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Research paper

A single-blind randomized comparative study of Asafoetida *vs* Mefenamic acid in dysmenorrhea, associated symptoms and health-related quality of life

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ABSTRACT

Objective: To compare the efficacy and safety of asafoetida (*Ferula assafoetida* L. oleo-gum-resin) with mefenamic acid (NSAID) to alleviate dysmenorrhea, associated systemic symptoms and improvement in health-related quality of life.

Methods: Patients (n = 60) were randomly allocated to receive asafetida (n = 30) or mefenamic acid (n = 30) in this single-blind, randomized, standard controlled trial. Test and control drug, 250 mg was administered and given orally twice daily for 5 days; 2 days prior to and first three days of menstruation for two consecutive cycles. The primary outcomes included the severity of pain assessed with visual analogue scale, verbal multi-dimensional scale and safety assessment. Secondary outcomes included health-related quality of life (HRQoL) determined using SF-36 health survey questionnaire, pain duration, associated systemic symptoms and PBLAC (Pictorial Blood Loss Assessment Chart) score for menstrual blood loss. The data was statistically interpreted with 5% level of significance.

Results: Between the groups, at baseline, pain severity did not differ significantly ($P > 0.05$) however, after the intervention, a significant decrease in pain severity was noted in both groups ($P < 0.001$). At third menstrual cycle, asafetida showed a significant decrease in pain severity compared to mefenamic acid on day one ($P < 0.0004$) however no significant difference was observed on day two and day three ($P > 0.05$). At post-intervention improvement in HRQoL and decrease in pain duration was significantly higher in the test group compared with control group. Systemic symptoms decreased significantly in both groups after intervention. No side effects were reported.

Conclusion: Asafoetida was effective and safe to relieve menstrual cramps and to improve HRQoL. Further, its effect was comparable with mefenamic acid.

1. Introduction

Dysmenorrhea, a Greek word, refers to painful uterine contractions during menstruation (Younesy et al., 2014). Of all menstrual complaints, the foremost gynecologic complaint (Ju et al., 2014)that is underdiagnosed and undertreated is dysmenorrhea and affects 50% women at childbearing age (Park et al., 2013). In developing countries, it poses a greater burden of disease than any other gynecological complaint. Being an incapacitating condition for many women, it has a major impact on work productivity, health-related quality of life, health-care utilization and is accountable for considerable economic losses due to the costs of medical care medications, and decreased productivity(Ju et al., 2014).

In Unani medicine, *usr-i-tamth* or *auja al-rahim* refers to pain associated with menstruation (Khan, 1983) or pain of uterine origin, analogous to dysmenorrhea (Sina, 2010). In conventional medicine, dysmenorrhea is defined “as chronic, cyclical pelvic pain associated with menstruation. Typically, it is characterized by cramps in the lower abdomen occurring just before and/or during menstruation”. In primary dysmenorrhea, there is no structural abnormality whereas in secondary dysmenorrhea there is a structural abnormality and women usually have chronic pelvic pain (Onur et al., 2012).Elevated prostaglandins also play a role in secondary dysmenorrhea with concomitant pelvic pathology(Onur et al., 2012).The causes of secondary

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dysmenorrhea include congenital malformations (e.g., bicornuate uterus, subseptate uterus, and transverse vaginal septum), intrauterine uterine contraceptive device, endometriosis, fibroids, uterine polyps, adenomyosis, cervical stenosis, uterine synechiae, PID, pelvic congestion syndrome, ovarian cysts and tumour (Calis and Rivlin, 2014). Dysmenorrhea is commonly associated with systemic symptoms such as nausea, vomiting, diarrhea, dizziness, fatigue, back pain, mild fever, and headache or lightheadedness (Kamini and Kiran, 2012; Rigi et al., 2012). These systemic symptoms are caused because of raised levels of prostaglandins.

Women with primary dysmenorrhea have a comparatively high concentration of $PGF_{2\alpha}$ in menstrual fluid (Nahid et al., 2009; Ziaei et al., 2005). $PGF_{2\alpha}$stimulates uterine contractions, cervical narrowing, and increases vasopressin release, which causes ischemia that results in abdominal pain (Nahid et al., 2009). Prostaglandins are also implicated in secondary dysmenorrhea (Onur et al., 2012). Therefore, dysmenorrhea is mainly treated with suppression of PG synthesis. Pain or systemic symptoms can be relieved with paracetamol, aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs) that affect prostaglandin production and act through disruption of specific steps in PG formation (Nahid et al., 2009).These drugs have useful effects such as anti-inflammatory, antipyretic and analgesic activities (Rahnama et al., 2012). However, taking NSAIDs may lead to many adverse effects including indigestion, headache, drowsiness, nausea, dyspepsia, and vomiting. Furthermore, the rate of failure with the use of NSAIDs to reduce dysmenorrhea may reach 20% (Ke et al., 2012). Hence, the general population is looking beyond orthodox medical care as the first line of defense to combat such conditions. The desire to pursue a drugless approach towards the prevention and treatment of disease and negative experiences with allopathic methods may have led to this trend. A focus study carried out at a medical center revealed that a growing number of gynecological patients (56%) have already turned towards alternative care (Spears, 2005). As a result, complementary and alternative medicine (CAM) is becoming a more popular alternative to treat dysmenorrhea (Ke et al., 2012). The treatment modalities include herbal products, dietary supplements, healthy lifestyle (proper diet and exercise),dry cupping (Sultana et al., 2010), acupressure, aromatherapy (Ou et al., 2012), transcutaneous electrical nerve stimulation (TENS) and behavioral interventions.

Asafoetida an oleo-gum-resin is obtained by incision of the roots or removal of the stems of the plant *F. asafetida L* (Alqasoumi, 2012). Hardened exudates (oleo-gum-resin) are collected and then packed for export (Iranshahy and Iranshahi, 2011). Some other names are *Shajarat-ul-Heltit*, '*Angudân*', '*Hing*' 'Anghouzeh' and 'Khorakoma' (Iranshahy and Iranshahi, 2011). It has been used as a spice and a folk phytomedicine for centuries in Unani and other traditional medicinal systems for the treatment of gastrointestional, nervous and respiratory disorders (Iranshahy and Iranshahi, 2011). It is also used in various female diseases, including unusually painful, difficult menstruation (Mahendra and Bisht, 2012). The phytochemical analysis of the oleo-gum-resin fractionation of asafoetida demonstrated that it consists of gum, resin, and essential oil as three major components (Bagheri et al., 2014). Recent pharmacological and biological studies have shown several properties of asafetida such as anti-inflammatory, antinociceptive, (Bagheri et al., 2014) antispasmodic and hypotensive (Fatehi et al., 2004), and antioxidant properties (Kassis et al., 2009), in animal models. In a study by Bagheri et al. (2014) they discussed that the analgesic effect of asafoetida is probably because of inhibition of production/action of prostaglandins. In animal studies, nontoxicity has been reported in therapeutic doses. A study reported that at concentrations as high as 360 mg/ml did not show any sign of cellular toxicity as evidenced bylactate dehydrogenase (LDH) release. A very high dose of 5 g/kg was necessary to obtain the LD50 in rats (Kassis et al., 2009).

