EveCare capsule

Evaluation of efficacy and safety in menorrhagia

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ABSTRACT

The present study was planned to evaluate the efficacy and safety of EveCare capsule, a polyherbal formulation, in menorrhagia. Menstrual problems account for much of the morbidity that occurs in women of reproductive age. Menorrhagia is defined as excessive uterine bleeding occurring at regular intervals or prolonged uterine bleeding lasting more than seven days. Patient distress may be related more to disruptions in work, sexual activity, or quality of life than menstrual volume alone.

This study was an open, non-randomized, prospective clinical trial conducted as per the ethical guidelines of Declaration of Helsinki. Thirty one patients, who complained of excessive, irregular/prolonged bleeding per vaginum, were included in this study. Patients who had systemic illness and those who had organic lesion of the reproductive tract, especially any benign or malignant growth, extensive cervical erosion, cervical polyps, endometriosis, tubercular endometritis and acute infective disorder, and patients with history of recent delivery or abortion were excluded from the study.

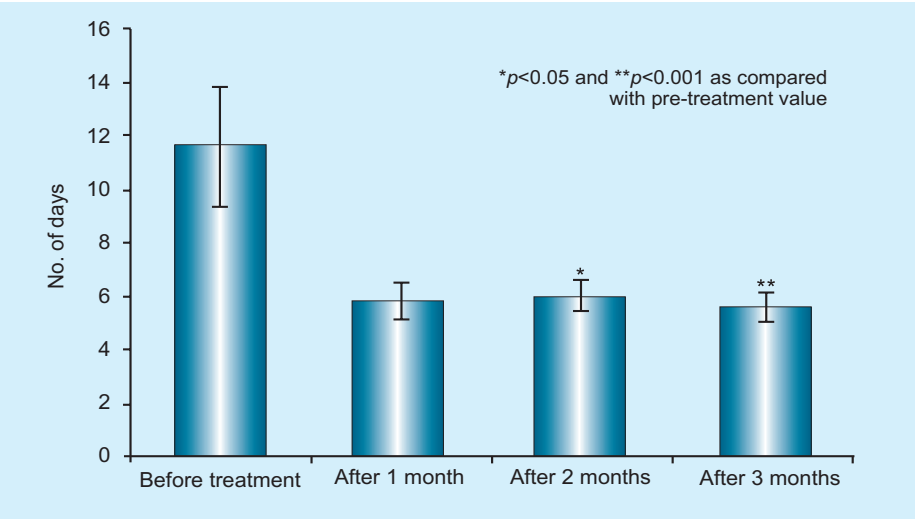
Thorough history, clinical examination and symptomatic evaluation were carried out and the details were noted down in the CRF. All patients were followed up every month till the end of treatment on 3rd month and symptomatic evaluation and clinical examination was done, along with recording the occurrence of any adverse event/s (either reported or observed). All the patients were investigated before and after treatment for routine blood examination for Hb, TC, DC and ESR, endometrial biopsy, ultrasound scan, and pap smear.

Thirty one patients were enrolled in the study and all the patients completed the study. A significant ($p<0.001$) reduction was observed in the mean score of duration of menstruation, quantity of blood loss and blood flow loss at the end of the 3-month treatment. The reduction in the symptoms started appearing from the 2nd month of therapy itself. A significant change in the mean score of character of blood flow was observed at the end of 3 months of treatment with EveCare. There was a significant rise in the mean Hb level from 9.12 ± 1.87 to 10.76 ± 1.54 at the end of therapy as compared to the baseline. Out of 13 patients who had associated dysmenorrheal symptoms, 9 patients obtained (63%) significant ($p<0.05$) complete relief from the symptoms. Therefore, it may be concluded that EveCare capsule is clinically safe and effective in the management of menorrhagia.

INTRODUCTION

Menstrual problems account for much of the morbidity that occurs in women of reproductive age, being one of the four most common reasons for consulting a general practitioner.[1] Specifically, menorrhagia (excessive menstrual loss) is one of the most common reasons for referral to gynecology clinics.[2] Menorrhagia

Figure 1. Reduction in duration of menstruation with EveCare capsule treatment (Mean ± SEM)



represents a major public health problem in women. As many as 10-15% of women experience menorrhagia during their lifetime.[3] Menorrhagia is defined as excessive uterine bleeding occurring at regular intervals or prolonged uterine bleeding lasting more than seven days.[1] The classic definition of menorrhagia (i.e., greater than 80 mL of blood loss per cycle) is rarely used clinically. Women describe the loss or reduction of daily activities as more important than the actual volume of bleeding. Average menstrual blood loss is between 30 and 40 mL per cycle.[2] An early population-based study concluded that the upper limit of normal menstrual blood loss was between 60 and 80 mL. A greater prevalence of impaired iron status was noted with a loss of more than 60 mL.[4]

Organic disease is relatively uncommon with menorrhagia, but treatment typically involves powerful drugs or invasive surgery.[5] Patient distress may be related more to disruptions in work, sexual activity, or quality of life than menstrual volume alone.

