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Original Research Article

A feedback survey on the clinical performance and acceptability of levonorgestrel releasing intrauterine system (EMILY®) during two years of usage

Manoj G.[1], Amrutha C.[1], Rajmohan G.[1], Sunil Bhaskar[1], Rajeev A.[2], Abi Santhosh Aprem[1]*

[1]Corporate Research and Development Centre, HLL Lifecare Limited, Akkulam, Trivandrum, Kerala, India
[2]Department of Community Medicine, Pushpagiri Institute of Medical Sciences and Research Centre, Thiruvalla, Kerala, India

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***Correspondence:**
Dr. Abi Santhosh Aprem,
E-mail: emily@lifecarehll.com

ABSTRACT

Background: Objective of the study was to evaluate the long term clinical performance and acceptability of levenorgestrel releasing intrauterine system (LNG-IUS), 'Emily', for the treatment of abnormal uterine bleeding (AUB).
Methods: A two year feed back survey was carried out by telephonic conversation and the data obtained was fed in to the house web application system in the respective Emily users. Subjective perceptions were verbally assured based on a questionnaire framed on the quality of the life led by the Emily users.
Results: The treatment resulted in a significant reduction in the menstrual bleeding of 102 patients who completed the two year study. The mean bleeding score and SD 18.79 (13.36) in first year falls to 10.76 (12.40) in second year. 78 (76.47%) users were very satisfied with the product usage.
Conclusions: Use of 'Emily' LNG-IUS resulted in significant reduction of menstrual bleeding in women with AUB in two years and most of the users were very satisfied with the product.

Keywords: LNG-IUS, Emily, AUB

INTRODUCTION

Abnormal uterine bleeding (AUB) caused by a disruption in the normal cyclic pattern of ovulatory hormonal stimulation in the endometrial lining, is one of the most common bleeding symptom and a major health problem in many premenopausal women.[1,2] The bleeding may be excessively heavy or light and may be prolonged, frequent, or random.[3] AUB may be defined as any variation from the normal menstrual cycle such as changes in regularity and frequency, duration of flow or amount of flow. AUB by definitions may be subdivided into subcategories based on volume of menstruation, regularity, frequency, duration, chronicity and reproductive status.[4]

The levonorgestrel-releasing intrauterine system (LNG-IUS) is a small intrauterine device developed for safe, effective and acceptable reversible contraception for longer durations. It exhibits variety of clinical benefits including treatment for menorrhagia, endometriosis, endometrial hyperplasia etc.[5-7] Several studies including the recent ones have reported the clinical efficacy and safety of LNG-IUS in the treatment of AUB.[8-10] Despite all of the evident benefits of the LNG-IUS, utilization rates remain quite low in the developing countries. There

are various factors which influences the use of IUD's in developing countries. One of the major causes is the acceptability of family planning in certain countries due to socio-cultural and religious practises in their community. Other factors that influence IUD use are costs (the cost of the device, of its insertion and removal, and of clinic services for the management of possible side effects), quality of care, training and supervision of providers, and the geographical distribution and facility of access to these services. Uptake is also influenced by the views of clinicians: due to inappropriate training and updated knowledge of the IUD types available, while others lack the skills and experience for providing adequate counselling and care for safe IUD use.[11]

In order to overcome these issues, an affordable LNG-IUS was conceptualized and jointly developed by Sri ChitraTirunal Institute of Medical Sciences and Technology (SCTIMST) and Corporate Research and Development Division (CRDC) of HLL Lifecare Limited. Emily owing to its unique M-shape aids in easy insertion and releases 20 µg of levonorgestrel every 24 hours for a period of five years. Emily LNG-IUS is available in the Indian market since October 2012 as a cost-effective treatment option for AUB (priced at $42). Although, we recently found Emily LNG-IUS to be efficacious and well tolerated in Indian women with AUB, its clinical performance and acceptability in real world clinical setting remains elusive.[8] Therefore, the present telephonic feedback survey was conducted as part of post-marketing surveillance study to evaluate the two years clinical performance, patient acceptability and performance of Emily LNG-IUS in women with AUB.

METHODS

The study is retrospective study and for selecting participants the details of women using Emily for AUB was taken from the practicing clinicians and then they were contacted telephonically. Before final enrollment, women were verbally informed about Emily LNG-IUS, its benefits and side effects, and the nature of the information that would be collected by the users as part of the survey.