Some herbs such as *Zingiber officinale* (Rahnama et al., 2012; Ozgoli et al., 2009),*Foeniculum vulgare* (Nasehi et al., 2013), *Rosa damascene* (Bani et al., 2014), an Iranian herbal medicine formula (saffron, celery seed, and anise), *Anethum graveolens* (Heidarifar et al., 2014), *Trigonella foenum-graecum* (Younesy et al., 2014), and *chaturbeeja* (*Trigonella foenum-graceum, Lepidium sativum, Nigella sativa* and *Trachyspermummi*) (Kamini and Kiran, 2012) have proven efficacy in the treatment of dysmenorrhea. However, to date there is no randomized control trials conducted using asafetida for the treatment of dysmenorrhea. Hence, this study was planned to compare the efficacy and safety of asafetida *vs* mefenamic acid in amelioration of menstrual cramps, systemic symptoms and to improve health-related quality of life (HRQoL).

2. Material and methods

2.1. Study design

A single-blind, single-center, prospective, randomized standard controlled parallel design was conducted in the Department of AmrazeNiswan (Gynecology), National Institute of Unani Medicine, Bangalore, India. The study was registered in the ICMR, Indian registry of clinical trials (CTRI/2016/02/006655). The scientific review committee and Institutional Ethical Committee approved the present study [IEC No: NIUM/IEC/2012-13/011/ANQ/03]. Both written and oral information outlining the reasons for the present study were given to women invited to participate. The study was performed in accordance with the Declaration of Helsinki and GCP guidelines issued by the Ministry of AYUSH, Government of India.

2.2. Participants

A total of 60 patients who were within the age group of 12 to 45 years and who presented with pain during menstruation, suffered systemic symptoms, had a regular menstrual cycle (21 to 35 days) and average bleeding during periods that persisted for six months prior to the study were included. Patients with fibroids who had secondary dysmenorrhea but were not willing to agree to surgical intervention were also included. The patient who had pain caused by inflammatory or malignant diseases, were taking the oral contraceptive pill, suffered from chronic general illnesses, lactating women and patients with menorrhagia or were under 12 years of age were excluded.

2.3. Procedure

Patients were recruited from the outpatient Department of Amraze Niswan wa Qabalat (Gynecology and Obstetrics), National Institute of Unani Medicine Hospital, Bangalore. The pre-randomization screening included a clinical history, physical and gynecological examination, VAS score and VMSS for pain intensity, systemic symptoms severity, HRQoL assessment (SF-36 questionnaire), Pictorial Blood Assessment Chart (PBLAC) score and other investigations. If a patient experienced pain in the abdomen, groin and lumbar region for a few days prior to the menstrual period and/or the first day of a menstrual period, it was considered to be dysmenorrhea. Participants were also asked about other clinical features associated with dysmenorrhea such as nausea, vomiting, headache, fatigue, anxiety, diarrhea, abdominal bloating, vertigo, anorexia, and nervousness. The duration of pain and menstrual characteristics regarding the length of the cycle, days of bleeding, and the amount of bleeding was noted. A general and systemic examination was conducted to exclude general and systemic diseases respectively. Routine investigations (complete blood screen, erythrocyte sedimentation rate (ESR), random blood sugar and urinalysis) for the exclusion of general diseases were carried out. Ultrasonography of the whole abdomen was performed to exclude abdominal and pelvic pathology. For safety assessment clinical examination and laboratory investigation (Hb%, ESR, alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvate transaminase (SGPT), serum creatinine and blood urea) were carried out at baseline and after menstruation during the second menstrual cycle.

Patients were called daily for the first three days during menstruation for three consecutive menstrual cycles to assess VAS and VMSS score. Daily visits during each menstruation was labeled as day one (D1), day two (D2) and day three (D3) of each menstrual cycle. Treatment was given only for two menstrual cycles and in the third menstrual cycle no treatment was given. At each cycle, patient's symptoms (improvement and any clinical side effects) were recorded. The researcher reviewed the side effects and determined whether they were study related. If there were responses regarding side effects they were followed up until they were resolved. Patients who reported adverse drug reactions and/or failed to follow the protocol were withdrawn. Furthermore, patients were not allowed to take any other medications which had an analgesic effect during menstruation.

2.4. Assessment tools

The patient's initial severity of dysmenorrhea was evaluated with Visual Analogue Scale (VAS) for pain intensity and Verbal Multidimensional Scoring System (VMSS) at baseline for two consecutive cycles during treatment and once after treatment. The SF-36 questionnaire was used for Health-related Quality of life (HRQoL) assessment at baseline and third menstrual cycle. Systemic symptoms were recorded at baseline and at third menstrual cycle (Karunagoda et al., 2010)(Table 1a).Menstrual blood loss was assessed by PBLAC score at baseline and at each menstrual cycle. This method has been reported to have a sensitivity of 86% and a specificity of 89% (Higham et al., 1990).

VAS score for pain intensity is a "10 cm line labeled scale which has 'no pain' or 'zero' on the left side and 'worst possible pain' or 'ten' on the right side. The test-retest reliability of VAS was 0.896.The VAS score was further stratified into mild (0–3); moderate (3.1-6) and severe (6.1-10)" (Ziaie et al., 2005). VMSS is graded as Grade 0: no pain; Grade 1: mild pain; Grade 2: moderate pain; and Grade 3: severe pain. This scale also measures the effect on daily activity, and whether analgesia was required or not (see Table 1b) (Unsal et al., 2010).

Percentage of pain reduction (%PR) score was calculated as

$$\frac{\text{Baseline VAS score} - \text{Mean pain reduction score of 3 consecutive cycles}}{\text{Baseline VAS score}} \times 100$$

Satisfactory pain relief was considered to be when % pain reduction was more than or equal to 50% and taken as non-satisfactory when % pain reduction was less than 50%.

The SF-36 is a questionnaire containing 36 items covering eight domains: "physical functioning (PF), social functioning (SF), role limitations due to emotional problems (RE-role–emotional), role limitations due to physical problems (RF-role–physical), bodily pain (BP), vitality (VT), mental health (MH), and general health perception (GH). Unsal et al. (2010) state that 'SF-36 questionnaire demonstrated good reliability and validity and that it can be used to measure QOL. For each variable item, scores are coded, summed, and transformed on to a scale from 0 (worst possible health state measured by the questionnaire) to 100 (best possible health state)' (Unsal et al., 2010). It yields scale scores for each of these eight health domains, and two summary measures of physical and mental health: the Physical Component Summary (PCS) and the Mental Component Summary (MCS).The Physical Component Summary (PCS) includes "physical functioning (PF), role limitations due to physical problems (RF-role–physical), bodily pain (BP), general health perception (GH) and the Mental Component Summary (MCS) includes social functioning (SF), role limitations due to emotional problems (RE-role–emotional), vitality (VT), and mental health (MH)" (Onur et al., 2012).

