AN OPEN CLINICAL TRIAL TO EVALUATE THE EFFICACY OF A HERBAL PREPARATION FOR MENSTRUAL IRREGULARITIES

Chaudhari S[1], Kohli KR[2], Sharma G[2]

[1] Department of Stree Roga and Prasuti Tantra, R.A. Podar Ayurvedic Medical College & Hospital, Worli, Mumbai - 400 018, India.
[2] Dabur Research Foundation, 22 Site IV, Sahibabad, Ghaziabad-201010, U.P., India.

SUMMARY

Menstrual irregularity is a considerable nuisance for women because it leads to an unpredictable menstrual flow. It is most likely to occur at the extremes of reproductive life. Ayurveda describes *Artava* as the eighth *Dhatu* for females and also as a *Upadhatu* of *Rasa dhatu*. Ayurvedic literature has delineated different types of *Artava doshas* such as *Artava vriddhi* (menorrhagea), *Artava kshaya* (oligomenorrhea) and *Rakta pradara* (DUB) and other related conditions. The treatment of these disorders is mainly aimed at controlling *Vata,* which is primarily responsible for causation of such irregularities. The pharmacotherapy consists of herbs, which alleviate *Vata* e.g., *Ashoka, Triphala, Hingu, Trivrit,* etc. In the modern treatment periodic use of estrogens is most common. However, increasing risk of cancer restricts practice of hormonal therapy. Hence, a *polyherbal formulation* has been designed on the basis of available Ayurvedic literature for use in menstrual irregularities. In the present study, the effect of a polyherbal preparation, *Dabur Mensta,* was studied on 50 women in the mean age group of 25-30 years (±7.34), suffering from menstrual irregularities, in an open, prospective clinical study. The drug was administered through oral route at a dose of 10 ml b.i.d. for 90 days. The subjects were sub-grouped as increased duration of cycles, decreased duration of cycles, decreased bleeding days, increased bleeding days, decreased menstrual flow and increased menstrual flow. Majority of the subjects i.e., 8 out of 13 (61.54%) with increased duration of cycles showed mean reduction of 13.48 days from baseline to end of the study. All the 14 subjects with decreased duration of cycles showed mean increase of 08.69 days from baseline to end of the study. In subjects with increased or decreased number of bleeding days (n=22), the trial drug produced improvement. The trial drug was also found to be effective in reducing the increased flow, which was clinically significant. All the subjects falling under both irregular cycle duration and irregular bleeding days reflected relief from the respective clinical symptoms. The study reveals that the Ayurvedic preparation could be effective in correcting menstrual irregularities, and, therefore, subjected to more rigorous clinical trials.

Key words: Artava, Artavadosha, menstrual irregularities (MIs), polyherbal formulation

Glossary of Ayurvedic terms: Artava: Menstrual blood; **Artavadosha:** Menstrual disorders; **Dhatus:** Body's basic constituents; **Doshas:** Three basic metabolic principles responsible for all bodily functions, also know as biological humour; **Rasadhatu:** First among the seven body constituents; **Updhatu:** Supportive tissues of Dhatus; **Vata:** The dosha responsible for all movements in the body, biological air humor.

INTRODUCTION

Menstruation disorders are a common problem during adolescence (1,2). These disorders may cause significant anxiety for patients. Physical and psychological factors contribute to the problem. 24-32 days of cycle is considered as regular and the period of menstrual flow is considered to be normal if it lasts 4-6 days (3). Any deviation from this can be termed as menstrual irregularity. Amenorrhea (lack of bleeding) and oligomenorrhea (too little bleeding), dysmenorrhea (painful menstruation) (4), and menorrhagia (excessive bleeding) are the menstrual problems usually met with. Also, the practitioners have to deal with problems such as increased or decreased duration of cycle and increased or decreased duration of bleeding days (5-7).