Implementation of the patient management system is a partnership between HLL Lifecare Ltd and Emerging Soft labs Pvt. Ltd (Trivandrum). The system was developed with hypertext pre-processor (PHP) and MySQL (Structured Query Language). The system has entry restricted secured login platforms to maintain the confidentiality of the patient's survey data. Double data entry is restricted for each enrolled patients and access for data entry is limited to a single operator. The patient management system is linked to the website (www.emily.org.in) and in mobile phones through which it is easy to receive and address various queries and concerns related to the Emily (Figure 1).

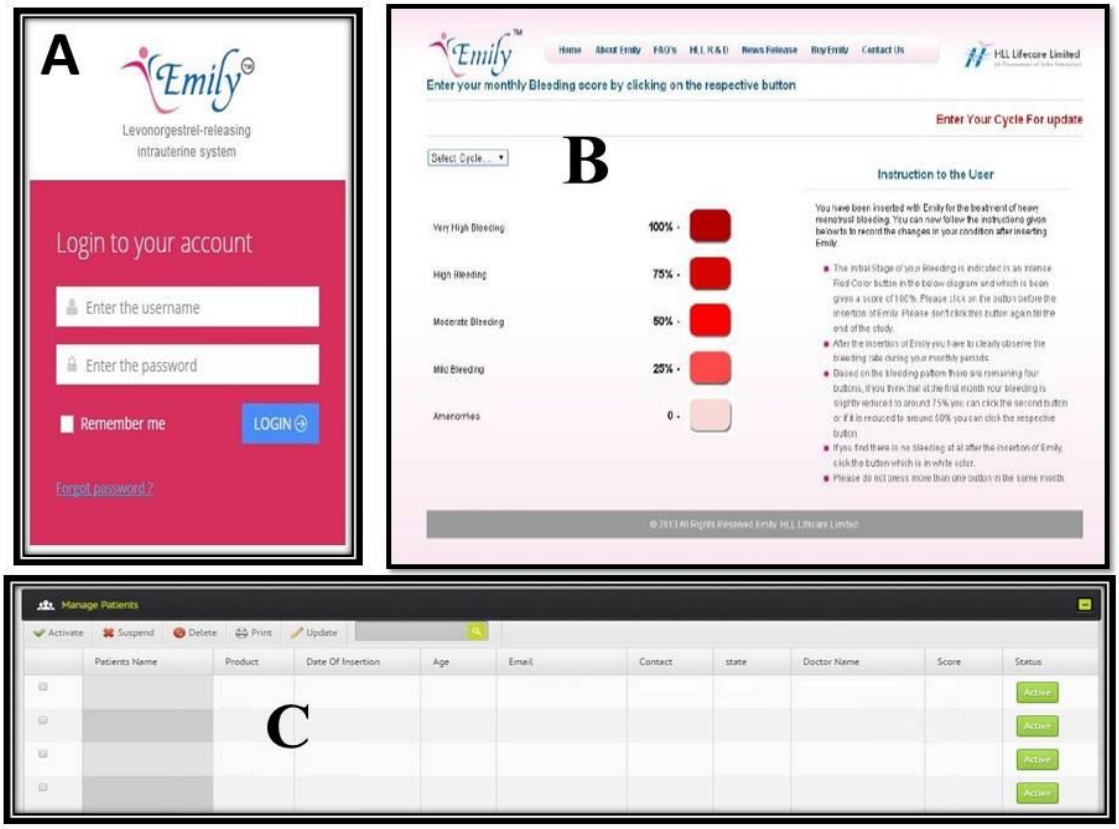

Figure 1: Emily patient management system.

