

An Open Label, Multicentric, Noncomparative Study of Gynova, A Ployherbal Formulation, in the Treatment of Menorrhagia and Metrorrhagia.

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ABSTRACT

Gynova, a polyherbal formulation, was studied for its efficacy and safety in patients with menorrhagia and metrorrhagia. A total of 100 patients were studied at two centers. Women below the age 45 and above the age of 16 years, who have menorrhagia or metrorrhagia with or without dysmenorrhea, were included. Patients with local causes of menstrual abnormalities: erosion of cervix, uterine leiomyomas, adenomyosis, polyps, intrauterine contraceptive device, malignancy of uterus or cervix, pregnancy-related problems like abortion and systemic causes like bleeding disorders and thyroid dysfunction were excluded. Also, patients with pelvic inflammatory disease, coagulopathies, diabetes mellitus, cardiac, hepatic or renal ailments, hypertension and pulmonary disease were excluded from the trial based on their medical history. Gynova in a dose of two tablets twice a day was given for 3 months and the patients were evaluated every month for 3 months. Efficacy was measured in terms of passage of clots, changes in quantity and duration of bleeding, pain during menstruation using visual analog scale and global assessment. Gynova produced a significant reduction in all the parameters assessed after 3 months treatment in both menorrhagia and metrorrhagia cases. In addition, a significant reduction in pain during menstruation was also observed. No adverse events were reported by any patient. This indicates that Gynova is very effective in controlling and regularizing menstrual disorders.

Key words: Dysfunctional uterine bleeding phytoestrogen, anti-inflammatory, analgesic antispasmodic hemostyptic, hemoglobin

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Introduction

Disturbances of menstrual bleeding can be major social and medical problems for women. Menstrual disorders are the second most common gynecological condition resulting in hospital referral accounting for 12 % of all gynecological referrals. In India, this condition is common in 58% reproductive and 38 % perimenopausal periods. It is encountered more in multipara women i.e. 87% then in nullipara and primipara i.e. 13%.

The term ‘dysfunctional uterine bleeding’ (DUB) is taken to mean “excessively heavy, prolonged or frequent bleeding of uterine origin which is not due to pregnancy or to recognizable pelvic or systemic disease”. Ovarian cycles associates with bleeding may be ovulatory, associated with normal hormonal cycles or anovulatory, with abnormal, with abnormal hormonal patterns. Women from their adolescent years to perimenopause, the time preceding the menopause, can be affected and anovulatory DUB occurs most commonly at the extremes of reproductive life.

In recent times phytoestrogens have been used to regulate hormonal imbalances and various gynecological disorders. Gynova tablets is one such formulation containing medicinal plants like Ashoka (*Saraca indica*), Lodhra (*Symplocos racemosa*), Daruharidra (*Berberis aristata*), Shatavari(*Asparagus racemosus*) and Dashmool (Clerodendrum phlomidis, Solanum indicum, solanum xanthocarpum, Aegle marmelos, Gmeline arborea, Stereospermum suaveolens, Oroxyllum indicum, Desmodium gangeticum, Uraria Picta, Tribulus terrestris), etc. that are used in traditional system of medicine for the treatment of DUBs. It acts by virtue of its strengthening action on uterine musculature and capillaries including anti-inflammatory, analgesic, antispasmodic and hemostyptic properties. This is plausibly due to the specific phytoestrogens present in the herbs constituting Gynova tablets.

Material and methods

Selection of patients

Consecutive patients attending the Gynecology OPD were screened for the inclusion and exclusion criteria. All women below the age of 45 and above the age of 16 years, who had menorrhagia or metrorrhagia with or without dysmenorrhea were selected.