2.5. Intervention

The trial treatment, whole oleo-gum-resin (dry exudate) of *Ferula asafoetida* L. (Family: Umbelliferae) was selected from the Unani pharmacopeia (Unani Pharmacopoeia of India, 2007). The specimen of the trial drug was identified by the botanist Dr. Shiddamallayya N of Natural Ayurveda Dietetics Research Institute, Central Council for Research in Ayurvedic sciences, Jayanagar, Bangalore (Identification no. RRCBI-MUS-128) and submitted to the Department of Pharmacology of this Institute (voucher specimen no.28/UQ/Res/2015**).** After cleaning, asafetida was pounded, sieved through mesh no. 100 and mixed well to make a fine powder. This powder (250 mg) and mefenamic acid (250 mg) were filled into size number 2 capsules using a manual capsule filling machine in the National Institute of Unani Medicine hospital pharmacy. Patients were advised to take one capsule (250 mg) orally, twice daily with meals for 5 days (2 days prior to the menses and the first three days of menstruation) for two consecutive cycles. Ten

Table 1
a) Systemic symptoms and b) Verbal multidimensional scoring system for assessment of dysmenorrhea severity.

a. Systemic symptoms

Symptoms	0	1	2	3
Fatigue	No fatigue	Fatigue induced by having even single extra work in addition to the daily routine	Fatigued by the normal daily routine	Severe fatigue even without work
Nausea	Absent	2–3 times/day	4-5times/day	> 5times/day
Anorexia	Absent	Mild	Moderate	Severe
Fever	No fever	Mild fever at night	Moderate fever throughout day	Severe fever
Headache	Absent	Mild	Moderate	Severe
Vertigo	Absent	Occasionally	2-3times in 1–2 day	More than 4 times in 3–4 day
Diarrhea	Absent	Occasionally	2–3 times/day	> 3 times/day
Vomiting	Absent	Occasionally	1–2 times	> 2 times
Nervousness	Absent	Mild	Moderate	Severe

b. Verbal Multidimensional Scoring System

Severity grading	Working ability	Systemic symptoms	Analgesic
Grade 0: Menstruation is not painful and daily activity is unaffected.	Unaffected	None	None required
Mild (Grade 1): Menstruation is painful but seldom inhibits normal activity; analgesics are seldom required; mild pain.	Rarely affected	None	Rarely required
Moderate (Grade 2): Daily activity is affected; analgesics required and give sufficient relief so that absence from school is unusual; moderate pain.	Moderately affected	Few	Required
Severe (Grade 3): Activity clearly inhibited; poor effect of analgesics; vegetative symptoms (headache, fatigue, vomiting, and diarrhea); severe pain.	Clearly inhibited	Apparent	Poor effect

Table 2
Investigations in the test and control group.

Variables	Period	Test (n = 30)	Control (n = 30)	P value
Safety Profile				
Erythrocyte Sedimentation Rate (mm/h)	Baseline	34.3 ± 22.5	31.36 ± 18.96	0.76[a]
	2nd Menstrual cycle	29.3 ± 16.8	35.66 ± 19.43	0.27 [a]
	P value	0.20[b]	0.11[b]	
Haemoglobin (Hb)%	Baseline	12.18 ± 1.49	11.8 ± 1.74	0.3 [a]
	2nd Menstrual cycle	12.05 ± 1.75	12.1 ± 1.66	0.8[a]
	P value	0.06[b]	0.07[b]	
Serum glutamic oxaloacetic transaminase IU/ml)	Baseline	19.16 ± 4.2	20.80 ± 10.1	0.85[a]
	2nd Menstrual cycle	18.96 ± 4.6	19.7 ± 10.1	0.55[a]
	P value	0.97	0.12	
Serum glutamate pyruvate Transaminase (IU/ml)	Baseline	18.73 ± 4.98	23.1 ± 18.0	0.45[c]
	2nd Menstrual cycle	20.13 ± 6.2	23.5 ± 17.7	0.43[a]
	P value	0.31[b]	0.07[b]	0.43[a]
Alkaline phosphatase	Baseline	108.43 ± 18.92	108.7 ± 15.78	0.95[c]
	2nd Menstrual cycle	103.76 ± 17.10	105.4 ± 20.63	0.73[c]
	P value	0.21[b]	0.29[b]	
Blood urea (mg/dl)	Baseline	26.1 ± 4.97	28.13 ± 7.51	0.22[c]
	2nd Menstrual cycle	24.96 ± 6.11	26.06 ± 5.36	0.46[c]
	P value	0.38[d]	0.16[d]	
S. Creatinine (mg/dl)	Baseline	0.81 ± 0.11	0.82 ± 0.09	0.63[c]
	2nd Menstrual cycle	0.77 ± 0.08	0.77 ± 0.08	0.74[c]
	P value	0.22[d]	0.02[d]	

Data Presented: Mean ± Standard Deviation; $P > 0.05$,Considered not significant; Test used: [a]Mann Whitney *U* test; [b]Wilcoxon Matched Pair test; [c]Unpaired Student's 't' and [d]paired student's 't' test

capsules of either asafetida or mefenamic acid were supplied in an individual self-locking cover pack for each patient by the first investigator. Compliance was checked by the investigator and checked by counting the medication at each follow-up.

2.6. Outcomes

The primary outcome was a decrease in VAS and VMSS scores for pain intensity. The safety assessment included a clinical examination and biochemical parameters at baseline and after menstruation during the second menstrual cycle (Table 2). Patients were asked about possible common side effects such as nausea, vomiting, upset stomach, stomach pain, and diarrhea. Secondary outcomes were the improvement in the quality of life determined by SF-36 health survey questionnaire, reduction in the duration of pain, associated systemic symptoms, and PBLAC score for menstrual blood loss.

2.7. Sample size estimation

Considering the VAS mean score for pain intensity of an earlier study (Omidvar et al., 2012),a total sample size of 50 participants was required with an alpha 0.05 and 80% power (calculated with online sample size calculator). Hence, in the present study,a total sample size of 60 patients was taken with 15% dropout rate.

2.8. Randomization and blinding

Before starting the intervention, pre-study screening was carried out in the Institute hospital. Once the patient met the inclusion criteria she was included in randomization. Patients were randomly allocated in1:1 ratio by computer generated random list into test (n = 30) and control group (n = 30). (http://www.graphpad.com/quickcalcs/randomize2). The second investigator generated the allocation sequence and assigned the participants to their groups. The random allocation was made in a single block, using a single sequence of random assignment. The sequence was concealed from the first investigator until the interventions were assigned using an open list of random numbers. The participants were enrolled by the first investigator. The participants were blinded by masking and matching the test and control group. The test and control drug was filled in the identical color capsules and there was no detectable odor for any of the preparations.

2.9. Data analysis

The Statistical Software Graph Pad Instat version 3.00 for the window (Graph Pad Software, San Diego, Calif, USA), and the contingency table of more than 2 × 2, the online website was used for the analysis of the data and Microsoft word and Excel have been used to generate descriptive statistics (graphs and tables).

Descriptive analysis was performed by means of the frequencies of the category variables and measurements of the position and dispersion of the continuous variables. Results on continuous measurements were presented on Mean ± SD (Min-Max) and results on categorical measurements were presented in number (%). For all statistical tests, 2-sided P values were used and the type 1 error was set as 0.05 with 95% confidence interval. For comparison of the proportions, the chi-square test or Fisher exact test was utilized. Statistical comparisons between groups were evaluated by using Mann–Whitney *U* test, X^2 test or unpaired *t*-test, and within-group comparisons were assessed with paired *t* test or Wilcoxon matched pairs rank sum test for paired data as appropriate.

