

Evaluation of Efficacy and Safety of a Herbal Formulation Evicare in the Management of Menstrual Irregularities: Meta-Analysis of 8 Clinical Studies

Dr. Mukta P Umarji¹, Dr. Jyothi .G .S.²

MBBS., MD., DGO., Consulting Gynecologist, Umarji Hospital, Shukrawarpet, Pune, Maharashtra, India

MBBS., MD(OBG)., PGDMLE., Professor of OBG, Department of OBG, M.S. Ramaiah Medical College and Hospital, Bangalore 560054, Karnataka, India

Abstract: *Aim of the study: The aim is to carry out the meta-analysis of 8 clinical trials for evaluating the efficacy and safety of menstrual irregularities. Material and Methods: This is a meta-analysis of 8 clinical trials on Evicare in various menstrual irregularities. Inclusion criteria: Clinical studies, which evaluated the role of Evicare in various menstrual irregularities, were included in the meta-analysis. The outcome variables included measurement data on changes in clinical symptoms and signs, laboratory results, and incidence of adverse events during/after treatment. Exclusion criteria: Experimental, Phase I and Phase II clinical studies were excluded from the meta-analysis. Study procedure: The list of 08 clinical studies included for the meta-analysis is provided in Table 1. From each study, the demographic data of patients on entry was tabulated Table 2. The duration of treatment varied from 2 -3 months and in most of the studies, Evicare was given at a dose of 1-2 capsules twice daily or Evicare Syrup-10-15 ml twice daily. Summary and conclusion: Present Meta -analysis of clinical studies indicate safety and efficacy of Evicare in normalizing menstrual irregularities, along with reduction in excessive menstrual bleeding and normalization of character and duration of menstrual flow. Improvement in anemia and altered hormonal levels was also noted in clinical studies.*

Keywords: Meta-analysis, Evicare, menstrual irregularities

1. Introduction

Menstrual irregularities are problems with a woman's normal monthly period and decide women's health. After a teen has been menstruating for a few years, her menstrual cycle typically becomes more regular. For most women, a normal menstrual cycle ranges from 21 to 35 days¹. However, up to 14% of women have irregular menstrual cycles or excessively heavy menstrual bleeding.

Menstrual irregularities have complex presentations with involvement of psyche, neuronal and endocrinal systems. Menstrual irregularities or their symptoms, such as abnormal vaginal bleeding, can be caused by a wide variety of abnormal conditions, including pregnancy, hormonal imbalances or changes, infection (sexually transmitted diseases and other infections), malignancy (cervical, uterine or vaginal cancer), trauma, and certain medications. In premenstrual syndrome, there is a cyclic reappearance of symptoms during the last 7-10 days of menstrual cycle, which are not caused by any organic disease.

As per statistical analyses and surveys, the presence of decreased menstruation was reported in 11.3% and 6.7% of college and urban population respectively^{2,3}. Approximately 4-8% of women have menstrual periods longer than 7-8 days when interviewed^{4,5}. Similarly, the self-reported prevalence of excessive, profuse or heavy bleeding is 4-9%,^{4,6-8}. Self-reported prevalence of bleeding between periods is 5-17%,^{9,10} Short cycles of less than 21 days were self-

reported by 1-6% of^{11,5}. Severe pain or pain that kept a woman from work or her daily activities ranged from 3% to 18%^{4,8,12} Prevalence of abnormal uterine bleeding were higher when women were interviewed by a physician.

Most abnormal uterine bleeding can be divided into anovulatory (Irregular/infrequent periods with absent, minimal, or excessive bleeding) and ovulatory (Periods that occur at regular intervals but are characterized by excessive bleeding or duration of greater than 7 days) patterns.¹³

Although many women experience some discomfort, these premenstrual changes do not disrupt their daily routine. In some women, however, they are characterized by debilitating mood and behavioural changes, in the week preceding menstruation, that interfere with their normal daily functioning. Overall, approximately 75% of the general population encounter some kind of premenstrual symptom¹⁴. If specific diagnostic criteria for PMS are used, 3 to 8% of women with regular cycles can be diagnosed with PMS.