Benign disorders of the uterus may present with the complaint of excessive menstrual blood loss and/or an associated irregularity in the pattern of menstrual bleeding. Such benign disorders include endometrial polyps, fibroids and adenomyosis. However, the vast majority of women complaining of excessive menstrual blood loss have normal endometrium.[6]

Menorrhagia can result in severe anemia. One consequence of excessive menstrual loss is iron deficiency anemia. In the western world, menorrhagia is the commonest cause of iron deficiency anemia, and low hemoglobin concentrations may predict objectively heavy menstrual loss.[7]

Treatment of menorrhagia results in substantial improvement in quality of life. The treatment of choice for anovulatory bleeding is medical therapy with oral contraceptive pills or progestogens. Oral progestogens are the most commonly prescribed therapy for menorrhagia.[8] Although used as a contraceptive, the levonorgestrel-releasing intrauterine device (IUD) produces significant

Table 1. Improvement in clinical response with EveCare capsule treatment (Mean ± SEM)

Menstrual symptoms		Before treatment	After 1 month	After 2 months	After 3 months
Duration of menstruation (No. of days)	Mean	11.58	5.808	6.00	5.538
	SEM	2.248	0.7212	0.5602	0.5526
	p value		NS	*p*<0.05	*p*<0.001
Quantity of blood loss (No. of diapers changed/day)	Mean	5.452	3.968	4.258	3.839
	SEM	0.4516	0.5153	0.3738	0.3118
	p value		NS	*p*<0.05	*p*<0.001
Blood flow loss (Profuse to normal) (Mean score)	Mean	1.533	1.033	1.000	0.6000
	SEM	0.1417	0.1552	0.1269	0.1232
	p value		NS	NS	*p*<0.001
Character of blood flow (Clot or Flow) (Mean score)	Mean	1.000	0.7333	0.8000	0.5000
	SEM	0.0000	0.0821	0.0242	0.0928
	p value		NS	NS	*p*<0.05

Statistical analysis was carried out using Repeated ANOVA test and Friedman test, followed by Dunnett's Multiple Comparison Test.

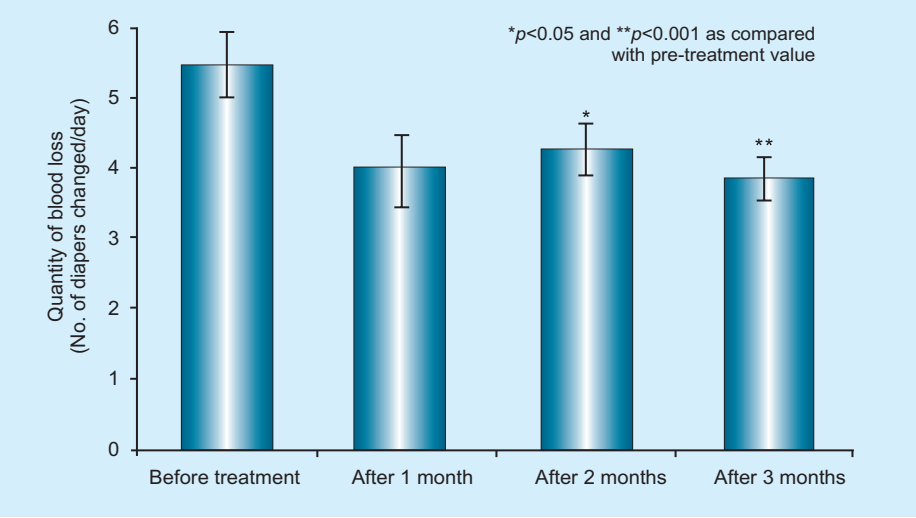
Abbreviations: NS : Not significant

Table 2. Improvement in hemoglobin level after treatment with EveCare capsule (Mean ± SEM)

Parameters	Before treatment	After treatment	Significance
Hb (%)	9.119 ± 1.875	10.76 ± 1.537	$p<0.0001$, t=6.726 df=30, $R^2=0.6013$

Statistical analysis was carried out using paired '*t*' test.