Efficacy analysis was performed according to the intention-to-treat principle using data from all randomized subjects with at least two post-randomization outcome measures. Missing data were imputed using the last observation carried forward method. Changes from baseline in the primary efficacy parameter (VAS and VMSS scores) were calculated for the test and control group at follow-up points (every month during treatment and one-month post treatment). Changes from baseline to the third menstrual cycle for secondary outcomes were calculated for the test and control group.

3. Results

3.1. Participant flow

A total number of 363 patients were interviewed for eligibility whereby 303 patients did not meet the criteria for inclusion for a variety of different reasons (Fig. 1). A total of 60 patients were randomly assigned to either test (n = 30) or control (n = 30) group allowing for a 15% drop out. Two and three patients in the test and

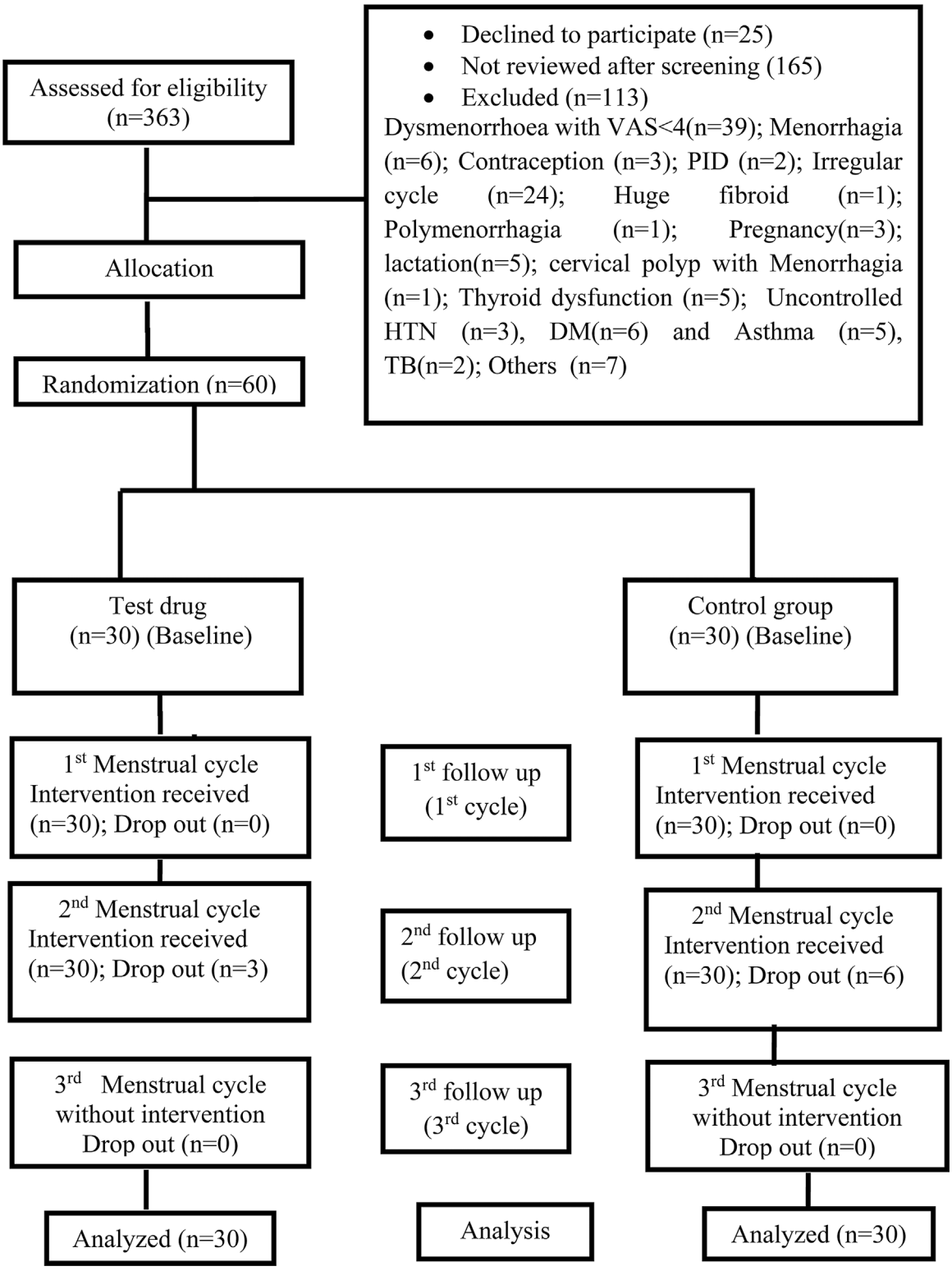

Fig. 1. Flow chart of participants (CONSORT format).

control group respectively did not engage with a review after second menstrual cycle as they lived too far away. However, these patients were contacted by mobile telephone and symptoms were checked. One and three patients in the test and control group respectively did not engage with a review after second menstrual cycle and no contact was available.

3.2. Recruitment

Participants were recruited between February 6, 2014, and February 28, 2015.

3.3. Baseline characteristics

At trial entry, the randomized groups were comparable for most

baseline characteristics. The mean age was 21.4 ± 5.72 years in the test and 24.53 ± 7.05 years in the control group. The mean age of menarche was 12.76 ± 1.05 years in the test group and 12.93 ± 0.98 years in the control group. The mean duration of dysmenorrhea was 6.86 ± 4.63 and 6.03 ± 4.77 years in the test and control group respectively. In the test and control group, 80% (n = 24/30) and 20% (n = 6/30) and 43.33%(n = 13/30) and 56.66% (n = 17/30) were unmarried and married respectively. In the test and control group, 20% (n = 6/30), and 50% (n = 15/30) were parous respectively. The mean duration of the cycle was 28.8 ± 1.75 and 29.06 ± 5.21days in the test and control group respectively. No concomitant use of any medications, pharmaceutical or herbal and complementary were allowed during the course of the research i.e., 2 days prior to and then three days of menstruation. However, participants were allowed to treat any acute illnesses if they occurred during the period of the trial.

3.4. Primary outcome

At baseline, comparison between control and test group for pain intensity (VAS and VMSS scores) showed no statistical difference ($P > 0.05$). Mean pain intensity for VAS on day one, day two and day three of each menstrual cycle showed no statistical difference ($P > 0.05$) between the test and control group except on day one of the third menstrual cycle whereby mean intensity for the VAS score was statistically significant with $P = 0.004$. VMSS score at second menstrual cycle ($P = 0.04$) and third menstrual cycle ($P < 0.0001$) showed a statistically significant difference between the test and control group.

The intra-group comparison of the test and control group at each follow-up for VAS and VMSS scores showed a statistically significant difference ($P < 0.01$). The percentage of pain reduction in the test group on day one, two and three was 64.02%, 78.88%, and 78.88% respectively. Whereas in the control group the percentage pain reduction on day one, two and three was 53.71%, 71.86% and 86% respectively. Fig. 2a and b summarizes the comparison of mean pain intensity between the test and control group assessed with VAS and VMSS scores respectively.