Patients with local causes of menstrual abnormalities: erosion of cervix, uterine leiomyomas, adenomyosis, polyps, intrauterine contraceptive device, malignancy of uterus or cervix, pregnancy- related problems like abortion and systemic causes like bleeding disorders and thyroid dysfunction were excluded. Also, Patients with pelvic

inflammatory disease, coagulopathies, diabetes mellitus, Cardiac, hepatic or renal ailments, hypertension and pulmonary disease were excluded from the trial based on their medical history. They were informed consent was obtained from them before being recruited into the study.

The Patient’s detailed history, clinical examination, and disease- specific history like passage of clots, duration of bleeding and regularity of cycle, etc. were recorded. Appropriate investigations like hemogram, bleeding time, clotting time, platelet count and Pap smear was done. Presence of anemia was noted and its severity was recorded by estimation of hemoglobin level. Routine laboratory investigation such as CBC, SGOT, SGPT, bleeding time, clotting time, total creatinine, serum bilirubin were done before and after treatment to assess the safety of the drug. Severity of pain during the cycle (dysmenorrhea) was measured on a visual analog scale (VAS) from 0 to 100 where 0 is no pain and 100 is unbearable pain.

Patients were asked to take two Gynova tablets in the morning and two in the evening after meals, from the first day of menstruation, for three months. The menstrual blood loss was assessed as primary efficacy parameter along with pain in the subsequent cycles while the drug administration was continued. The amount of blood loss was measured subjectively with passage of clots, duration of bleeding and number of pads used in the cycle. Patients’ global assessment was taken as a secondary efficacy variable. The adverse events were observed and recorded with suspected causal relationship to the study drug. For the analysis of laboratory investigations student’s paired test was used and for the analysis of efficacy variables the Friedman nonparametric test was used to compare the overall increase or decrease at various time points.

Results

In the present study, the demographic data and the vitals of patients in both the study indications viz. menorrhagia and metrorrhagia were matching (Table 1). Although it is not a comparative study, the patient distribution was uniform.

Table 1. Demography and vitals

Parameter	In menorrhagia group			In metrorrhagia group		
	Min.	Max.	Mean ± SD	Min.	Max.	Mean ± SD
Age(years)	16	45	30.65 ± 8.25	14	42	26.73 ± 7.50
Height(cm)	130	164	153.82 ± 6.32	125	170	153 ± 8.63
Weight(kg)	35	74	51.75 ± 8.37	25	80	51.21 ± 10.86
Temperature(F)	36	37.6	37.21 ± 0.31	36.8	37.6	37.24 ± 0.26
Pulse(min)	72	112	87.37 ± 6.59	37	120	85.86 ± 10.20
Respiration(min)	12	27	19.13 ± 6.59	12	28	18.56 ± 5.32
Systolic BP(mmHg)	100	130	117.11 ± 5.98	100	130	117.21 ± 6.09
Diastolic BP(mmHg)	60	86	74.52 ± 6.38	60	90	75.41 ± 6.57

Menorrhagia

A significant increase in hemoglobin content from 10.58 ± 2.07 to 11.47 ± 2.17 ($p < 0.001$) was observed as well as a significant decrease in clotting time, from 4.33 ± 1.94 to 2.51 ± 0.30 ($p < 0.001$) (Table 2).

In efficacy parameters, the passage of clots was reduced from 2.26 ± 0.54 to 1.33 ± 0.47 which was significant ($p < 0.001$) after three months of treatment. Similarly, the duration of bleeding during menses was also significantly reduced. The duration of bleeding before treatment was 6.97 ± 1.55 days which reduced to 3.92 ± 0.95 days ($p < 0.001$). Numbers of pads used during treatment were reduced from 5.84 ± 1.47 to 3.04 ± 0.88 . The severity of pain during menses measured on VAS was 59.68 ± 22.47 before treatment which reduced significantly to 41.05 ± 16.20 after treatment (Table 2, Fig. 1).