Figure 2. Reduction in quantity of blood loss with EveCare capsule treatment (Mean ± SEM)



reductions in menstrual blood loss. There is insufficient evidence to assess the effectiveness of monthly oral contraceptive pills for reducing menorrhagia.[9] But currently there is no safe, effective therapy available for menorrhagia.

EveCare capsule is a polyherbal formulation that comprises extracts of *Saraca indica, Boerhaavia diffusa, Symplocos racemosa, Tinospora cordifolia, Solanum nigrum, Aspargus racemosus, Aloe vera, Santalum album, Cyperus rotundus, Adhatoda vasica,* Triphala, Dashamoola, Trikatu, *Bombax malabaricum;* and powders of *Kasisa, Godanti bhasma* and *Yashada bhasma*. The present study was planned to evaluate the efficacy and safety of EveCare, a polyherbal formulation, in menorrhagia.

PATIENTS AND METHODS

Inclusion criteria

Thirty one patients, who complained of excessive, irregular/prolonged bleeding per vaginum and attended the gynecology OPD of the Department of Obstetrics & Gynecology, Safdarjang Hospital, New Delhi, India were included in this study. A written informed consent was obtained from all patients.

Exclusion criteria

Patients who had systemic illness like hypertension, renal disease, tuberculosis, hepatic disease, diabetes, coagulation disorder, etc., and those who had organic lesion of the reproductive tract, especially any benign or malignant growth, extensive cervical erosion, cervical polyps, endometriosis, tubercular endometritis and acute infective disorder, and patients with history of recent delivery or abortion, and those patients who refused to give informed consent, were excluded from the study.

STUDY PROCEDURES

The study was an open, non-randomized and non-comparative, prospective, phase III clinical trial, conducted at the Department of Obstetrics & Gynecology, Safdarjang Hospital, New Delhi, India as per the ethical guidelines of Declaration of Helsinki. The study protocol, case report forms (CRFs), regulatory clearance documents, product related information and informed consent forms (in English and Hindi) were submitted to the institutional ethics committee and were approved by the same.

The patients who attended the OPD gynecology unit of Safdarjang Hospital, New Delhi were informed about the study drug, its effects, patient's duration of stay in the trial, and overall plan of the study. The patient was included in the clinical study only after a written informed consent was obtained from them, and a witness, independent of the clinical trial, signed the informed consent form.

The history was noted by interviewing the patient. Thorough clinical examination and symptomatic evaluation was carried out and the details were noted down in the CRF. Patients were advised to take 2 capsules of EveCare, twice daily for 3 months.

All patients were followed up every month till the end of treatment (3rd month) and symptomatic evaluation and clinical examination was done, along with recording the occurrence of any adverse event/s (either reported or observed).

All the patients were investigated before and after treatment for routine blood examination for Hb, TC, DC and ESR, endometrial biopsy, ultrasound scan, and pap smear.

Primary and secondary outcome measures

The predefined primary outcome measures were reduction in the

Table 3. Number of patients with improvement in dysmenorrhea (pain in abdomen) after treatment with EveCare capsule

	Present (No. of patients)	Absent (No. of patients)	Significance
Pre-treatment	13	18	$p<0.0212$
Post-treatment	4	27	

Statistical analysis was carried out using Fisher's exact test.

symptom scores of menorrhagia and improvement in the anemic status of patients. The predefined secondary endpoints were short- and long-term safety, and overall compliance to the drug treatment.