3.5. Safety assessment

Parameters used for safety monitoring of both groups are summarized in Table 2. Random blood sugar in the test and control group at baseline was 96.9 ± 27.10 and 100.87 ± 21.92 mg/dl ($P = 0.53$) respectively, not statistically significant. Furthermore, none of the participants of the test or control group reported any adverse events.

3.6. Secondary outcomes

3.6.1. Health-related quality of life questionnaire-SF 36

Comparison of SF-36 health survey questionnaire is summarized in Fig. 3.

3.6.2. Systemic symptoms

Tables 3 and 4 summarizes the findings of systemic symptoms and their severity grading respectively.

3.6.3. PBLAC mean score

The total PBLAC mean score at baseline was 64.93 ± 25.94 and 77.53 ± 25.74 in the test and control group respectively with $P = 0.06$ not statistically significant. At the third menstrual cycle the mean score was 70.4 ± 20.92 and 66.43 ± 20.35 in the test and control group respectively, not statistically significant ($P = 0.61$). The intra-group comparison at each menstrual cycle when compared with baseline in both groups was statistically significant ($P < 0.001$).

4. Discussion

This study displayed sufficient evidence that asafoetida (*hilteet*) had a significant and similar effect in dysmenorrheic patients as mefenamic acid and was safe to ameliorate menstrual pain, shortened the duration of pain, decreased associated systemic symptoms and improved health-related quality of life

4.1. Primary outcome

4.1.1. VAS and VMSS for pain intensity

Baseline total VAS mean score was 8.2 ± 1.18 and 7.8 ± 1.09 in the test and control group respectively in this study. This finding is comparable with previous studies where baseline total VAS score was more than seven (Jenabi, 2013; Heidarifar et al., 2014).The pain reduction started immediately after starting the intervention and continued to decline in the subsequent two menstrual cycles. The percentage of pain reduction on day one, day two and day three of third menstrual cycle was 64.02, 78.88 and 77.90,and 53.71, 71.86 and 86 percent in the test and control group respectively. The results of this study are similar to previous studies such as vitamin E (Ziaei et al., 2005), fennel/vitamin E (Nasehi et al., 2013), Iranian herbal medicine formula (saffron, celery seed, and anise) (Nahid et al., 2009), ginger (Rahnama et al., 2012; Jenabi, 2013), dill (Heidarifar et al., 2014), rose (Bani et al., 2014) and exercise intervention (Onur et al., 2012). The magnitude of the reduction was significantly greater in the test than the control group on day one and day two thus showing that *F. asafetida* had a better effect than mefenamic acid for pain reduction.

4.1.2. Safety

In this study, no side effects were reported with regard to asafetida and mefenamic acid consumption. Hence, in the present study test and control drug were shown to be safe. All the biochemical parameters were comparable and no statistical difference was found when compared with baseline in both groups except serum creatinine ($P = 0.02$) in the control group which was statistically significant but laboratory value was within normal range. Bagheri et al. (2014) in their study reported that asafoetida did not show any toxic effects in an animal model. Furthermore, asafetida has been shown to have hepatoprotective (Kareparamban et al., 2012) and nephroprotective properties (Javaid et al., 2012).

Unani scholars in their classical texts have surmised that asafoetida has *muharrik-i-a'sab* (stimulant), *musakkin-i-alam* (analgesic), *dafi-i-tashannuj* (antispasmodic), *mudirr-i-hayd* (emmenagogue) and *mudirr-i-bawl* (diuretic) properties (Ghani, 2001; Unani Pharmacopoeia of India, 2007). Further, they opined that emmenagogue drugs have *harr*(hot), *mulattif* and *mufatteh* (dilator) properties (Sina, 2010) therefore, fluidifies blood to induce smooth blood flow (A'zam, 2010), dilates the uterine blood vessel and increase blood circulation in uterine vessels. Furthermore, emmenagogue drugs rectify the functional defect of the uterus and relieve the menstrual cramps. A similar hypothesis has been discussed in a recent study by Rigi et al. (2012).

To explain the effects of the test drug on pain reduction in the dysmenorrheic patient, it has been reported that asafetida has antinociceptive, anti-inflammatory antispasmodic and anti-oxidant properties that suggests a NSAID-like mechanism.

4.1.3. Antinociceptive and anti-inflammatory properties

Bagheri et al. (2014) showed the antinociceptive effect of asafoetida on chronic and acute pain in mice. They concluded that this effect was probably because of involvement of central opioid pathways and peripheral anti-inflammatory action. In addition, numerous studies have shown that terpenoids have anti-inflammatory activities and asafoetida is a rich source of terpenoids. Another possible mechanism of action for the active principles of asafoetida is probably linked to lipoxygenase and/or cycloxygenase in the arachidonic acid cascade at the peripheral