About 85.5% of patients said that their cycles were regularized after treatment and about 14.5% reported it as unchanged. The frequency i.e. mean duration between two cycles was 27.90 ± 7.21 days before treatment, which

Table 2. Effect of Gynova on signs and symptoms of menorrhagia

Parameter	Before treatment mean \pm SD	After treatment mean \pm SD
Hb(g%)	10.58 ± 2.07	11.47 ± 2.17
Passage of clots(No.)	2.26 ± 0.54	1.33 ± 0.47
Duration of bleeding (days)	6.97 ± 1.55	3.92 ± 0.95
Number of Pads	5.84 ± 1.47	3.04 ± 0.88
Severity of pain during menses(VAS, 0-100)	59.68 ± 22.47	41.05 ± 16.20

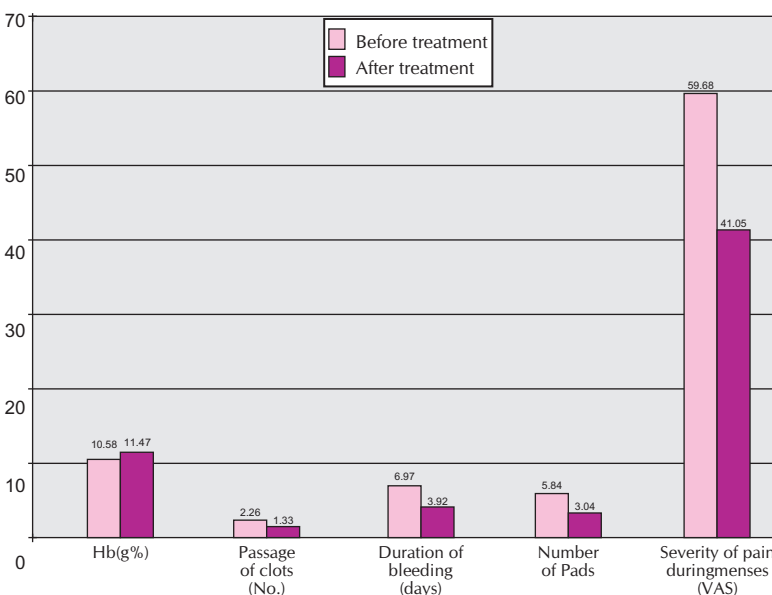


Figure 1. Results of menorrhagia.

changed to 29.48 ± 6.07 days after treatment which was significant ($p < 0.001$). About 85.5% of patients complained of dysmenorrhea before treatment but only 30.6% of patients still complained of its presence which, is a significant reduction ($p < 0.001$) in patients' improvement.

Metrorrhagia

The result of treatment with Gynova tablets in patients with metrorrhagia were almost similar to that of menorrhagia. In efficacy parameters, the severity of pain during menses measured on VAS before treatment was 50.48 ± 17.29 , which significantly reduced to 37.06 ± 16.10 after treatment ($p < 0.001$). Similarly, the duration of bleeding before treatment was 10.40 ± 9.55 days which significantly reduced to 4.06 ± 1.01 days ($p < 0.001$). The passage of clots were significantly reduced from 1.98 ± 0.68 to 1.52 ± 0.50 ($p < 0.001$) after 3 months of treatment. Number of pads used were significantly reduced from 5.25 ± 1.62 to 3.57 ± 0.86 . The frequency i.e. mean duration between two cycles was 25.67 ± 6.02 days before treatment, which significantly changed to 28.11 ± 3.36 days after treatment ($P < 0.001$). About 76% of patients had moderate - to - severe passage of clots before treatment whereas only 33% showed moderate-to-severe passage of clots. About 77.8% of patients said that their cycles were regularized after treatment and about 22.2% said it was not changed. About 81% of patients complained of dysmenorrhea before treatment but only 42.9% of patients still complained of its presence which is a significant reduction in patients improvement ($p < 0.001$). There were no significant changes in laboratory parameters in case of metrorrhagia (Table 3, Fig.2)

Global assessment: Patients reported treatment as very good (21 %) good (41.9%), average (24.2%) and only 12.9% said it is poor. Physicians had almost similar opinion that the drug was safe.