Apart from the hormonal or drug therapies available for the treatment of menstrual irregularities of various forms, usage of medicinal plants with known therapeutic benefits individually or in polyherbal formulations will also contribute to treat and improve the quality of life in menstrual irregularities. Holistic herbal therapies like Evicare, have been studied clinically for their safety and efficacy in menstrual irregularities.

1.1 Aim of the Study

The aim is to carry out the meta-analysis of 8 clinical trials for evaluating the efficacy and safety of menstrual irregularities.

2. Material and Methods

This is a meta-analysis of 8 clinical trials on Evicare in various menstrual irregularities.

2.1 Inclusion criteria

Clinical studies, which evaluated the role of Evicare in various menstrual irregularities, were included in the meta-analysis. The outcome variables included measurement data on changes in clinical symptoms and signs, laboratory results, and incidence of adverse events during/after treatment.

2.2 Exclusion criteria

Experimental, Phase I and Phase II clinical studies were excluded from the meta analysis.

2.3 Study procedure

The list of 08 clinical studies included for the meta-analysis is provided in Table 1. From each study, the demographic data of patients on entry was tabulated Table 2. The duration of treatment varied from 2-3 months and in most of the studies, Evicare was given at a dose of 1-2 capsules twice daily or Evicare Syrup-10-15 ml twice daily. The incidence and type of adverse events reported by various studies were also tabulated separately.

2.4 Primary and secondary endpoints

The predefined primary endpoints are normalization of clinical symptoms of menstrual disorders and additionally improving Hemoglobin levels and normalizing the hormone levels. Secondary end points were the safety of the formulation from the Meta-analysis.

2.5 Statistical analysis

Statistical analysis was carried out according to intention-to-treat principles. Changes in various parameters from baseline values and values at the end of the study were pooled and analyzed cumulatively using Paired 't' test or Friedman test, followed by Dunnett's Multiple Comparison test. Values are expressed as Mean \pm SD. The minimum level of significance was fixed at 95% confidence limit and a 2-sided *p* value of <0.05 was considered significant. Statistical analysis was performed using GraphPad Prism, Version 4.03 for Windows, GraphPad Software, San Diego, California, United States. www.graphpad.com

3. Results

Eight clinical trials were included in the Meta-analysis involving 421 women with various menstrual irregularities. The list of clinical trial which were included for the Meta-

analysis are listed in Table 1. The age (Mean \pm SD) of patients included in all studies was 31.30 ± 4.86 years and the duration of treatment was for period of 3 months Table 2.

The following parameters were evaluated in this Meta-analysis. It included Clinical parameters like Dysmenorrhea, Menorrhagia, Character, Menstrual duration and the laboratory parameters included were Hemoglobin and Hormonal assay comprising of FSH, LH, Oestrogen and Progesterone levels.

Dysmenorrhea was evaluated in 155 patients and analysis of this data indicates that there was a significant decrease in Dysmenorrhea Score, which was 1.89 ± 1.37 at baseline to 1.39 ± 1.13 , 0.86 ± 0.91 to 0.53 ± 0.79 mean score at 1st, 2nd and 3rd month of treatment respectively (Figure 1).

Menorrhagia was analyzed in 166 patients who had received Evicare for 3 months and the results showed that there was a significant decrease in the number of pads used from 5.90 ± 2.32 to 4.89 ± 2.36 , 4.34 ± 2.14 to 4.02 ± 2.09 from baseline to 1st, 2nd and 3rd month of treatment, respectively (Figure 2).

In 103 patients, data was available regarding the Character of menstruation. Analysis of this data indicates that there was a significant decrease in Severity of menstrual flow. The score improved from 2.67 ± 1.59 from baseline to 2.21 ± 1.59 , 1.73 ± 1.50 to 1.40 ± 1.52 at 1st, 2nd and 3rd month of treatment respectively with statistical significance of $p < 0.001$ (Figure 3). The outcome indicates that the character of menstruation from profuse heavy bleeding improved to normal menstruation.

Menstrual duration was analyzed in 166 patients and the results showed that there was a significant improvement in the menstrual duration. It decreased from 7.90 ± 3.35 to 5.92 ± 2.45 , 5.34 ± 1.98 to 4.93 ± 1.97 from baseline to 1st month 2nd month 3rd month respectively with a significant improvement was observed, which indicates that menstrual duration was normal with Evicare treatment (Figure 4).