Hormones such as gonadotrophin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), estrogen and progesterone play roles during the ovulatory cycle. An equilibrium and balance between the release and circulating levels of these hormones make the cycle rhythmic and regular (8, 9). Ayurvedic literature describes *Artava* as the eighth *Dhatu* for females and also as a *Upadhatu* of *Rasa dhatu* which is correlated with menstruation. Sushruta delineated types of *Artava doshas*, *Artava vriddhi* (increased menstrual bleeding), *Artava kshaya* (decreased menstrual bleeding), *Rakta pradara* (dysfunctional uterine bleeding) etc. Need for maintaining female reproductive health was emphasized in all the classical texts of Ayurveda. About 20 types of *Yoni Vyapads* (gynecological conditions) have been described in detail by Charaka (C.S.Ci.30) and Sushruta (S.S.Ut.39). The treatment of these disorders was mainly aimed at controlling *Vata,* which is the main factor responsible for causation. Therefore, the pharmacotherapy principally

Correspondence to be addressed to : Dr. K.R. Kohli. Email : Kuldipr@dabur.com, krkohli@rediffmail.com

consists of herbs, which alleviate *Vata* e.g. *Ashoka, Triphala, Hingu, Trivrit,* etc.

The modern medications used in the management of menstrual disorders depend on the type as well as etiology of the disorder. Usually, hormones, non-steroidal anti-inflammatory drugs (NSAIDs) and mineral supplementations are used depending on the causative factors and symptoms (3). In India many polyherbal formulations, in the form of syrups, capsules and tablets, are marketed for comprehensive relief from menstrual irregularities. These preparations are based on traditional formulations and are usually known as cycle regulators. One such formulation was investigated in this study to find its effect on the various menstrual irregularities.

MATERIALS AND METHODS

An open label, non-comparative, prospective study design was formulated. The trial drug was in the form of a syrup and consisted of Ashok Chhal (*Saraca asoka*), Daru Haridra (*Berberis aristata*), Rakt Chandan, Dhatki Pushpa, Amla, Bahera, Haritaki, Amarasthi (*Mangifera indica*), Neelkamal (*Nymphaea stellata*), Shunthi, Mustak, Safed Jeera, Vasaka, Pippali, Nishoth, Kalaunji, Ajwain and Hing as the ingredients. The complete composition of the formulation is given below (Table 1).

Table 1. Composition of Dabur Mensta - Each 10 ml contains extracts derived from:

S. No.	Ingredient	Quantity
1.	Ashok Chhal	1000 mg
2.	Ghrit Kumari	24 mg
3.	Daru Haridra	24 mg
4.	Rakt Chandan	24 mg
5.	Nishoth	48 mg
6.	Kalaunji	48 mg
7.	Ajwain	48 mg
8.	Shunthi	48 mg
9.	Amla	48 mg
10.	Bahera	48 mg
11.	Haritaki	48 mg
12.	Mustak	48 mg
13.	Safed Jeera	48 mg
14.	Vasaka	48 mg
15.	Pippali	48 mg
16.	Amarasthi	24 mg
17.	Neelkamal	24 mg
18.	Hing	10 mg
19.	Dhatki Pushpa	280 mg
20.	Madhu	2000 mg
	Excipients	Q.S.

The trial drug had undergone acute oral toxicity and repeated dose (90 days) toxicity study and was found to be safe for human use. The LD_{50} values of *Dabur Mensta* in rats and mice by oral route were found to be greater than 2000mg/kg body weight. The 90 days repeated dose toxicity study revealed no observed effect level (NOEL) of *Dabur Mensta* in Sprague Dawley rat through oral route was found to be 1000 mg/kg body weight for male and female rats. The project got approval from Ethics Committee of M. A. Podar Ayurvedic Medical College and Hospital, Worli, Mumbai. The study was conducted at M. A. Podar Ayurvedic Medical College & Hospital, Worli, Mumbai, and the subjects were enrolled from O.P.D. of Department of Stree Roga and Prasuti Tantra (Gyanecology & Obstetrics). Prior informed consent was taken from all subjects. Complete history was recorded and general and systemic examinations were done to satisfy the inclusion and exclusion criteria. Subjects with diagnosis of menstrual irregularities in the age group 13-45 years and diagnosed cases of dysfunctional uterine bleeding were included. The general health, nutritional status and haemoglobin levels of all subjects were assessed before and after the trial. Subjects were explained about the complete study procedure. Patients having organic causes of menstrual abnormalities like uterine myeloma, pelvic inflammatory disease, adenomyosis, polyps, fibroids, endometriosis, etc., those participating in any other clinical study, those having systemic disorders like thyroid dysfunction, pituitary disease or coagulation disorders, those having any other chronic infections like respiratory and cardiac problems, diabetes or renal dysfunction or those having moderate or severe mental retardation were excluded as per the pre-determined criteria of exclusion. Nursing, pregnant or lactating women were also excluded. On day 0 the subjects were evaluated and recruited into the study. The investigations like complete blood profile, routine urine analysis and LFT and RFT for evaluation of safety of the trial drug were conducted both at the start and at the close of the trial. Pelvic ultrasonography was done at the baseline for exclusion purposes. At each visit the following observations were made: regularity of menstrual cycle (date-wise), status of menstrual flow (along with the number of days of bleeding) and VAS scores for subjective evaluation were recorded. After enrollment, all the subjects were given placebo syrup till the date of start of menstruation. The treatment was started from day 5 of menstruation (5^{th} day from the start of the menstrual cycle). All subjects were evaluated thereafter fortnightly (at two weekly intervals). A total of 7 visits were planned over a period of 120 days. Difference in the mean scores from baseline to the last follow up was analyzed to find the efficacy of the trial drug. The drug was administered at a dose of 10 ml b.i.d. for 12 weeks and further followed up for another visit without trial medicine after four weeks. The data were subjected to statistical analysis adopting hierarchical ANOVA. Multiple comparisons among the successive time periods of each group were analyzed by Dunnet's procedure at 95% confidence level.