ADVERSE EVENTS

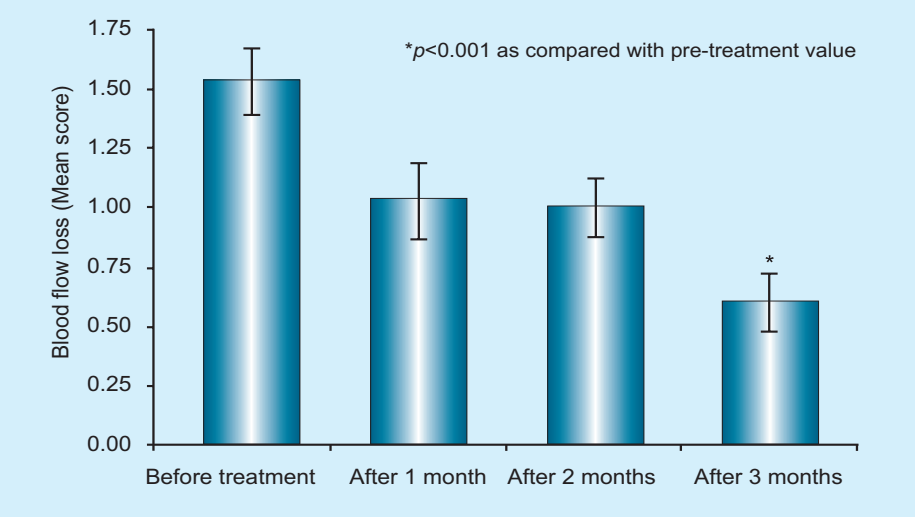
All adverse events, reported or observed by patients, were recorded with information about severity, date of onset, duration, and action taken regarding the study drug. Relation of adverse events to study medication were predefined as unrelated (a reaction that does not follow a reasonable temporal sequence from the administration of the drug), possible (follows a known response pattern to the suspected drug, but could have been produced by the patient's clinical state or other modes of therapy administered to the patient), and probable (follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the patient's clinical state).

Patients were allowed to voluntarily withdraw from the study, if they experienced serious discomfort during the study or sustained serious clinical events requiring specific treatment. For patients withdrawing from the study, efforts were made to ascertain the reason for dropout. Non-compliance (defined as failure to take less than 80% of the medication) was not regarded as treatment failure, and reasons for non-compliance were noted.

STATISTICAL ANALYSIS

Statistical analysis was done according to intention-to-treat principles. Repeated ANOVA and Friedman's test followed by Dunnett's multiple comparison test for evaluation of symptomatic scores, and Paired Student '*t*' test for evaluation of Hb% improvement by comparing baseline values and end-of-the-treatment values was used. The minimum level of significance was fixed at 95% confidence limit and a 2-sided p value of <0.05 was considered significant.

Figure 3. Improvement in mean score of blood flow loss with EveCare capsule treatment (Mean ± SEM)



RESULTS

Thirty one female patients were enrolled in the study and all the patients completed the study. The mean age of the patient was 34.55 years.

On starting EveCare capsule therapy, a significant ($p<0.001$) reduction was observed in the mean score of duration of menstruation, quantity of blood loss as assessed by the number of diapers changed per day, and blood flow loss graded as profuse to normal at the end of the 3-month treatment. The reduction in the symptoms started appearing from the 2nd month of therapy itself. A significant change in the mean score of character of blood flow from clot to flow was observed at the end of 3-month treatment with EveCare capsules (Table 1 and Figures 1 to 4).

There was a significant rise in the mean Hb% level from 9.12 ± 1.87 to 10.76 ± 1.54 at the end of the therapy as compared to baseline (Table 2 and Figure 5). Out of 13 patients who had associated dysmenorrheal symptoms, 9 patients obtained (63%) significant ($p<0.05$) complete relief from the symptoms (Table 3 and Figure 6).

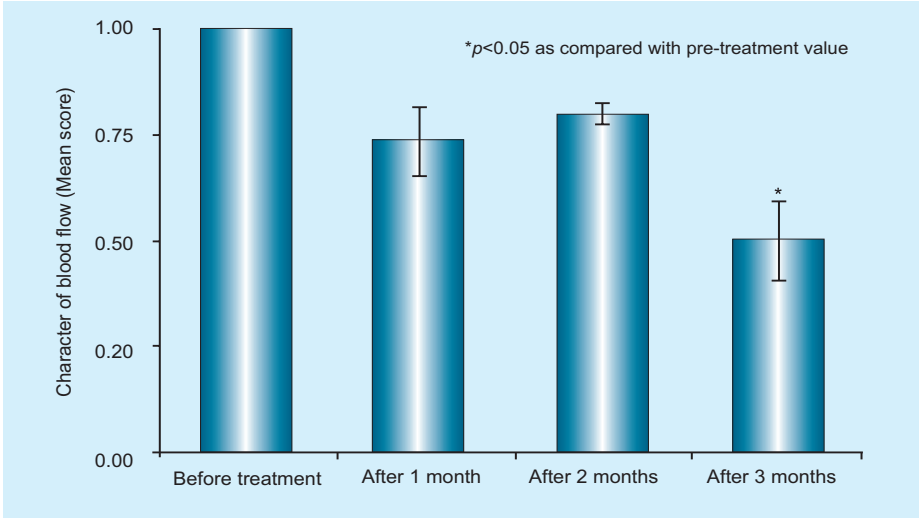
There was no change in the hematological investigations (TC, DC or ESR), pap smear, or ultrasound scan, or endometrial biopsy done before and after treatment.