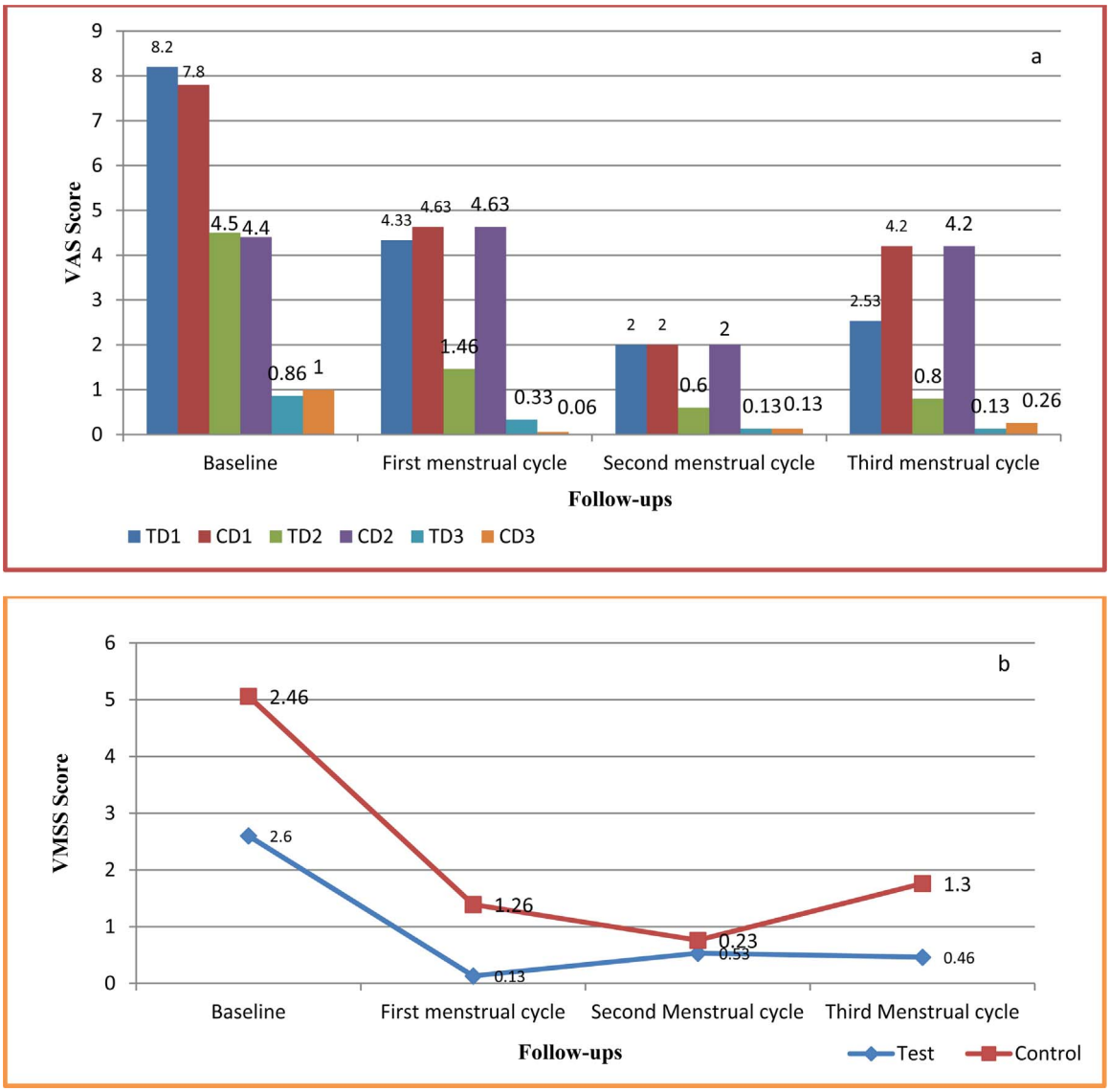

Fig. 2. Primary Outcome-Comparison of pain intensity with (a) Visual Analogue Scale (VAS) score for pain intensity and (b) Verbal Multidimensional Scoring System (VMSS) score.
Data presented: Mean; **VAS**: Visual Analogue Scale; **VMSS**: Verbal Multidimensional Scoring System; TD1, TD2, TD3: Test group day one, two and three; CD1, CD2, CD3: Control group day one, two and three

route (Rajendra et al., 2004). Umbelliprenin (sesquiterpene coumarins) has been reported to inhibit the activity of 5-lipooxygenase and has shown anti-inflammatory action (Iranshahi et al., 2009).

4.1.4. Antispasmodic property

The antispasmodic activity of aqueous extract of asafetida was demonstrated on isolated guinea pig ileum by Fatehi et al. (2004). This may justify its efficacy in dysmenorrhea. It has also been reported that the relaxant effect of asafoetida extract is because of its potent inhibitory effect on the muscarinic receptor. It may also be due to the partial inhibitory property of the herb on the histamine (H1) receptor (Kareparamban et al., 2012).

4.1.5. Anti-oxidant property

Ferulic acid which is an important component of asafoetida has a potent antioxidant activity (Bagheri et al., 2014; Kareparamban et al., 2012) hence, suppresses the oxidation of arachidonic acid and decreases the production of prostaglandin (Nasehi et al., 2013). Further, anti-oxidant activity enhances the immunity and general strength of the body. It increases the pain threshold and facilitates better pain tolerance capacity (Kamini and Kiran, 2012).

4.2. Secondary outcomes

4.2.1. HRQoL

In this study, patients had a very low HRQoL value as the authors included women with moderate to severe dysmenorrhea, consistent with the study by Unsal et al. (2010) and Onur et al. (2012). In this study, both interventions provided a significant improvement in health-related quality of life measured by the SF-36. All eight domains of the SF-36 (physical functioning, role − physical, bodily pain, general health perception, vitality, social functioning, role − emotional, mental health) and both component scores showed significant improvements at post-intervention, which was in agreement with a previous study carried out by Witt et al. (2008). However, quality of life improvement was higher in the test than the control group. This shows that asafetida was more effective than mefenamic acid for improving in HRQoL. Two recent surveys conducted in Turkey demonstrated that most of the domains of the SF-36 scale were lower in women with dysmenorrhea when compared with women without (Onur et al., 2012; Kumbhar et al., 2011). This clearly indicates that dysmenorrhea is disrupting their lives more compared with the lives of the non-dysmenorrheic patients (Kumbhar et al., 2011). Another study found that participants