The effect of the trial drug on renal, hepatic and haematological parameters was assessed. The tests were carried out before and after administration of the trial drug. All the safety tests were within normal limits before and after administration of the trial drug. There was no visible / clinical sign or symptom related to central nervous system observed during the trial and also no ADR/AE was recorded in any subject.

RESULTS

A total of 50 females suffering from MIs were enrolled in the study. Out of them, 48 completed the total duration of the study i.e., 120 days. The remaining two subjects were drop-outs due to reasons not relating to the trial drug. The mean age of the study sample was 25.80 (±7.34) year. Majority of the subjects (21) who completed the study were in the 13-25 year age group. The subjects were sub-grouped as shown in the table 2.

Table 2. Sub–grouping of the subjects in the study

Symptoms	Increased cycle duration	Decreased cycle duration	Normal duration of cycles	Total
Increased bleeding days	02	05	02	09
Decreased bleeding days	07	02	04	13
Increased menstrual flow	02	06	15	23
Decreased menstrual flow	00	00	00	00
Normal bleeding days	02	01	00	03
Total	**13**	**14**	**21**	**48**

Effect of the trial drug on irregular duration of cycles

Effect on increased duration of cycles (n=13)

In subjects reporting with increased duration of cycles (n=13), there was a gradual decrease in the duration of cycles by the end of 120 days of study (Table 3). 09 out of the 13 (69.23%) achieved normal duration of cycles by the end of the third cycle. However, in two subjects (15.38%) no further cycle in terms of menstrual flow was observed and no effect of the treatment was observed. The over all mean change observed was statistically significant ($p<0.05$). 4 subjects reached fourth cycle also within this span of 120 days.

Table 3. Pattern of improvement in the subjects with increased duration of cycles

	Cycle I (n=13)	Cycle II (n=11)	Cycle III (n=9)	Cycle IV (n=4)	Mean change Baseline-cycle3	%
Mean duration	44.23	31.36	30.33	30.75	13.48	30.48
S.D.	±13.03	±5.41	±2.50	±4.19		

Effect on decreased duration of cycles (n=14)

In subjects reporting with decreased duration of cycles (n=14), there was a gradual increase in the duration of cycles by the end of 120 days of study (Table 4). All the subjects (100%) achieved near normal duration of cycles by the end of the third cycle, with a mean duration of 30.71 (± 06.91) days. The mean change was 08.69 days, i.e., 39.50% increase in the duration of cycle with $p<0.05$. All except one subject showed normal mean duration in the fourth cycle also.

Table 4. Pattern of improvement in the subjects with decreased duration of cycles

	Cycle I (n=14)	Cycle II (n=14)	Cycle III (n=13)	Cycle IV cycle 4	Mean change Baseline-cycle	%
Mean duration	22.00	25.57	30.71	30.69	8.69	39.50
S.D.	±2.18	±4.38	±6.91	±7.25		

Effect of trial drug on irregular bleeding days

Effect on increased bleeding days (n=9)

The mean number of days of improvement was 2.75 days (from 7.88±2.20 to 5.13 ±0.60) i.e., a reduction of 34.90% with $p<0.05$ (Table 5).

