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Levonorgestrel-releasing intrauterine device for management of tamoxifen-induced menorrhagia in breast cancer patients

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This study aimed to evaluate the therapeutic yield of levonorgestrel-releasing intrauterine device (LNG-IUD) for management of tamoxifen induced menorrhagia in women who had mastectomy for treatment of breast cancer. This study included 34 patients who had breast cancer, underwent mastectomy, were maintained on tamoxifen post-operatively for at least 6 months, and had also newly developed menorrhagia throughout their follow-up period. All the patients underwent clinical examination for determination of duration and heaviness of menstrual blood loss (MBL), transvaginal ultrasonography (TVU) and endometrial biopsy for exclusion of abnormal pathology, estimation of blood iron indices and quality of life (QoL) scoring. Baseline endometrial biopsy detected simple endometrial hyperplasia (EH) in 4 patients and 30 patients had proliferative endometrium. Three patients were excluded and 31 patients completed the follow-up period without the need for shift to hysterectomy. Both mean duration and heaviness of MBL showed significant progressive decrease throughout the observation period as compared to baseline data. At the end of follow-up period, 5 women became amenorrheic, 2 women had moderate MBL and 24 women had mild MBL. Iron indices studies showed significant improvement at the end of follow-up as compared to baseline indices and total QoL scoring recorded at 6 and 12 months after enrollment were significantly higher as compared to baseline scores with significantly higher scores at 12 months. LNG-IUD could be considered as an appropriate therapeutic modality for tamoxifen-induced menorrhagia in patients who had mastectomy for breast cancer with significant reduction of duration and severity of MBL and improved QoL and iron indices.

Key words: Levonorgestrel-releasing intrauterine device, mastectomy, menstrual blood loss, transvaginal ultrasonography.

INTRODUCTION

Premenopausal women with a new diagnosis of breast cancer are faced with many challenges. Providing health care for issues such as gynecologic co-morbidities, reproductive health concerns, and vasomotor symptom control can be complicated, because of the risks of hormone treatments and the adverse effects of adjuvant therapies. It is paramount that health care professionals understand and be knowledgeable about hormonal and non-hormonal treatments and their pharmacological parameters so that they can offer appropriate care to women who have breast cancer, with the goal of improving quality of life (Hind et al., 2007).

Tamoxifen is an orally active selective estrogen receptor modulator that is used in the treatment of breast cancer

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and is currently the world's largest selling drug for that purpose. According to the International Breast Cancer Intervention Study, tamoxifen was found to reduce the risk of invasive estrogen receptor-positive tumors by 31% in women at increased risk for breast cancer and this risk-reducing effect of tamoxifen appears to persist for at least 10 years (Jahanzeb, 2007; Cuzick et al., 2007).

However, tamoxifen has some side effects including hot flashes, menstrual irregularity, vaginal discharges, uterine bleeding, uterine endometrial cancer, hyper-coagulability, steatosis hepatitis, and risk of thrombo-embolism. Long-term data from clinical trials have failed to demonstrate a cardioprotective effect and beneficial effects on serum lipid profiles. Arrhythmia secondary to tamoxifen is very rare (Zhou et al., 2007).

Chronic heavy menstrual bleeding is a common gyne-cologic condition that causes significant health problems and negatively impacts a woman's quality of life. Surgical treatments should be reserved for women who have pelvic pathology and for those who fail medical therapy. The recent United State Food and Drug Agency (US FDA) approval of the levonorgestrel-releasing intrauterine system as an indicated treatment for heavy menstrual bleeding in women who want to use intrauterine devices for birth control highlights the potential that this top tier contraceptive method offers as a first-line therapy for treatment of heavy menstrual bleeding (Nelson et al., 2010).

This study aimed to evaluate the therapeutic yield of levonorgestrel-releasing intrauterine device (LNG-IUD) for management of tamoxifen-induced menorrhagia in women who had mastectomy for treatment of breast cancer.

PATIENTS AND METHODS

This study was conducted at the Departments of Obstetrics and Gynecology and General Surgery, Benha University Hospital from January, 2007 till January, 2009 so as to allow at least 12 months follow-up for the last enrolled case. Inclusion criteria included patients who had breast cancer, underwent mastectomy, were maintained on tamoxifen post-operatively for at least 6 months and had also newly developed menorrhagia throughout their follow-up period.