Hemoglobin levels (n=208), showed a significant improvement from baseline values versus 3 months after treatment (9.94 ± 1.75 to 10.70 ± 1.43 ; $p < 0.001$) in all patients. The severity of anemia were categorized as mild, moderate and severe anemic based on the WHO classification. Improvements in patients with severe anemia was from 7.36 ± 0.57 to 9.25 ± 0.72 ($p < 0.0001$) followed by in moderate anemia cases where it improved from 8.87 ± 0.56 to 9.81 ± 0.78 ($p < 0.0001$) and 10.74 ± 0.61 to 11.2 ± 0.91 ($p < 0.0001$) in mild anemic cases. No significant difference in hemoglobin was observed in the patient with normal baseline values. 12.63 ± 0.58 to 12.74 ± 0.86 though there was a trend in improvement (Figure 5).

The mean differences in the increase of hemoglobin levels from the baseline to end of the treatment period was based on severity of anemia (mild, moderate and severe) at baseline (Figure 6).

The Serum hormone levels such as Oestrogen (125 subjects), progesterone (56 subjects), FSH(56 subjects), and LH(56 subjects), were estimated before and after treatment. No significant changes were observed in FSH and LH levels. Oestrogen levels showed a significant decrease at 3 months of treatment compared to baseline (116.20 ± 75.24 to 99.42 ± 64.90 ; $p < 0.0001$). Normal levels of estrogen will frequently fluctuate in a menstrual cycle. Normal levels ranges between 45 pg/ml during menstruation and increases to 400 pg/ml at ovulation which quickly fall during secretory phase. Hence the changes in the level of Oestrogen cannot be considered as critical parameter in menstrual disorders. Progesterone levels, significantly improved from 6.51 ± 7.84 to 9.27 ± 10.72 with a significance of $p < 0.0493$ (Table 3).

The Overall impression by the investigator is presented in the (Figure 7). Treatment with Evecare for 3 months showed cured in 20% of the patients, marked to moderate improvement was observed in 45% of the patients and slight improvement in 22.5% of the patients, which shows that 87.5% of the cases showed mild to excellent improvements. No change in symptoms was seen in 10% and /worsening of the symptoms was observed in 2.5% of the patients.

4. Discussion

Diagnosis starts with a thorough medical history, including a detailed discussion of a woman's menstrual periods, what is normal for her, and what irregularities are occurring. A physical examination will also be conducted and when necessary, a pelvic exam. In cases where a woman is sexually active, a pregnancy test and screening for infections may also be performed. Treatment of menstrual irregularities varies and is tailored to the individual case, the underlying cause, the severity of symptoms, and the presence of any complications.

Various aetiological factors, the most common being oligomenorrhoea, polymenorrhoea, menorrhagia, metrorrhagia, menometrorrhagia, hypomenorrhoea and intermenstrual bleeding, have been implicated as causes. Emotional and behavioral problems may exacerbate menstrual cycle problems.

Thorough literature survey on herbal formulations has provided a list of natural remedies for symptoms related to hormonal and physiological imbalances. Several plants are known to be effective in treating hypogonadism, irregular menses, amenorrhoea and other menopausal problems¹⁵. EveCare capsule is a polyherbal formulation that comprises extracts of *Saraca indica*, *Boerhaavia diffusa*, *Symplocos racemosa*, *Tinospora cordifolia*, *Solanum nigrum*, *Asparagus racemosus*, *Aloe vera*, *Santalum album*, *Cyperus rotundus*, *Adhatoda vasica*, Triphala, Dashamoola, Trikatu, and *Bombax malabaricum*; and powders of Kasisa, Godanti bhasma and Yashada bhasma.

Saraca indica has been well proven for its effectiveness in menorrhagia and dysmenorrhoea.¹⁶ 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.¹⁷ *Symplocos racemosa* exhibits

relaxant and antispasmodic effects on several spasmogens on uterine smooth muscles, attributing favorable actions to the drug in dysmenorrhoea and as a uterine sedative.¹⁸

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.¹⁹

Cyperus rotundus has been utilized in the treatment of anemia and general weakness.²⁰ *Aloe vera* also possesses oxytocic property.²¹ *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.²² *Tinospora cordifolia*²³ and *Solanum nigrum*²⁴ have adaptogenic activity. Therefore, the observed clinical benefits of EveCare capsule might be due to the synergistic actions of its ingredients.