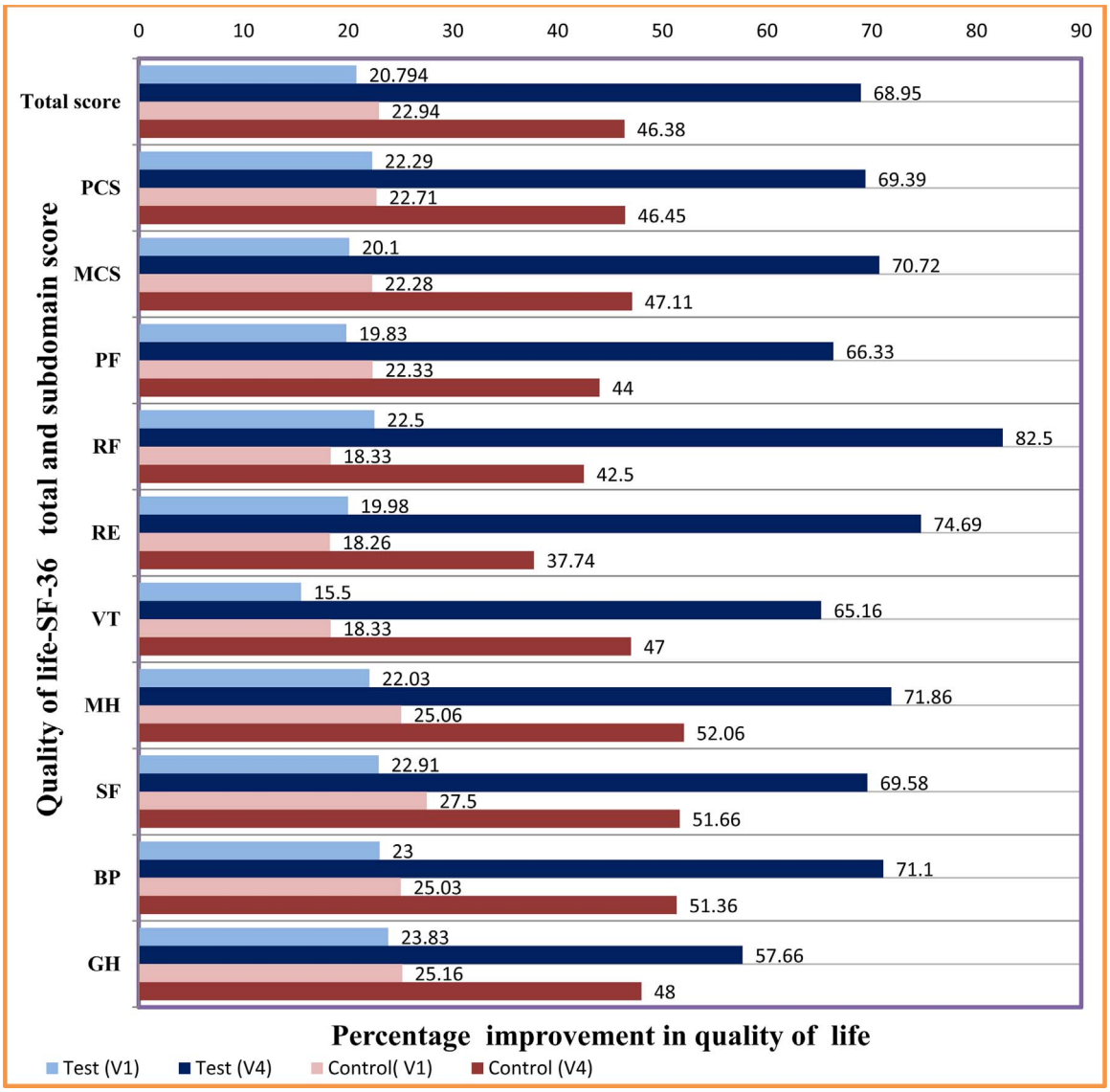

Fig. 3. Secondary outcome-Comparison of SF-36 health survey.
Data Presented: Mean; **V1**: Baseline visit **V4**: Third menstrual cycle; **Test used:** Mann Whitney *U* test; Wilcoxon Matched Pair Test; Unpaired Student's't' and paired student's 't' test; **V1** of test and control group comparison was $P > 0.05$, Considered not significant; V4 of test and control group comparison was $P < 0.0001$, considered extremely significant; **Abbreviation:** Physical function (PF); Role limitation due to Physical problems (RF); Role limitation due to emotional problems (RE); Energy/fatigue/Vitality (VT); Emotional well being (Mental Health-MH); Social Functioning (SF); General Health (GH)Bodily Pain (BP) Physical Health composite score (PCS) Mental Health composite Score (MCS)

who had dysmenorrhea were 6.6 times more likely to stay in bed all day when compared to women who had a normal quality of life with respect to their menstrual cycle (Charu et al., 2012).

4.2.2. Associated systemic symptoms

The most common symptom associated with dysmenorrhea in the present study was lethargy and tiredness, consistent with the previous study conducted by Agarwal and Agarwal (2010). Both groups in this study exhibited a decrease in the severity of systemic symptoms (fatigue, nausea, anorexia, fever, headache, vomiting, vertigo, and nervousness) linked with dysmenorrhea consistent with previous studies (Heidarifar et al., 2014; Younesy et al., 2014; Ziaei et al., 2005).

Significant improvement in the symptoms such as fatigue, headache, nausea, vomiting, anorexia, anxiety and nervousness was observed in the test group. Asafoetida increases appetite, aids digestion and reduces nausea and vomiting due to its bitter taste (Younesy et al., 2014). Alqasoumi et al. (2012) reported a dose-dependent anxiolytic and analgesic activity of asafoetida, with a mild sedative effect in high doses and concluded that compared to diazepam, asafoetida seems to be a better alternative for the treatment of anxiety disorders. Hence, the positive effects of asafetida consumption on fatigue, headache, mood, and energy level are attributed to its antioxidant, sedative (Bagheri et al., 2014; Kareparamban et al., 2012; Moghadam et al., 2013) and anti-anxiety properties (Alqasoumi et al., 2012).

4.2.3. Duration of pain

Many studies reported that menstrual pain starts on the first day of menstrual flow and continued for 24–72 h (Ou et al., 2012). Similarly, the authors found that mean duration of pain was 60.4 ± 14.29 h. Morrow and colleagues also reported that dysmenorrhea lasts for up to 72 h, typically peaking in the first 24 to 48 h of the menstrual cycle (Dawood, 2006) as the levels of prostaglandins are highest during this period (Nahid et al., 2009; Ziaei et al., 2005). At post-intervention, a significant difference was noted between asafetida and mefenamic acid, showing that asafetida was more effective at shortening the duration of pain. A similar shortening of pain duration was noted in previous studies after intervention with an Iranian herbal medicine formula (saffron, celery seed, and anise) (Nahid et al., 2009), fenugreek (Younesy

Table 3
Secondary outcome: Systemic symptoms in dysmenorrhea.

Symptoms	Baseline	First menstrual cycle	Second menstrual cycle	Third menstrual cycle	P value
Duration of pain (Hours)					
Test (n = 30)	60.4 ± 14.29	13.26 ± 5.38[b]	2.63 ± 3.6[b]	3.1 ± 3.7[b]	[b]P < 0.0001
Control (n = 30)	53.4 ± 20.80	14.86 ± 13.6[c]	2.16 ± 3.11[c]	11.3 ± 6.6[c]	[c]P < 0.0001
P value	0.09[a]	0.92[a]	0.95[a]	< 0.0001[a]	
Fatigue					
Test (n = 30)	2.06 ± 0.58	1.03 ± 0.49 [b]	0.36 ± 0.49 [b]	0.6 ± 0.62 [b]	[b]P < 0.0001
Control (n = 30)	2.36 ± 0.66	1.26 ± 0.63 [c]	0.26 ± 0.44[c]	0.96 ± 0.67 [c]	[c]P < 0.0001
P value	0.08[a]	0.15[a]	0.49 [a]	0.05 [a]	
Nausea					
Test (n = 30)	0.46 ± 0.57	0.1 ± 0.30[b]	0	0	[b]P < 0.0001
Control (n = 30)	0.56 ± 0.56	0.13 ± 0.3 [c]	0	0.06 ± 0.25 [c]	[c]P < 0.0001
P value	0.51 [a]	0.82 [a]	0		
Anorexia					
Test (n = 30)	1.4 ± 0.72	0.63 ± 0.49[b]	0.16 ± 0.37[b]	0.33 ± 0.54[b]	[b]P < 0.0001
Control (n = 30)	1.1 ± 0.75	0.46 ± 0.50[c]	0	0.23 ± 0.43[c]	[c]P < 0.0001
P value	0.14 [a]	0.26 [a]	0.16 [a]	0.61 [a]	
Headache					
Test (n = 30)	0.56 ± 0.85	0.26 ± 0.44 [d]	0.06 ± 0.2 [e]	0.13 ± 0.34[f]	[d]V1vsV2 P = 0.02
Control (n = 30)	0.46 ± 0.81	0.23 ± 0.43[g]	0.06 ± 0.25[g]	0.23 ± 0.50[g]	[e]V1vsV3 P = 0.002
P value	0.67[a]	0.82 [a]	0.99 [a]	0.62 [a]	[f] V1vsV4 P = 0.003 gV1vs FU P < 0.01
Vertigo					
Test (n = 30)	0.26 ± 0.52	0.1 ± 0.30[h]	0	0	[h]V1vsV2 P = 0.06;
Control (n = 30)	0.16 ± 0.46	0.1 ± 0.35	0	0.03 ± 0.18[c]	[c]P < 0.0001
P value	0.05[a]	0.99 [a]	0		
Vomiting					
Test (n = 30)	0.3 ± 0.65	0.06 ± 0.25[i]	0	0.03 ± 0.18[i]	[i]V1vsV2P = 0.03
Control (n = 30)	0.23 ± 0.50	0	0	0.13 ± 0.34[j]	[j]V1vsV4P = 0.25
P value	0.93[a]	0	0	0.42[a]	
Nervousness					
Test (n = 30)	0.6 ± 0.93	0.3 ± 0.53[k]	0.033 ± 0.18[k]	0.16 ± 0.37[k]	[k]V1vs FU P < 0.01
Control (n = 30)	0.33 ± 0.75	0.16 ± 0.37[l]	0	0.06 ± 0.25[l]	[l]V1vsFU P = 0.06
P value	0.28[a]	0.47 [a]	0	0.23 [a]	

Data presented: Mean ± SD; $P > 0.05$, considered not significant; **Test used:** [a]Mann Whitney *U* test; [b]P < 0.0001, considered significant calculated by Wilcoxon Matched Pair Test (Intra group comparison) P value from baseline to follow-up in the test group;[c]P < 0.0001 considered significant calculated by Wilcoxon Matched Pair Test) P value from baseline to follow- up in the control group;

et al., 2014) and vitamin E (Ziaei et al., 2005).