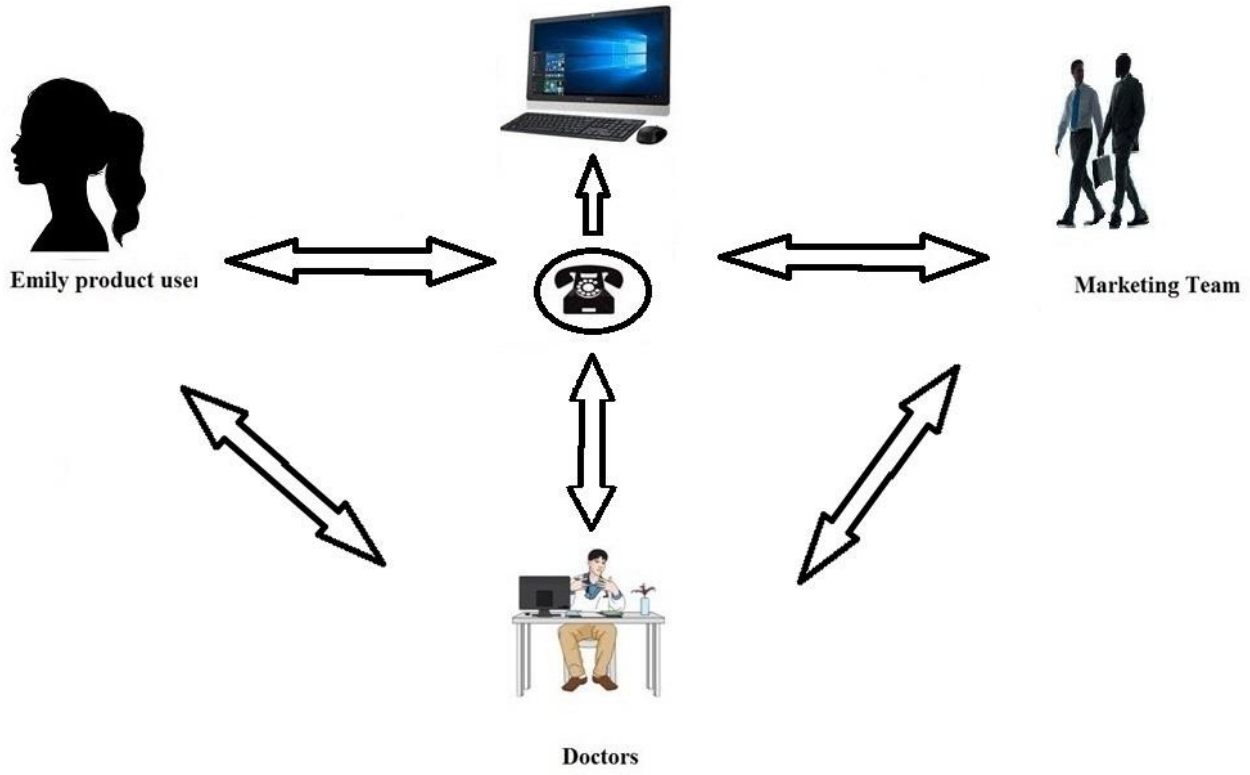

Figure 2: Data flow of Emily patient management system.

The data of Emily users across India were collected by local field staffs and transferred to the master admin having the access to the system. The master administrator will enrol the Emily user's details into the system (Figure 2). The enrolled Emily users were contacted telephonically for recording their subjective perception about their menstrual bleeding pattern after inserting Emily for a period of two years from date of insertion. A color coded menstrual bleeding score capturing system is used to enter monthly individual bleeding score. The color coding used for this survey is qualitatively designed by HLL based on the inputs from gynecologists and data recorded is based on the verbal information given by the users. The color coded system has five levels to capture different intensity of bleeding (100% - very high bleeding, 75% - high bleeding, 50% - moderate bleeding, 25% - mild bleeding, and 0% - amenorrhea). Subjective satisfaction of Emily users was recorded using a verbal quality of life questionnaire (VQoL).

Efficacy of Emily LNG-IUS was assessed by measuring mean bleeding score at baseline, year 1 and year 2. There was no SAE observed during the survey period.

Patient demographics were summarized descriptively. Categorical variables were presented as counts and percentages and continuous measures were presented as means and standard deviations. Statistical analysis was performed using repeated measures analysis of variance using SPSS version 17. A p value <0.05 was considered statistically significant.

RESULTS

Between November 2013 to January 2016, 132 women with AUB were enrolled in the feedback survey. The Emily users in the study were geographically distributed. Of the enrolled patients, 20 (15.1%) patients experienced treatment failure and 10 (7.6%) patients lost to follow up. Most common reason for lost follow up was relocation to other areas and could not be traced due to lack of contact information. In the treatment failure group, 14 (11%) patients reported expulsion, 4 (3%) patients opted hysterectomy due to heavy bleeding, and 2 (1.5%) patients opted for other hormonal methods to control bleeding. A total 102 (77.3%) Emily users successfully completed two-year of two-year follow up online survey.