The following parameters were evaluated in this Meta-analysis with 8 studies where Evecare was evaluated in various menstrual irregularities. It included Clinical parameters like Dysmenorrhoea, Menorrhagia, Character, Menstrual duration and the laboratory parameters included were Hemoglobin and Hormonal assay comprising of FSH, LH, Oestrogen and Progesterone levels. There was a significant improvement in parameters like clinical parameters, improvement in anemia (Hemoglobin), Oestrogen and Progesterone levels.

A useful definition of meta-analysis was given by Huque as: "A statistical analysis that combines or integrates the results of several independent clinical trials considered by the analyst to be combinable".²⁵

A single study often cannot detect or exclude with certainty clinically relevant differences in the effects of two treatments. Cumulative meta-analysis is defined as the repeated performance of meta-analysis whenever a new trial becomes available for inclusion. Such cumulative meta-analysis can retrospectively identify the point in time when a treatment effect first reached conventional levels of significance.²⁶

Meta-analysis thus not only consists of the combination of data but also includes the epidemiological exploration and evaluation of results ("epidemiology of results").²⁷ Therefore, new hypotheses that were not posed in single studies can be tested in meta-analyses.²⁸ The number of patients included in clinical trials is often inadequate, as in some cases the required sample size may be difficult to achieve.²⁹ Meta-analysis may, nevertheless, lead to the identification of the most promising or urgent research question and may permit a more accurate calculation of the sample sizes needed in future studies.³⁰ Goals of the meta-analysis are to enable the overall significance of an effect to be evaluated, based on the multiple studies available, to estimate an overall effect size by combining the individual estimates in multiple studies.³¹

5. Conclusion

Present Meta-analysis of Evicare clinical studies indicate safety and efficacy in normalizing menstrual irregularities. In addition, Evicare reduces excessive menstrual bleeding and normalizes character and duration of menstrual flow. It improves hemoglobin levels and normalizes altered hormonal levels. There was a significant improvement in parameters like clinical parameters, like dysmenorrhea, menorrhagia, improvement in anemia (Hemoglobin) levels, character of blood flow, duration of blood flow. There were also improvement in Oestrogen and Progesterone levels. This Meta-analysis clearly shows that Evicare may be beneficial in women suffering from menstrual irregularities.

6. Acknowledgement

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Table 1: Individual study details on Evicare

Sl.no	Investigator name	Number of subjects
1	Dr.Mangaiyarkarasi	50
2	Dr.Mukta	50

3	Dr.Urmila	51
4	Dr.Deepak Desai	38
5	Dr.DN.Misra	47
6	Dr.Sudha Salhan	35
7	Dr.vijay Zusthi	50
8	Dr.Gauri Ganguli	100

Table 2: Demographic data

Demographic data	Details
Number of trials	: 08
Number of patients	: 421
Age of patients	: 31.30 ± 4.86 years
Dose	: Evicare Capsule 1-2 tablets twice daily Evicare Syrup-10-15 ml twice daily
Duration of treatment	: 3 months

Table 3: Effect of Evicare on Hormone Levels

Parameters	Number	Before treatment (Mean±SD)	After Treatment (Mean±SD)	Significance
FSH mIU/ml	56	8.68 ±6.12	9.22±6.53	NS
LH mIU/ml	56	10.69±14.44	10.95±10.35	NS
Oestrogen pg/mL	125	116.20±75.24	99.42±64.90	p<0.0001
Progesterone ng/mL	56	6.51±7.84	9.27±10.72	p<0.0493