4.2.4. Menstrual blood loss

A gradual reduction in the amount of menstrual blood loss was noted in the control group at each menstrual cycle and this effect was attributed to the reduction of PG synthesis as mefenamic acid has anti-PG action (Ziaei et al., 2005). There was a significant difference in the amount of menstrual blood loss in the test group at each menstrual cycle however, clinically the amount was within normal limits and this effect was attributed to the emmenagogue property of the test drug. The finding of this study that the test drug increases the menstrual blood loss is similar to a previous study by Heidarifar et al., 2014 however, contradictory to another previous study conducted by Ziaei et al. (2005).

4.3. Strength

The use of asafetida for dysmenorrheic women was shown to be effective in regard to a reduction in the common symptoms associated with dysmenorrhea, coupled with the absence of significant side effects in the therapeutic doses used in this study. It was also a randomized, standard controlled study with use of intent-to-treat analysis and good compliance.

4.4. Limitation

Although the current findings are important, the limitations of the present study are that it was only single-blind, the treatment was only for 2 months and follow-up assessment took place only once post-intervention. It can be anticipated, that the efficacy and QoL of the patients could improve even further if the treatment was prolonged.

4.5. Further recommendation

A longer double-blind study is recommended. The exact mechanism of action of asafetida on menstrual pain is unclear; therefore, further studies are recommended to ascertain their direct effect on the uterus. Furthermore, the authors propose monitoring the concentration of PGs in plasma pre- and post-intervention to observe the effect of asafetida on PGs as decreasing the amounts of PGs may relieve menstrual cramps. Additionally, examining blood flow of uterine vessels by color Doppler ultrasound may be a further clinical research choice.

5. Conclusion

These data suggest that asafetida represents a safe, effective, easily available and economical alternative treatment for menstrual pain, its associated systemic symptoms and to improve health-related quality of life.

Conflict of interest

The authors declare that they have no conflict of interests. Funding has been received from Ministry of AYUSH, India as the unrestricted

Table 4
Secondary outcome-Grading of severity of systemic symptoms.

Symptom	Test (n = 30)			Control (n = 30)			P value
Fatigue	Baseline	Third menstrual cycle	% C	Baseline	Third menstrual cycle	% C	
None	0(0)	14(46.66)	+46.66	0(0)[b]	7(23.33)[c]	+23.33	[a]P < 0.001
Mild	4(13.33)	14(46.66)	+33.33	3(10)	17(56.66)	+46.66	[b]P = 0.10;
Moderate	20(66.66)	2(6.66)	−60.66	13(43.33)	6(20)	−23.33	[c]P = 0.113
Severe	6(20)	0[a]	−20	14(46.66)	0(0) [a]	−46.66	
Nausea							
None	17(56.66)	30(100)	+43.34	14(46.66)[b]	29(96.66)[c]	+50	[a]P < 0.001
Mild	12(40)	0(0)	−40	15(50)	1(3.33)	−46.67	[b]P = 0.79;
Moderate	1(3.33)	0(0)	−3.33	1(3.3)	0(0)	−3.3	[c]P = 1.00
Severe	0(0)	0(0) [a]	0	0(0)	0(0) [a]	0	
Anorexia							
None	4(13.33)	21(70)	+56.67	7(23.33)[b]	23(76.66)[c]	+53.33	[a]P < 0.001
Mild	10(33.33)	8(26.66)	−6.67	13(43.33)	7(23.33)	−20	[b]P = 0.3;
Moderate	16(53.3)	1(3.33)	−49.97	10(33.3)	0	−33.3	[c]P = 0.0.77
Severe	0	0 [a]	0	0	0 [a]	0	
Fever							
None	28(93.33)	28(93.33)	0	30(100)[b]	30(100)[c]	0	[b]P = 0.49;
Mild	1(3.33)	2(6.66)	+3.33	0	0	0	[c]P = . 49;
Moderate	1(3.3)	0	−3.3	0	0	0	[d]P = 1.0
Severe	0	0[d]	0	0	0[d]	0	
Headache							
None	20(66.66)	26(86.66)	+20	22(73.33)[b]	24(80)[c]	+6.67	[b]P = 0.84;
Mild	3(10)	4(13.33)	+3.33	2(6.66)	5(16.66)	+10	[c]P = 0.73
Moderate	7(23.33)	0	−23.33	6(20)	1(3.33)	−56.67	[e]P = 0.02;
Severe	0	0[e]	0	0	0[f]	0	[f]P = 0.09
Vertigo							
None	23(76.66)	30(100)	+23.34	26(86.66)[b]	29(96.66)[c]	+10	[b]P = 0.73;
Mild	6(20)	0	−20	3(10)	1(3.33)	−6.67	[c]P = 1.0
Moderate	1(3.33)	0	−3.33	1(3.33)	0	−3.33	[g]P = 0.01;
Severe	0	0[g]	0	0	0 [h]	0	[h]P = 0.03
Vomiting							
None	26(86.66)	29(96.66)	+10	24(80)[b]	28(93.33)[c]	+13.33	[b]P = 0.8;
Mild	3(10)	1(3.33)	−6.66	5(16.66)	2(6.66)	−10	[c]P = 1.0
Moderate	1(3.33)	0	−3.33	1(3.33)	0	−3.33	[i]P = 0.35;
Severe	0	0[i]	0	0	0[j]	0	[j]P = 0.25
Nervousness							
None	20(66.66)	25(83.33)	+16.66	25(83.33)[b]	28(93.33)[c]	+10	[b]P = 0.19;
Mild	3(10)	5(16.66)	+6.66	0	2(6.66)	+6.66	[c]P = 0.42
Moderate	6(20)	0	−20	5(16.6)	0	−16.6	[e]P = 0.02;
Severe	1(3.33)	0[e]	−3.33	0	0[e]	0	

Data presented: No (%); **%C:** percent change; **Test used:** Fisher exact test; **P** > 0.05; considered not significant; **P** < 0.01 < 0.001 considered statistically significant; [b & c]P value: Inter group comparison at baseline and post intervention (PT); [d,e,f,g,h,i,j]P value: Intra group comparison of both groups

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