Discussion

Gynova tablets, a polyherbal Ayurvedic menstrual modulator, is used in the management of DUB, particularly in patients with menorrhagia and metrorrhagia. Medical plants containing phytoestrogens do have a definite role in menstrual disorders¹.

Gynova tablets contain extracts of herbs *Saraca indica*, *Aloevera*, *Triphala* (*Terminalia chebula*; *Terminalia bellerica*; *Emblica officinalis*), *Asparagus racemosus*, *Glycyrrhiza glabra*, *Symplocos racemosa*, *Valeriana wallichii*, *Cyperus rotundus*, *Piper longum*, *Dashmool*: (Equal mix of roots of following ten plants, *Clerodendrum*

phlomis, Solanum indicum, Solanum xanthocarpum, Aegle marmelos, Gmelina arborea, Stereospermum suaveolens, Oroxyllum indicum, Desmodium gangeticum, Uraria picta, Tribilus terrestris), Berberis aristata, Abroma augusta and Carum copticum oil in therapeutic dosage. Many of the above mentioned herbs have been screened positive for phytoestrogens.

Phytoestrogens are naturally occurring diphenolic compounds from plants that are structurally similar to the hormone 17 β-estradiol. They are absorbed from stomach, circulate in the bloodstream and are excreted in urine. Of the several groups of phyoeatrogens, the isoflavones and lignans are the most commonly found plants derived estrogens. They may also act as antioxidants² or inhibit several key enzymes such as tyrosine kinase and DNA topoisomerase³. However, phytoestrogens are weak estrogens and also inhibit sulfotransferases involved in the removal of endogenous estradiol⁴.

Saraca indica have specific oxytocic activity, it acts as tonic for the endometrium or the uterus, and it is useful in many diseases of uterus⁵. It has stimulating effect on the endometrium and the ovarian tissue⁶. This may product an estrogen- like activity that enhances the repair of the endometrium and stops bleeding. Aloe vera also possesses oxytocic property⁷. Triphala possess antioxidant and antibacterial activity. Asparagus racemosus show estrogen-like activity and acts as selective estrogen modulator receptor. Glycyrrhiza glabra contains phytoestrogens, plausibly acting as uterine tonic (Hudson, 1998). Symplocos racemosa has been reported to be useful in the treatment of menorrhagia and other uterine disorders⁸. It also exhibits relaxants and antispasmodic effects on several spasmogens on uterine smooth muscles, attributing favorable actions to the drug in dysmenorrhea and as a uterine sedative⁹.

The bark of Symplocos racemosa is known for its estrogenic activity¹⁰. Since it is a coagulant, it is used in bleeding disorders. It causes excellent vasoconstriction of the capillaries thus stopping bleeding and reducing swelling¹¹. Valeriana wallichii works as an analgesic and antispasmodic^{12,13}. Cyprus rotundus is highly anti inflammatory and useful in spasmogenic pain associated with uterus¹⁴. piper longum possesses analgesic properties¹⁵. It is a known bioavailability enhancer^{16,18}. It enhances the bioavailability of all other ingredients of Gynova tablets.

Dasmool has been used for ages in painful inflammatory disorders of various systems of body. Equal quantities of these 10 types of roots are useful in maintaining the balance between three humors (i.e. tridoshas) in the body. Berberis¹⁹ aristata is a hemostatic agent. It is useful in menorrhagia and uterine inflammation. The total extract shows oxytocic activity²⁰. Abroma augusta shows contractil action on the uterus and is used for the treatment of dysmenorrhea, amenorrhea, sterility and other menstrual disorders.