Table 5. Effect of the trial drug in subjects with increased bleeding days

	Cycle I (n=9)	Cycle II (n=9)	Cycle III (n=9)	Cycle IV (n=9)	Mean change	%
Mean bleeding days	7.88	7.63	6.13	5.13	2.75	34.9
SD	±2.20	±1.74	±1.73	±0.60		

Effect on decreased bleeding days (n=13)

After intervention with the trial drug all subjects showed normal bleeding days by the 2nd cycle, which remained within the normal range during further trial duration. The mean increase in bleeding days was 0.86 (till cycle III), i.e., 22.81% increase (Table 6).

Table 6. Effect of the trial drug in subjects with decreased bleeding days

	Cycle I (n=13)	Cycle II (n=13)	Cycle III (n=10)	Cycle IV (n=8)	Mean change	%
Bleeding days	3.77	4.23	4.30	4.63	0.86	22.81
S.D.	±1.24	±0.83	±0.82	±0.74		

Effect on subjects with normal duration of cycles and bleeding days with heavy flow (n=15)

Among the subjects with heavy flow (under normal duration of cycle and bleeding days), only one

subject showed improvement by the 2nd cycle. But by the third cycle it was found that all subjects had improvement and had only moderate flow (Table 7).

Table 7. Efficacy of the trial drug in the amount of flow in subjects with normal duration of cycles and bleeding days with heavy flow

Amount	Baseline	Cycle 1	Cycle 2	Cycle 3	Cycle 4
Heavy	15	15	14	0	0
Moderate	0	0	1	15	15
Scanty	0	0	0	0	0

(Data: Number of subjects)

Change in number of pads used

The samples used less number of pads with progression of the treatment (Table 8).

Table 8. Mean number of pads used at each visit by subjects with increased bleeding days

	Baseline	Cycle I	Cycle II	Cycle III	Cycle IV
Mean	21.44	18.00	13.56	12.00	10.89
S.D.	2.70	1.80	2.60	2.65	2.98

Safety of the trial drug

No ADRs were observed during the entire study period in any of the subjects. The pre- and post-safety investigations (complete blood profile, routine urine analysis, LFT, RFT and USG) did not show any significant change, which revealed the safety of the trial drug. Only 12 subjects had Hb values below 10% (lowest 8.5). Out of them seven had complained of heavy bleeding, four had scanty bleeding and one had moderate bleeding.

DISCUSSION

In the present study the effect of a polyherbal formulation, *Dabur Mensta,* was investigated for efficacy in various menstrual irregularities in women. Such polyherbal formulations are believed to produce lesser side effects because of the small dosage of each herb in the formulation. However, there could be summation/synergy of individual ingredients in rendering higher therapeutic efficacy than individual ingredients. A herbal cycle-regulator to replace HRT is an ideal choice, and, hence this study. During the study 50 female subjects suffering from MIs were treated with this herbal preparation. The subjects were grouped into various subgroups. The herbal preparation offered relief to most of the subjects and, interestingly, worked as a cycle-regulator. It, on the one hand, brought about increase in the duration of cycle in those subjects who at baseline complained reduced duration of cycle and, on the other hand, decreased the cycle duration in subjects who at baseline complained longer cycle durations. Subjects with complaint of heavy bleeding also demonstrated a promising effect in reducing the duration and extent of bleeding. Significant clinical relief was observed in the majority of subjects. The mechanism of action of the trial drug is not yet established, though some of the ingredients have been individually reported to have effect on the female reproductive system (12-14). None of the subjects showed any type of ADR either during or after the trial period. The safety profile in terms of blood biochemistry and other investigations also did not show any change in pre- and post-treatment readings. Looking at the high risk associated with the hormonal replacement/ supplement therapy (11,15-19), this can prove to be a safe alternative to the modern treatment.

It can be concluded from this study that all the subjects falling under both irregular cycle duration and irregular bleeding days gained relief from their respective clinical symptoms on treatment with the Ayurvedic preparation. The data generated point to scope for more extensive clinical trials, with more number of subjects under each category and introduction of additional parameters and end points as practiced in the modern clinical medicine.

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