There were no clinically significant adverse events, either reported or observed, during the study period.

DISCUSSION

Unacceptable heavy menstrual blood loss affects 10-30% of women of reproductive age and up to 50% of

Figure 4. Improvement in mean score of character of blood flow with EveCare capsule treatment (Mean ± SEM)



perimenopausal women.[11,12] It is also estimated that 5% of women aged 30-49 years will consult their general practitioner for excessive blood loss each year. These patients account for 15% of all referrals to gynecologists and over 300,000 hysterectomies annually.[13]

The clinical features associated most strongly with blood loss volume include the rate of change of sanitary protection during full flow, and the total number of pads and tampons used. Other associations include the size of clots and the number of clots greater than about 1 inch in diameter. A low ferritin level correctly predicts 60% of women with periods with measured losses of more than 80 mL; therefore, a loss of more than 80 mL can be predicted moderately well by a model that includes ferritin levels, clot size, and the rate of pad change during full flow.[14-16]

Menorrhagia can be associated with both ovulatory and anovulatory ovarian cycles. It is important to distinguish the menstrual consequences of each cycle. Ovulatory ovarian cycles give rise to regular menstrual cycles whereas anovulatory cycles result in irregular menstruation or, extremely, amenorrhea. Other disorders may be associated with excessive loss, for example, fibroids and adenomyosis, but the association may not always be causal. Endocrine disorders do not cause excessive menstrual loss, with the exception of the endocrine consequences of anovulation. Equally, except in selected populations, hemostatic disorders are rare causes of menorrhagia despite suggestions to the contrary.[17]

Medical treatment can be conveniently divided into non-hormonal and hormonal therapy. The two main first line treatments for menorrhagia associated with ovulatory cycles are non-hormonal; the antifibrinolytic tranexamic acid and non-steroidal anti-inflammatory drugs. Traditionally, hormonal therapy for menorrhagia has been progestogens given during the luteal phase of the cycle. Such treatments are ineffective. Progestogens are effective when given for 21 days in each cycle, but the side effects may be such that patients would not choose to continue with treatment.[18,19]

The combined contraceptive pill is both an effective contraceptive and treatment for menorrhagia when compared with other medical treatment.[20] More fully evaluated is the recently licensed levonorgestrel-releasing intrauterine device.

In the present study, a significant reduction was observed in the mean score of duration of menstruation, quantity of blood loss as assessed by the number of diapers changed per day, and blood flow loss graded as profuse to normal at the end of 3 months of treatment with EveCare capsule. The reduction in the symptoms started appearing from the 2nd month of therapy itself. A significant change in the mean score of character of blood flow from clot to flow was observed at the end of 3-month treatment with EveCare. There was a significant rise in the mean Hb% level at the end of the therapy as compared to baseline. Out of 13 patients, who had associated dysmenorrheal symptoms, 9 patients obtained (63%) significant complete relief from the symptoms. These clinical benefits might be due to the actions of its main ingredients whose effects are already well documented.

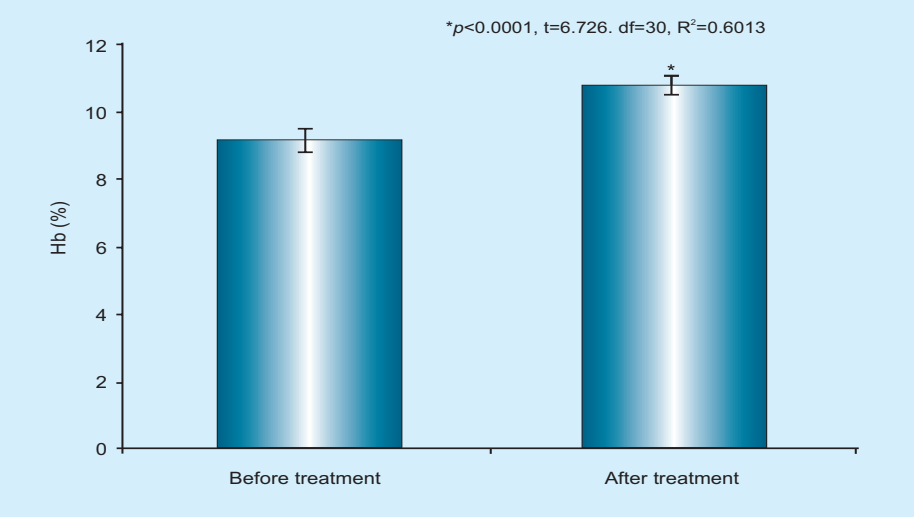
Saraca indica has been well proven for its effectiveness in menorrhagia and dysmenorrhea.[21] It also has a stimulatory effect on the ovarian tissue, which may produce an oestrogen-like activity that enhances the repair of the endometrium and stops bleeding. *Symplocos racemosa* has been reported to be useful in the treatment of menorrhagia and other uterine disorders.[22] *Symplocos racemosa* exhibits relaxant and antispasmodic effects on several spasmogens on uterine smooth muscles, attributing favorable actions to the drug in dysmenorrhea and as a uterine sedative.[23]