Table 3. Effect of Gynova on signs and symptoms of menorrhagia

Parameter	Before treatment mean ± SD	After treatment mean ± SD
Severity of pain during menses(VAS, 0-100)	50.58 ± 17.29	37.06 ± 16.10
Duration of bleeding (days)	10.40 ± 9.55	4.06 ± 1.01
Passage of clots(No.)	2.26 ± 0.54	1.33 ± 0.47
Number of Pads	5.25 ± 1.62	3.57 ± 0.86
Mean during between two cycles	25.67 ± 6.02	28.11 ± 3.36

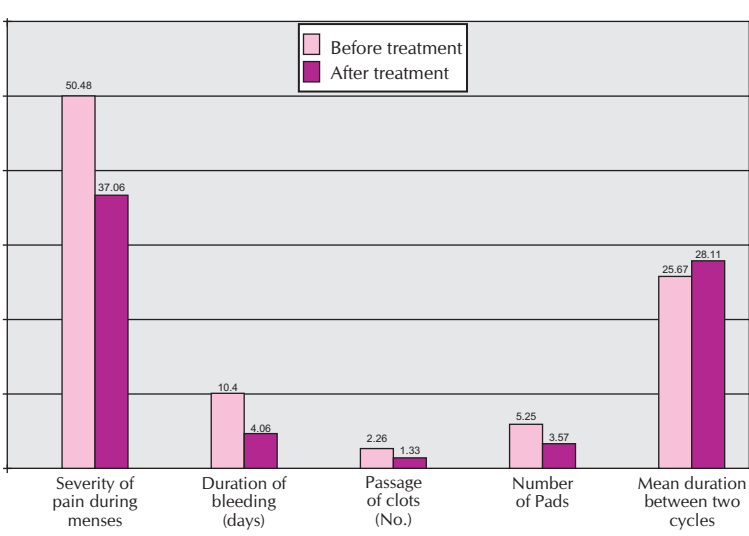


Figure 1. Results of menorrhagia.

The aqueous extract of the root has oxytocicaction²¹. Conventional treatment may include taking medications such as the oral hormonal pills and possibly taking iron supplements to reduce the chances of developing anemia. Hormonal pills tend to balance erratic hormone levels and suppress excessive bleeding. These pills could have side effects like nausea, weight gain, etc. Surgical treatments include endometrial ablation or in serious cases, hysterectomy.

Alternative systems of medicine claim to improve these conditions with minimal or no side effects. In the present study an attempt is made to assess the efficacy and safety of Gynova Tablets, a polyherbal formulation. It appears that Gyneva tablets produced

aa significant improvement in patients with menorrhagia and metrorrhagia. A highly significant change ($p < 0.001$) in all the parameters was noted after the treatment.

Gynova tablets significantly increased the hemoglobin content which can be a substantial treatment mode in case of chronic DUB. In majority of patients (95%) suffering from moderate passage of clots showed significant reduction. The duration of bleeding in terms of days reduced significant reduction. The quantity of blood passed during the period which is measured indirectly by the number of pads used, showed a significant reduction, the clotting time was also reduced. All these results indicate that the drug is effective in controlling symptoms of menorrhagia and metrorrhagia. Majority of the patients felt that their cycles were regularized after 3 months of treatment. Even dysmenorrhea experienced by about 85% of patients was reduced with only about 30% patients still experiencing it after the treatment. Both the patients and the physicians were highly satisfied with the drug. The corresponding figures of physicians' opinion were almost matching with that of patients. During the study no major adverse events were noted. All these results indicate that Gynova tablets is safe and effective in controlling excessive bleeding in patients with menorrhagia and regularizing their cycles.

Therefore, It is observed that the ingredients of Gynova tablets exert estrogen modulator activity, including analgesic, muscle relaxant, antispasmodic, and antioxidant activities. The overall effect of the formulation may reduce oxidative stress, regulate hormonal functions and balance the hypothalamo-pituitary-ovarian (HPO) axis and control the irregular or excessive bleeding and its complications.

Conclusion

The present study indicates that Gynova tablets, a polyherbal formulation is effective and safe in controlling the signs and symptoms of menorrhagia, metrorrhagia and associated complications.

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