quality of life suggest that women value the improvements in menstruation reported with LNG-IUS in spite of continuing bleeding.⁽¹⁷⁾ The largest randomized study to date comparing hysterectomy with LNG-IUS has recently reported 5 years of follow up.^(4,18) Among 119 women randomized to LNG-IUS, 50 (42%) eventually underwent hysterectomy, so the LNG-IUS is clearly not a completely effective treatment for menorrhagia. Despite this relatively high proportion of women eventually requesting hysterectomy, satisfaction rates were similar in both groups and the discounted direct and indirect costs associated with the LNG-IUS remained significantly lower than those associated with hysterectomy. A number of randomized trials have compared thermal balloon ablation^{9, (19)} and other second-generation devices⁽²⁰⁾ with hysteroscopic endometrial resection or ablation and not shown any significant differences in effectiveness. No randomized trials has compared second-generation devices with hysterectomy. The variety of second-generation devices that have been

developed and the apparent effectiveness of the LNG-IUS make such a comparison less clinically useful than comparisons between individual second-generation ablation devices or with the LNG-IUS. Some devices such as microwave endometrial ablation. (MEA_; Microsulis, Portsmouth, UK) (21, 22) may be more versatile than thermal balloon ablation in that larger or distorted uterine cavities can be treated. It is also possible that some newer devices will result in higher rates of amenorrhea and less menstrual blood loss than thermal balloon ablation. NovaSure (Cytac, Palo Alto, CA, USA),^(10,23) a global ablation device that uses bipolar electrosurgical energy, has been shown in a randomized trial to produce a significantly higher rate of postoperative amenorrhea over 12 months of follow up than Cavaterm (Wallsten Medical SA, Morges, Switzerland),⁽²⁴⁾ a thermal balloon ablation device (16 of 37 women [43%] versus 2 of 18 women [11%]). Novasure has also recently been compared with Thermachoice in a larger, double blind randomized trial, and at 12 months of follow up, amenorrhoea rates were 43% in the Novasure group (34 of 83 women)

compared with 8% (3 of 43 women) in the Thermachoice group ($P < 0.01$), with significantly higher rates of post-operative satisfaction also reported.²⁵ The reversibility of treatment with LNG-IUS, its contraceptive efficacy and the opportunity it provides to maintain future fertility will make it an attractive alternative to ablation therapy even if other devices do prove to be more effective than thermal balloon ablation. Importantly, this study demonstrates that 24 months of follow up, treatment with the LNG-IUS is associated with lower PBAC scores and a higher amenorrhea rate than thermal balloon ablation. Most randomized and observational studies of new endometrial ablation therapies have a relatively short duration of follow up of no more than 12 months, and this study highlights the importance of a long duration of follow up when the LNG-IUS and the ablation therapy are compared. In conclusion, this study has shown that the LNG-IUS results in a significantly lower objectively measured blood loss and higher amenorrhea rates than thermal balloon ablation over 24 months of follow up. However, following treat-

ment with both LNG-IUS and thermal balloon ablation, at least 25% of women with a normal sized uterus and menorrhagia will have requested an alternative treatment within 2 years. Neither treatment is clearly superior to the other, nor should the treatment chosen be based on the individual preferences of each woman.

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الملخص العربى

مقارنة استخدام اللولب الرحمى ليفونورجستريل وبالون الحرارى فى حالات النزف الرحمى الشديد دراسة عشوائية مستقبلية

د/ عمرو الفيومي

الهدف من هذه الدراسة هو مقارنة الطريقتين فى علاج حالات النزف الرحمى الشديد وقد صممت هذه الدراسة كدراسة عشوائية مستقبلية. واجريت هذه الدراسة بمستشفى الجهاز - قسم التوليد وامراض النساء فى الفترة من يوليو ٢٠٠٥ وحتى ديسمبر ٢٠٠٧ وقد تم اختيار السيدات بطريقه عشوائية للعلاج باستخدام اللولب الرحمى لتيفونورجستريل وبالون الحرارى وتم متابعة المرضى عن طريق المراسلة او التليفون وتم قياس كمية الدم الفاقد فى الدورة الشهرية بعد العلاج باستخدام منظومة معينة تسمى (PBAC) عن ٣، ٦، ١٢، ٢٤ شهرا. وكذلك تم حساب كل من الآثار الجانبية ومعدل الفشل فى طرق العلاج المستخدمة وأظهرت الدراسة أن كلتا الطريقتين ساهمتا بصورة جيدة فى نقص كمية الدم الفاقد فى الدورة الشهرية عند ١٢، ٢٤ شهرا بعد العلاج. لكن معدل كمية الدم الفاقد باستخدام اللولب الرحمى المعالج أقل بالمقارنة باستخدام البالون الحرارى (١٥,٥ - ٠,٥٥) بعد ١٢ شهرا من العلاج و(١٤-٥١,٣) بعد ٢٤ شهرا من العلاج وأن حوالى ١٩,١% من السيدات اللائى يستخدمن اللولب المعالج انقطعت الدورة الشهرية لديهن بالمقارنة بحوالى ٤,٢% باستخدام البالون الحرارى فى العلاج وأظهرت أيضا أن معدل الفشل باستخدام اللولب المعالج هو ٢٠% بالمقارنة بحوالى ١٧,٢% باستخدام البالون الحرارى وتؤكد هذه الدراسة أن استخدام اللولب الرحمى ليفونورجستريل أفضل من استخدام البالون الحرارى فى علاج حالات النزف الرحمى الشديد بالنسبة لمعدل انقطاع وكمية الدم الفاقد للدورة الشهرية.