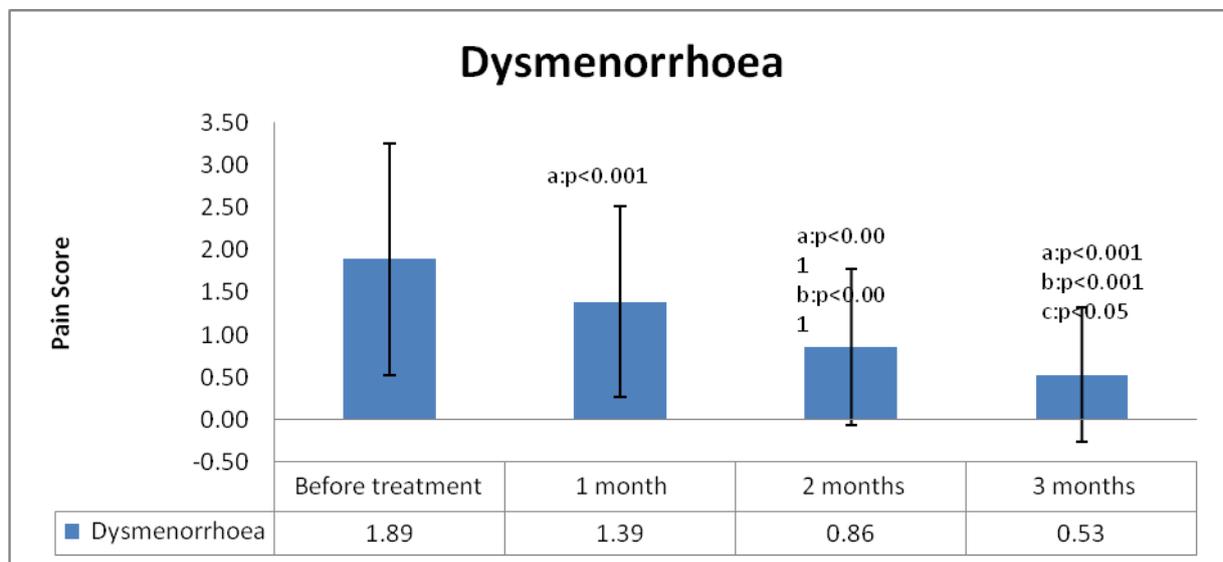


Figure 1

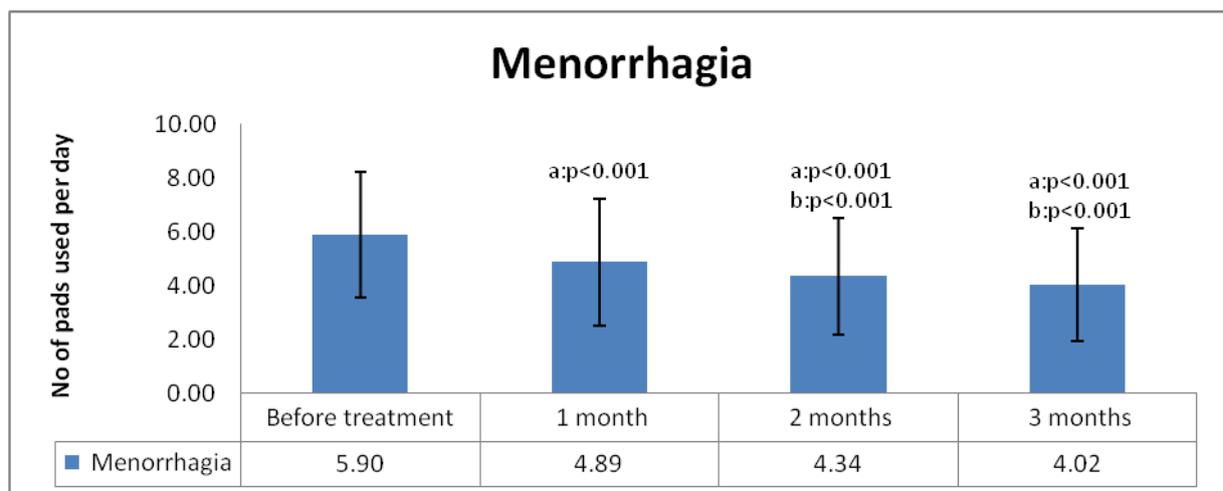


Figure 2

