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Fenugreek dermal patch, a new natural topical antinociceptive medication for relieving the postherniotomy pain, a double-blind placebo controlled trial

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Abstract:

Background: Fenugreek seeds have shown antinociceptive effect in animal studies. This double-blind placebo controlled trial was designed to study the effect of fenugreek transdermal patch 10% (FDP) for management of inguinal hernia (IH) post-operative pain.

Methods: Standardized extract of fenugreek seeds was used for FDP formulation. Ninety patients treated with 10% FDP, diclofenac dermal patch 1% (DP) and placebo twice daily after IH surgery. The pain intensity score was evaluated using a visual analogue score (VAS) up to 48 h after operation. Morphine consumption and diclofenac suppository demand were evaluated too.

Results: The pain score was significantly reduced in FDP group in comparison with the placebo group. This effect was also significantly different from DP up to 6 h after surgery ($p < 0.05$). Morphine consumption and diclofenac suppository demand were significantly decreased in FDP group ($p < 0.05$).

Conclusion: In all, results of the present study indicated that FDP decreases pain score and demand for morphine in post-surgery patients in comparison to diclofenac patch, and this preparation could be a suit option as a natural antinociceptive agent for pain management.

Keywords: antinociceptive, double-blind placebo controlled trial, fenugreek, inguinal hernia, transdermal patch

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Introduction

Pain is uncomfortable experience and remains a challenge for both physician and patient in spite of great advances in drug research. Apart from the pathophysiology of pain and individual experience, current drug regiments exhibit less or more side effects which might be more severe than the pain [1]. As the definition of International Association for the Study of Pain (IASP), pain is an unpleasant sensory and emotional experience which is associated with tissue damage. In the condition of pain persistence beyond the expected time, for example in post-operative pains, despite the injury removal, acute pain bridges to chronic one which in turn progresses consequent socioeconomic problems [2].

Inguinal hernia (IH) is a common disease especially in men in which the content of abdominal cavity bulges outside and causes symptoms such as pain and distress especially in exercise. Surgery is a routine option in these patients [3] and usually the use of antinociceptive drugs especially narcotic ones in combination with Na diclofenac is needed after surgery [4]. As the IASP guiding principle, post-operative pains are classified in urgent or semi-urgent pains, and it is important to treat pain for preventing the CNS plasticity changes that conduce to persistent post-operative pain [2]. Topical antinociceptives can minimize drug side effects and are feasible for pain control. These types of drugs affect the site of pain and can decrease the risk of drug interactions in elders who take concomitant several types of systemic medications.

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Fenugreek (*Trigonella foenum-graecum* L.) belongs to Fabaceae family and is cultivated throughout the world for its seeds. Traditionally, this plant has been recommended for the pain relief in different conditions such as painful rheumatism [5, 6]. Plant seeds are a source of alkaloids such as trigonelline and choline, steroidal saponin of diosgenin, proteins (20–30%), mucilage (about 20%), free amino acids of lysine, arginine (25.8%), fat (6.53%), fiber (6.28%), minerals, vitamins like nicotinic acid, essential oils and phenolic compounds [7]. Flavonoid content of fenugreek is estimated about 100 mg/g seeds. Fenugreek seeds have been used as conditioner and possess hypoglycemic and antioxidant effects [8–10]. On the other hand, peroxynitrite and its reactive oxygen precursor superoxide have shown critical importance in the pain development, so antioxidant compounds such as flavonoids which can scavenge these radicals in human might have analgesic effect [11, 12]. The plant seeds reduce the skin irritation and have not shown toxicity in topical applications [13]. Gastro-protective effect of the plant has been reported too [14]. Recently, antinociceptive and anti-inflammatory effects of the seeds have been attributed to the plant alkaloids and flavonoids [15, 16]. This project was designed to study the antinociceptive effect of fenugreek transdermal patch (FDP) in IH post-operative patients.

Materials and methods

Chemicals

Morphine ampule (Daroupakhsh, Tehran, Iran), Diclofenac suppository (Lofedic, Caspian Tamin Pharmaceutical Co., Tehran, Iran), was used in this study.

Plant materials

Fenugreek seeds were prepared from Kerman and authenticated by a botanist. A voucher specimen was deposited in the Herbarium Center of Pharmacognosy Department (voucher specimen number. KF156). Seeds were milled and passed through sieve (mesh 30) and the total extract was prepared using warm maceration method with ethanol 80%. The extract was concentrated in the vacuum to dryness and stored at -20°C until the trial.

Plant standardization

Trigonelline, the known plant compound, was used for plant standardization by spectrophotometric method. For this, UV spectrum of a stock solution of trigonelline (10 ppm) was scanned at 200–400 nm and λ_{max} was determined. The calibration curve of trigonelline was prepared at λ_{max} of 270 nm and total content of trigonelline was estimated in the plant seeds [16].