In the two-year survey, all 102 patients experienced changes in their menstrual pattern −71 (69.6%) women experienced an absence of menstruation after few cycles of insertion, 6 (5.9%) women did not menstruate after insertion of the device. More than half of the patients (39 women) who had amenorrhea considered this as a positive change whereas 40.3% (31 women) expressed their concerns on possibility of developing uterine cancer or pregnancy in the absence of menstruation. Only 7 (9.1%) women were not concerned about amenorrhea. 5 (4.9%) women experienced menstruation after

approximately eight months of amenorrhea. A decrease in menstrual blood loss was reported by 20 (19.6%) women. Vaginal spotting was observed in 86 (84.3%) women. Menstrual pain after device insertion was not observed in 53 (52%) women and the device was not found to have any effect on mobility in most of the women (97.1%) (Table 1).

Table 1: Subjective perception of women's during Emily usage.

	n=102	%
Changes in the intensity of menstrual flow		
Remained Un changed	0	0
Experiencing amenorrhea after few cycles of menstruation	71	69.60
Less intense	20	19.60
Still having intense flow	0	0
Now having menstruation after having amenorrhea	5	4.901
No menstruation after insertion	6	5.88
Subjective perception on amenorrhea		
Is positive	39	54.92
Is negative	25	35.21
Doesn't bother me	7	9.85
Vaginal spotting		
Yes	43	42.15
No	59	57.84
Menstrual pain after insertion		
Yes	49	48.03
No	53	51.96
Mobility		
I have no problems in walking	99	97.05
I have some problems in walking	3	2.94
I am confined to bed	0	0

Table 2: Results of ANOVA test.

Tests of Within-Subjects Effects						
Source		**Type III sum of squares**	**Difference**	**Mean square**	**F**	**Sig.**
Months	Sphericity assumed	62919.475	11	5719.952	58.962	.000
	Greenhouse-Geisser	62919.475	2.801	22463.108	58.962	.000
	Huynh-Feldt	62919.475	2.858	22011.496	58.962	.000
	Lower-bound	62919.475	1.000	62919.475	58.962	.000
Months* Year	Sphericity assumed	41575.521	11	3779.593	38.961	.000
	Greenhouse-Geisser	41575.521	2.801	14843.026	38.961	.000
	Huynh-Feldt	41575.521	2.858	14544.613	38.961	.000
	Lower-bound	41575.521	1.000	41575.521	38.961	.000
Error (months)	Sphericity assumed	215557.087	2222	97.010		
	Greenhouse-Geisser	215557.087	565.805	380.974		
	Huynh-Feldt	215557.087	577.413	373.315		
	Lower-bound	215557.087	202.000	1067.114		

Based on VQoL data, 78 (76.5%) women were highly satisfied with the LNG-IUS device, 16 (15.7%) were moderately satisfied, and 8 (7.8%) users were not willing to provide any comments. None of the Emily users were dissatisfied with the usage (Figure 3).

All 102 patients were included in the efficacy analysis. Mean bleeding score reduced from 100 (SD=0) at baseline to 18.79 (SD=13.36) at the end of year 1 and 10.8 (SD=12.4) at the end of year 2 (paired t-test = 9.37; $p<0.0001$). The repeated measures using ANOVA (tests of within-subjects effect) performed with Greenhouse-Geisser correction, demonstrated a decrease in the mean scores in the intensity of menstrual bleeding scores between the two years as well as months within those years. (Figure 4) shows the monthly trend in the change in the mean intensity of menstrual bleeding over two-year study period The tests showed that the mean intensity of

menstrual bleeding decreased significantly over the two 12 month periods of study (F (2.801, 565.805)= 38.961, p<0.0001) (Table 2). The F value is termed as the ratio of the mean regression sum of squares divided by the mean error sum of squares. The value ranges from zero to an arbitrarily large number. The value of Prob (F) is the probability that the null hypothesis for the full model is true (i.e., that all of the regression coefficients are zero). The ANOVA F-test statistic is the ratio of the average variability among groups to the average variability within groups.

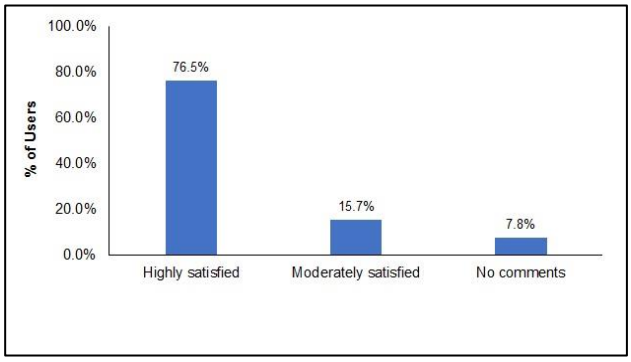

Figure 3: Emily user satisfaction rate.