After obtaining fully-informed patients and/or husbands' consents, enrolled patients underwent full history taking, complete general and pelvi-abdominal examination. Menorrhagia was diagnosed if the duration of menstrual blood loss (MBL) was ≥6 days and/or MBL was ≥80 ml and other pathological conditions have been excluded (O'Flynn and Britten, 2004; Istre and Qvigstad, 2007). For easiness of patients' interpretation of menorrhagia, heaviness of MBL in the last 6 months after start of tamoxifen therapy was graduated as light, moderate, heavy or very heavy loss and the frequency of bleeding or spotting between cycles was defined.

Patients were informed about the study design (including a 12-month trial using LNG-IUD for control of MBL) and to shift to surgical line of management if the trial failed or the patient requested for the shift. Transvaginal ultrasonography was used to exclude possible causes of menorrhagia, including myomas and endometrial polyps, as well as adnexal pathology, then all women underwent cervical smear and D&C biopsy for exclusion of cervical and endometrial pathologies.

All women had a negative urine pregnancy test prior to levonorgestrel-induced intrauterine system (LNG-IUS) insertion which was conducted as an office procedure one day after cessation of menstrual bleeding. The uterine cavity length was measured using uterine sounding, followed by LNG-IUS insertion. Feasibility of insertion was defined as difficult if there was moderate or severe pain on uterine sounding or if there was need for cervical dilatation, requirement for local anesthesia or intravenous sedation for accomplishment of dilatation and IUD insertion. Accurate LNG-IUS position was documented with transvaginal ultrasonography (TVU) immediately after insertion.

Enrolled women were followed-up every 3 months for grading MBL as regards duration and heaviness. Quality of life (QoL) was evaluated using the 5-Dimensional EuroQol (EQ-5D) which provides a single numeric score for mobility, self-care, usual activities, pain, and mood, each was scored as 0 or 1 and the total EQ-5D score index was calculated; higher scores indicated better QoL (EuroQol Group, 1990). The QoL scores were evaluated at time of baseline and 6 and 12 months after enrollment.

Laboratory investigations

Iron indices were evaluated prior to and 12 months after LNG-IUD insertion, collected venous blood sample were divided into two parts:

1) The first part was kept in a plane container and was left to clot, and then serum was separated by centrifugation at 3000 rpm for not less than 5 min and was stored at -20°C.
2) The second part was put in EDTA tube (about 1.8 mg trik EDTA/1 ml blood) for at once hemoglobin estimation.

Studied iron indices included

1) Hemoglobin concentration (Hb conc.) was determined by cyanomethemoglobin method (International Committee for Standardization in Hematology, 1967).
2) Serum iron concentration was estimated after the separation of Fe^{+3} from transferring by means of a detergent mixture in slightly acidic solution and reduction of Fe^{+3} to Fe^{+2} with ascorbic acid, which then react with ferrozine to give a colored complex (Siedel, 1984).
3) Serum ferritin level was determined by ELISA kit (supplied from Eurogenetics UK) and was based on a monoclonal antibody-sandwich technique to ensure an optimal sensitivity and specificity (Jacobs et al., 1975).

Statistical analysis

Results were expressed as mean±standard deviation (SD), range, numbers and percentages. Results were analysed using paired t-test. Statistical analysis was conducted using Statistical package for Social Sciences (SPSS) statistical program, (Version 10, 2002). P value <0.05 was considered statistically significant.

RESULTS

The study included 34 women fulfilling the inclusion criteria and all had menorrhagia with a mean duration of 9.8±1.5; range: 6 to 13 months. Four endometrial biopsies showed endometrial hyperplasia, while the other

Table 1. Patients' enrollment data.

Data			Value
Age (years)			43.5±4.3 (32-49)
Parity (para)			1.9±0.8 (1-3)
Menstrual data (%)	Duration of MBL (days)		8.7±1.1 (8-11)
	Cycle length (days)		27±3 (23-32)
	MBL heaviness	Mild	3 (8.8)
		Moderate	10 (29.4)
		Severe	13 (38.3)
		Very severe	8 (23.5)
	Duration of menorrhagia (months)		9.8±1.5 (6-13)
Endometrial biopsy (%)	Proliferative		4 (11.8)
	Hyperplasia		30 (88.2)

Data are presented as mean±SD and numbers. Ranges and percentages are in parenthesis. MBL: Menstrual blood loss.

Table 2. IUD data.