The ethanolic extract of *Boerhaavia diffusa* was found to stop intrauterine-contraceptive-device-induced bleeding in monkeys. This herb is also known for its anti-inflammatory and analgesic property which is comparable to that of ibuprofen. The drug has also proved useful as a hematinic.[24]

Cyperus rotundus has been utilized in the treatment of anemia and general weakness.[25]

Aloe vera also possesses oxytocic property.[26] *Adhatoda vasica* has antihemorrhagic activities, beneficial in DUB and thus a useful remedy in disorders of the uterus, and especially used as a uterine hemostatic in menorrhagia and metrorrhagia.[27] *Tinospora cordifolia*[28] and *Solanum nigrum*[29] have

Figure 5. Improvement in hemoglobin percentage level after treatment with EveCare capsule (Mean ± SEM)



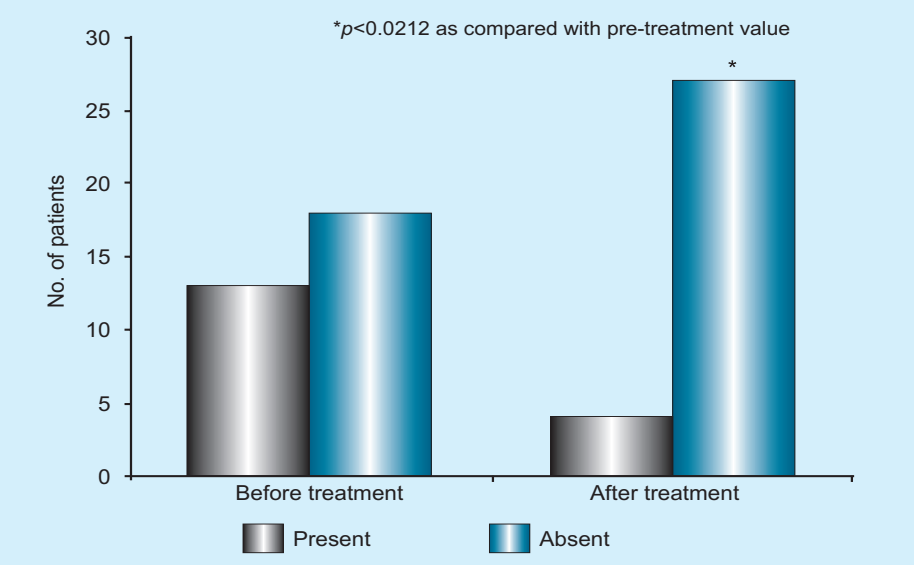
adaptogenic activity. Therefore, the observed clinical benefits of EveCare capsule might be due to the synergistic actions of its ingredients.

CONCLUSION

Menorrhagia represents a major public health problem in women. Women describe the loss or reduction of daily activities as more important than the actual volume of bleeding. There are no safe and effective treatment for menorrhagia available currently. The present study was planned to evaluate the efficacy and safety of EveCare capsule, a polyherbal formulation, in menorrhagia.

The present study showed a significant reduction in the mean score of duration of menstruation, quantity of blood loss and blood flow loss at the end of 3 months of treatment with EveCare capsule. The reduction in the symptoms started appearing from the 2nd month of therapy itself. A significant change in the mean score of character of blood flow was observed at the end of 3 months of treatment with EveCare capsule. There was a significant rise in the mean Hb% level at the end of the therapy as compared to baseline. There were no clinically significant adverse events, either reported or observed, during the study period. Therefore, it may be concluded that EveCare capsule is safe and effective in the treatment of menorrhagia.

Figure 6. Number of patients with improvement in dysmenorrhea (pain in abdomen) after treatment with EveCare capsule (Mean ± SEM)



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