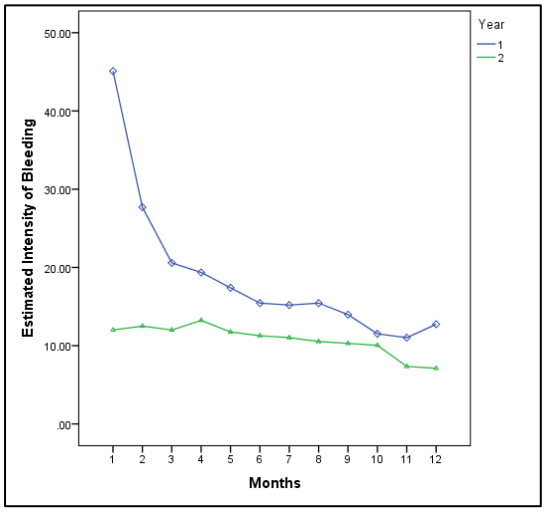

Figure 4: Mean 1st year and IInd year bleeding score of Emily users.

DISCUSSION

The present survey effectively showed that during the course of Emily usage there was a significant reduction of bleeding score by second year. LNG-IUS is a small drug delivery device that has proven efficacy to treat a range of gynaecological conditions including AUB, endometrial hyperplasia, adenomyosis, and uterine leiomyoma.[12] Numerous studies have demonstrated efficacy and safety of LNG-IUS device currently employed to treat an array of gynaecological disorders.[12-14] Despite its therapeutic benefits, its widespread usage and acceptance has been limited.[15] The high cost coupled with high discontinuation rate due to side effects and dissatisfaction has been the major issues for its limited use.[11]

Emily is an affordable LNG-IUS device developed to overcome these limitations and enhance its accessibility among women. Emily LNG-IUS is primarily marketed in India as a cost-effective therapeutic option for the treatment. In a recent clinical study, we have already demonstrated clinical efficacy and tolerability of Emily LNG-IUS use among patients with AUB. In this study, we used telephonic assessment of bleeding pattern of Emily users and entered the values in to the qualitative monitoring tool for measuring the bleeding score. Users with a 100% bleeding were considered to have AUB and the reduction in percentage of bleeding was subsequently assessed after insertion of Emily.

Results from the present survey showed that there was in the mean bleeding score significant reduction during the two year use. Additionally, this survey observed that this device lowered the incidence of treatment failures and most of the Emily users attained amenorrhea during the course of usage. Taken together, the data from this study suggests that Emily LNG-IUS is a potent and effective, interventional strategical device for treating AUB patients who have been referred to undergo hysterectomy. Its ability to release levonorgestrel hormone in controlled and sustained pattern for a period of five years, reduced the frequency and amount of menstrual bleeding. The ease of insertion and removal of this device and its cost-effectiveness makes it a better therapeutic option compared to its competitor. However, some menstrual disturbances were observed initially which could limit its use by clinicians, but the expulsion rate of Emily during this survey was equal to that of our previous reports only (11%).

Major limitations of this study include the data storage capacity of the in- house system and the nature of this survey as it was purely based on perception of the users. A validated and upgraded platform with robust data capacity and more options has been created to capture the data from all sites across India (data not shown). Mobile applications will also be developed to capture the data from users effectively for long term user feedbacks. Despite these limitations, the increased satisfactions together with clinical benefits are compelling and support benefit from the Emily LNG-IUS for women with AUB.

In conclusion, data from this survey suggests that Emily LNG-IUS could be an effective device for the treatment of AUB. Additionally, recent studies proved that use of LNG-IUS is effective in reducing menorrhagia associated with leiomyomas with improvement in haemoglobin levels and may be a simple and effective alternative to surgical treatment of AUB- Leiomyoma without significant influence on the volume of leiomyoma and ovarian and uterine volume.[12,13] Further, future explorative clinical studies with larger sample size are

warranted to assess the clinical efficacy and safety of Emily LNG-IUS in other indications.

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