Data			Finding
Uterine length data (%)	Mean±SD		7.4±1.6 (5-10)
	Frequency	≤6	13 (38.2)
		7-9	12 (35.3)
		≥9	9 (26.5)
Insertion data (%)	Pain on insertion	No	11 (32.4)
		Mild	18 (53)
		Moderate/severe*	5 (14.6)
	Cervical adhesions*		2 (5.9)
Follow-up data (%)	IUD expulsion	Partial	2 (5.9)
		Complete	1 (2.9)
	Exclusion	Stopped tamoxifen	1 (2.9)
		Cancer-related death	1 (2.9)
		Complete IUD expulsion	1 (2.9)

Data are presented as mean±SD and numbers. Ranges and percentages are in parenthesis. *Difficult IUD insertion.

30 biopsies showed normal but proliferative endometrium. Patients' enrollment data is as shown in Table 1.

Mean uterine sounding length was 7.4±1.6; range: 5 to 10 cm; 9 patients had uterine length of ≥9 cm, 12 patients had uterine length of 7 to 8 cm and 13 patients had uterine length ≤6 cm. Patients who had endometrial hyperplasia (EH) had a mean uterine length of 9.3±1; range: 8 to 10 cm, while patients who had proliferative endometrium had a mean uterine length of 7.1±1.5; range: 5 to 10 cm (Table 2).

Seven patients had difficult IUD insertion; 2 patients had cervical adhesions that were released under anesthesia during D&C for endometrial biopsy taking which facilitated the endometrial biopsy on IUD insertion and five patients had required intravenous sedation for completion of uterine sounding and IUD insertion. Three patients were excluded from the study; one patient had stopped tamoxifen according to surgeon's order and was excluded, because of loss of the study target, one patient had unnoticed complete IUD expulsion that was detected on follow-up at 3 months after insertion and the third died, because of extensive pulmonary metastasis progressed to acute respiratory failure and death. Two patients had partial IUD expulsion noticed throughout follow-up visits and the IUD was removed and another was successfully inserted (Table 2).

Table 3. MBL duration and severity reported throughout the study period compared to baseline data.

Data		Baseline	3 months	6 months	9 months	12 months
Duration	Mean±SD	8.7±1.1	5.2±1*	3.1±0.9*†	1.9±0.8*†‡	1.5±0.5*†‡∫
Severity (%)	No	0	0	0	2 (6.5)	5 (16.1)
	Mild	3 (9.7)	16 (51.6)	23 (74.2)	25 (80.6)	24 (77.4)
	Moderate	9 (29)	8 (25.8)	5 (16.1)	3 (9.7)	2 (6.5)
	Severe	12 (38.7)	7 (22.6)	3 (9.7)	1 (3.2)	0
	Very severe	7 (22.6)	0	0	0	0

Data are presented as mean±SD and numbers. Ranges and percentages are in parenthesis. *Significance versus baseline data. †Significance versus 3-m data. ‡Significance versus 6-m data. ∫Significance versus 9-m data.

Table 4. Mean levels of Iron study parameters estimated at the end of the study compared to baseline data.

Data	Baseline	12 months	Statistical analysis	
			t	p
Hemoglobin concentration (g/dl)	10±0.5 (9.2-10.9)	10.6±0.8 (9.7-11.6)	3.656	0.001
Serum iron (µg/dl)	56.7±9.1 (45-77)	61±7.5 (50-79)	1.841	>0.05
Serum ferritin (µg/dl)	111.1±18 (77-143)	119.8±22.1 (88-163)	1.913	>0.05

Data are presented as mean±SD; ranges are in parenthesis.

Both mean duration and heaviness of MBL showed significant progressive decrease throughout the observation period as compared to baseline data. At the end of follow-up period, 5 (16.1%) women developed amenorrhoea, 2 (6.5%) women had moderate MBL and 24 (77.4%) women had mild MBL with significantly higher frequency of those who had mild MBL as compared to baseline frequency (Table 3).

At the end of follow-up period, irrespective of the duration or severity of MBL, 8 patients had inter-menstrual spotting; however, 5 of these 8 had inter-menstrual spotting at the time of study enrollment, thus LNG-IUD induced increased frequency of women who had inter-menstrual spotting by 9.7%.

In parallel to improved MBL parameters, iron indices studies showed significant improvement at the end of follow-up compared to baseline indices that manifested as significant increase of hemoglobin concentration with non-significantly increased serum iron and ferritin (Table 4).

Total QoL scoring recorded at 6 month (3.7±0.8; range: 2 to 5) and 12 months (4.7±0.5; range: 3 to 5) after enrollment were significantly higher (t=3.943, 6.783; P<0.05, respectively) as compared to baseline scores (3.3±0.7; range: 2 to 4) with significantly (t=5.811, P<0.05) higher scores at 12 months compared to at 6 months. Differential score items showed non-significant difference as compared to baseline scores except for mood and pain scores that showed the significant change, (Figure 1 and Figure 2).