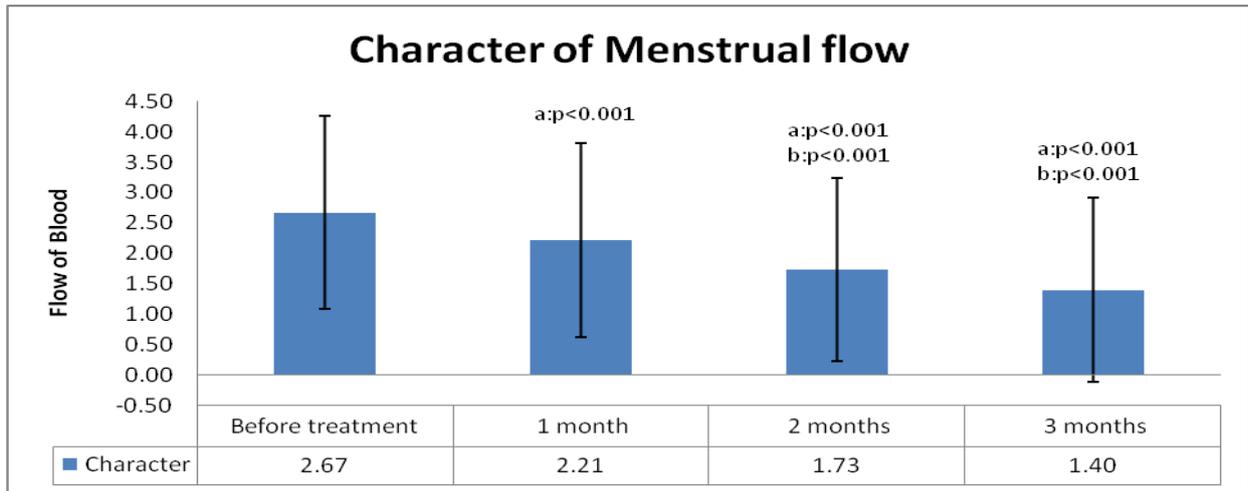


Figure 3

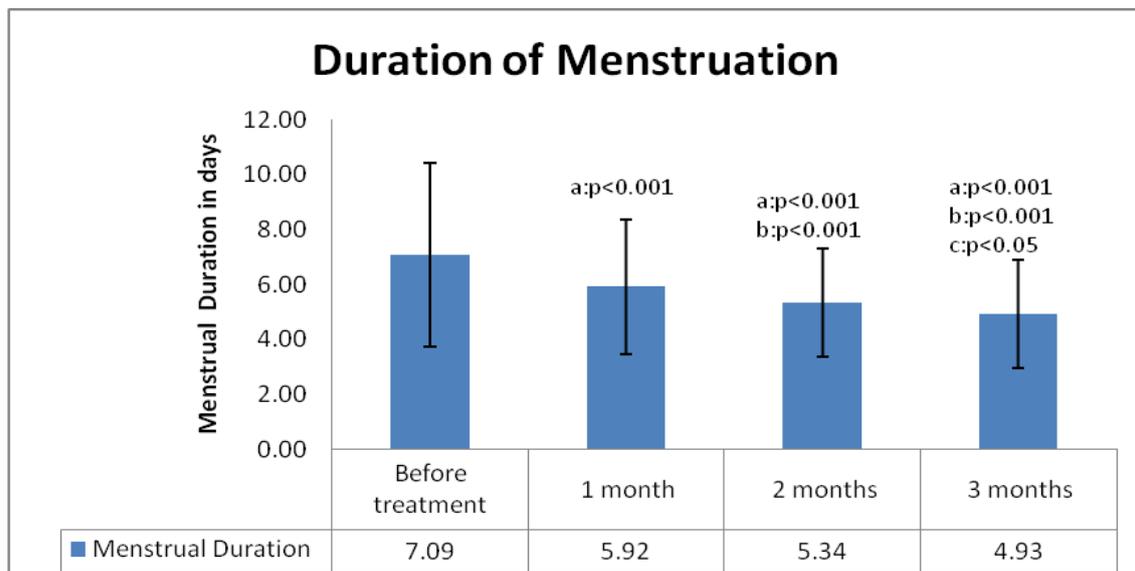


Figure 4