DISCUSSION

This study relied on the ease of administration of local progesterone, its single administration and longevity of the effect, and spares the need for daily or weekly administration, thereby reducing the possibility of dose loss that increases especially with those patients who surely receive other drugs or may be admitted for administration of chemotherapy or radiotherapy, thus, the use of LNG-IUD provided stability of dose and regularity of administration. Despite the fact that this study was not a comparable one, other previous studies proved the superiority of LNG-IUD over oral or injectable progesterone preparations. Kau and Ertan (2008) reported that the efficacies of oral and intramuscular medroxyprogesterone acetate in the treatment of menorrhagia were comparable to each other; however, the efficacy of LNG-IUS was superior to both. Also, Sayed et al. (2011) and Shabaan et al. (2011) found out that LNG-IUS was more effective in reducing MBL than the combined oral contraceptives in women with fibroid-related and idiopathic menorrhagia, respectively.

Three cases had IUD expulsion; 2 partial and a new one was inserted and the third case was excluded because of unnoticed complete IUD expulsion for a total expulsion of 8.8%; however, this higher expulsion rate could be attributed to the small sample size as Jensen et al. (2008) reported expulsion in 23 of 509 patients for a rate of 4.5%.

Local progesterone slowly release IUD provided

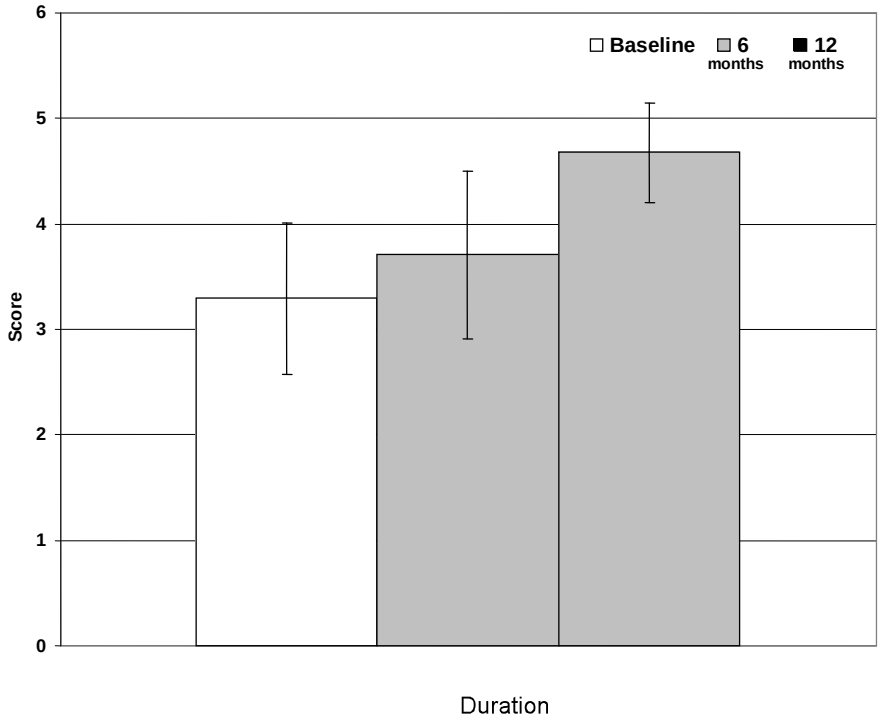

Figure 1. Mean(±SD) total QoL scores estimated at time of 6 and 12 months after enrollment.

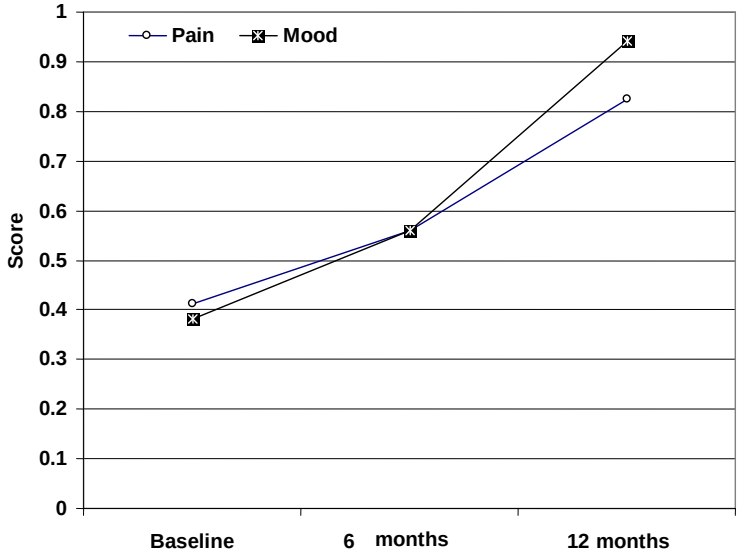

Figure 2. Mood and pain scores recorded at baseline and 6 and 12 months after enrollment.

appreciable outcome manifested as progressive decline of both duration and severity of MBL, and in parallel significantly increase hemoglobin concentration that could be attributed to the decreased loss and to complementary increased synthetic rate of red blood cells (RBCs) as manifested by the non-significant changes in serum iron and iron store ferritin. These beneficial effects are of great interest for this patients' group who had cancer-induced

anemia and anemia secondary to chemotherapy and/or radiotherapy, so their general health may not withstand a third cause of anemia in the form of excessive blood loss.

The obtained data is in line with the study of Zapata et al. (2010) who found out that most women with uterine fibroids are likely to have less MBL and higher serum levels of hemoglobin, hematocrit and ferritin after insertion of an LNG-IUD. Sayed et al. (2011) and Shabaan et al. (2011) compared the efficacy of LNG-IUS versus a low-dose combined oral contraceptive in reducing fibroid-related and idiopathic menorrhagia, respectively, and reported significant reduction of MBL and lost days with significantly increased hemoglobin levels in the LNG-IUS group.

One of the marvelous data reported in this study was the significant reduction of MBL duration and severity in the 4 patients with baseline EH, a finding indicating its applicability for management of such uterine pathology. This result is in line with Wildemeersch et al. (2007) who found continuous intrauterine delivery of LNG that appears to be a promising alternative to hysterectomy for the treatment of EH and could enhance the success rate when compared with other routes of progestagen administration, and the significant reduction of the progesterone receptor expression observed during treatment with the LNG-IUS appears to be a marker for the strong antiproliferative effect of the hormone at a cellular level resulting in an inhibition of estrogen bioactivity and endometrial suppression. Also, Chan et al. (2007) found out that LNG-IUS reduces the occurrence of de novo endometrial polyp in women treated with tamoxifen for breast cancer.

Moreover, Kesim et al. (2008) and Trinh et al. (2008) found out that LNG-IUS significantly prevent the increased risk of endometrial polyps and hyperplasia associated with the use of tamoxifen in women with breast cancer and this reduce patient discomfort while improving treatment adherence. Qi et al. (2008) reported that two infertile patients presented with complex atypical EH became pregnant following conservative treatment with LNG-IUS insertion, and histological morphology of endometrial samples after 6 months' exposure to LNG-IUS showed secretory or atrophic glands with decidualized stroma. Lee et al. (2010) reported that complete regression of simple EH was achieved, after insertion of LNG-IUS in all cases with the significant proportion achieving it within 3 months and all cases had regression within 9 months, and in the case of complex atypical hyperplasia, the regression was attained at the 9th month after insertion of LNG-IUS and as long as LNG-IUS was maintained, the EH did not recur.

Multiple studies tried to explore the underlying mechanisms for the beneficial effects of LNG-IUD on menorrhagia reduction; Koh and Singh (2010) reported enhanced endometrial expression of plasminogen activator inhibitor-1/2 in the presence of increased urokinase-like plasminogen activator receptor and tissue- type plasminogen activator antigen and concluded that the effects of LNG-IUD on hemostasis appear to be localized in the endometrium and systemic hemostasis was not duly affected and menstrual blood loss was reduced.

At the end of follow-up period, irrespective of the duration or severity of MBL, the frequency of women who had inter-menstrual spotting was increased by 9.7%. This finding was previously reported by multiple studies evaluating the outcome of LNG-IUD for menorrhagia management and could not be considered as obstacle for its use. In support of this assumption, all studied patients including those who had spotting showed significantly higher QoL score with special regard to mood parameter. These data go in hand with the study of Heikinheim et al. (2010) who found out that uterine bleeding was reduced during consecutive use of the LNG-IUS, but women with spotting at baseline continued to have more spotting than other women.

In conclusion, LNG-IUD could be considered as an appropriate therapeutic modality for tamoxifen-induced menorrhagia in patients who had mastectomy for breast cancer with significant reduction of duration and severity of MBL and improved QoL and iron indices.

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