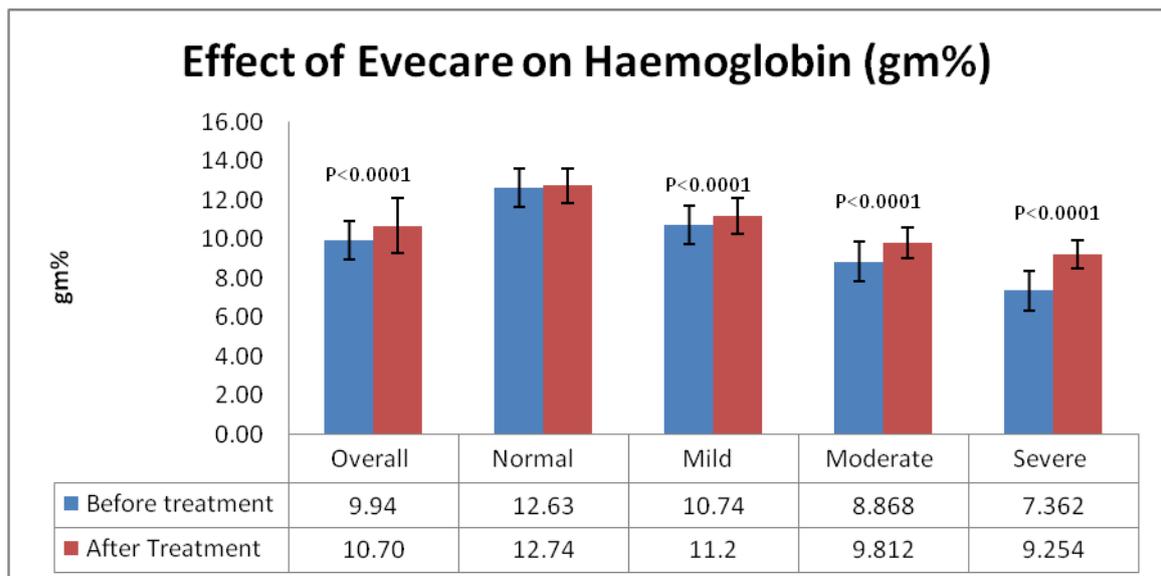


Figure 5

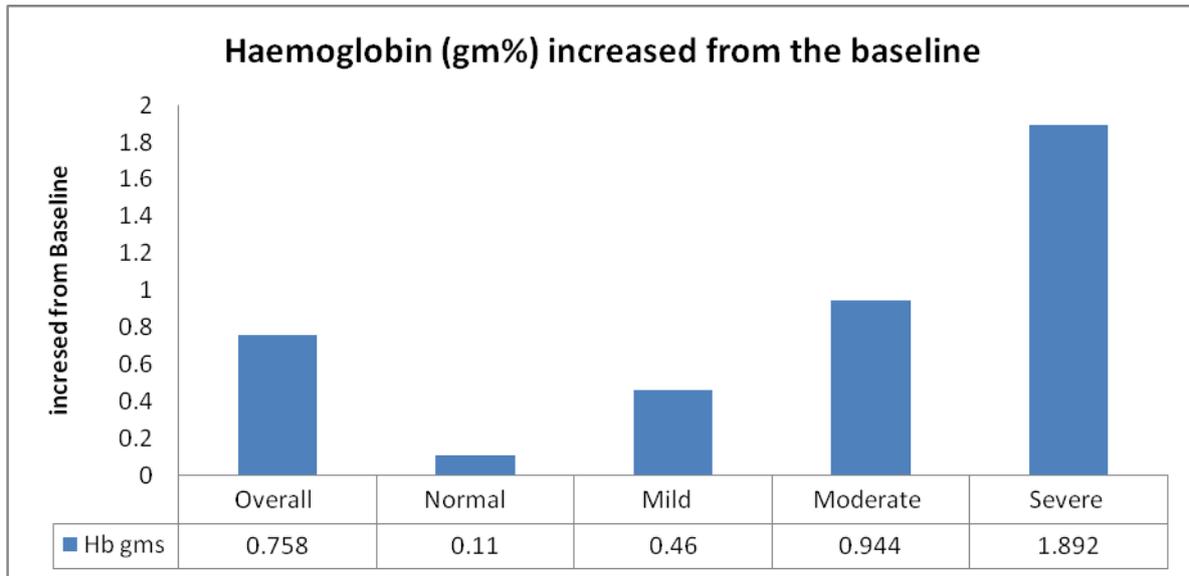


Figure 6