Fenugreek transdermal patch

Plant extract, polyethylene glycol and carbomer 940 in purified water were mixed and stirred at a moderate speed using a mechanical shaker. Sodium lauryl sulfate and oleic acid were added slowly to the mixture and a topical transdermal patch 10% was formulated in Iran Polymer and Petrochemical Institute (Figure 1). In patch formulations, the medication is put away in a source that is enclosed on one side with an impermeable matrix and adhesive which advocates skin on the contrasting side.



Figure 1: Fenugreek dermal patch for post-operative pain

Study design

This double-blind placebo controlled trial, randomized parallel-group study was approved by Ethic Committee of University and received the ethical code (92/321). All participants completed and signed the informed consent and agreed to cooperate. All the allocated patients in this study were operated by a similar technique of Lichtenstein tension-free hernioplasty after systemic anesthesia with isoflurane and midazolam. The participants and medical team which assessed the outcomes were blinded to the type of treated groups. The patients from both sexes, aged 18–85 years with equally scar size, were included in the trial. History of sensitivity to medicinal plants was considered for exclusion of the participants.

Data were collected on patient demographics and pain levels. Sample size was determined on the basis of previous work on diclofenac patch [17] and using the following formula, in which the level of significance 5% and power 80% have been considered.

$$N = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \times \{2(\delta)^2\}}{(\mu_1 - \mu_2)^2}$$

in which n is the sample size in each group, μ_1 and μ_2 are the mean of pain score in two groups ($\mu_1 - \mu_2 = 0.5$) and δ is the standard deviation = 0.7.

$Z_{\alpha/2}$ value associated to the level of significance 5% is $z = 1.96$; Z_{β} for power 80% is $z = 0.84$. So; a total of 90 patients were enrolled in the study and randomly divided into three groups using a computed table of random numbers, of them 79 patients accomplished the trial. The patients received the following treatments twice daily: FDP 10% (fenugreek group), diclofenac dermal patch 1% (DP) (reference group) and DP without any drug and/or fenugreek extract (placebo group) and were observed up to 48 h after operation for post-operative pain intensity, morphine demand and need to diclofenac suppository.

Measurements

The primary measured outcome was the severity of pain using a visual analogue score (VAS) in which level zero (0) meant 'no pain' and level 10 indicated intolerable pain in comparison to placebo and DP-treated ones.

For pain relief, morphine (subcutaneous injection, Daroupakhsh, Iran) and diclofenac suppository were administered on the demand or if VAS pain score was ≥ 4 in respect to the pain intensity. Observation was recorded at the first recovery time and in intervals of 1, 6, 12, 18, 24 and 48 h after operation. For assessment of nociception, consumption of morphine and demand for diclofenac suppository were recorded too. Satisfaction of patient was assessed up to 48 h after operation [18].

Statistical analysis

The SPSS software (Version11), one-way analysis of variance (ANOVA), was used for statistical analysis of antinociception requirements. For comparison of the pain score, Chi-square test was used and differences between experimental groups were compared with post hoc Tukey. Differences with p equal or less than 0.05 were considered significant.

Results

The UV spectrum of trigonelline was scanned at 200–400 nm and its calibration curve was provided at 270 nm ($y=0.0377x+0.0217$, $R^2=0.997$). Trigonelline content of fenugreek seeds was estimated 1.6 ± 0.04 mg/g dried plant extract (Figure 2 and Figure 3).

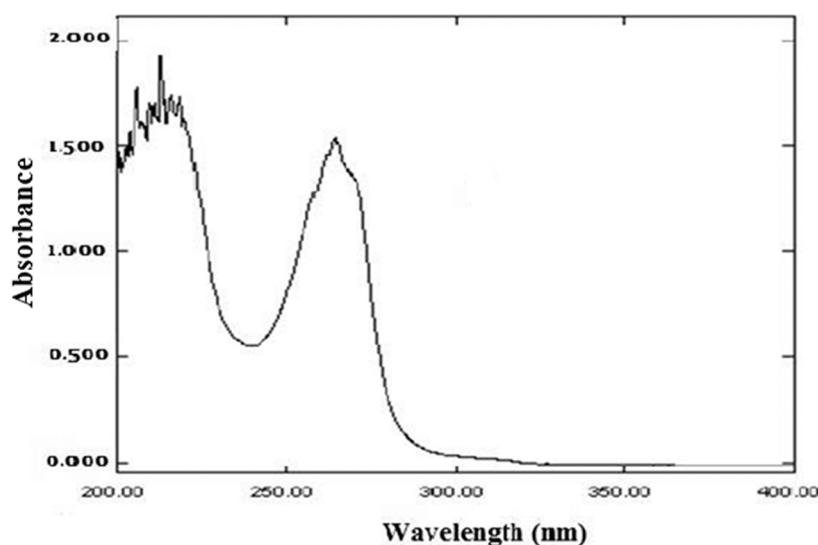


Figure 2: UV-absorption spectra of trigonelline (10 ppm) in deionized water ($\lambda_{\max}=270$ nm)

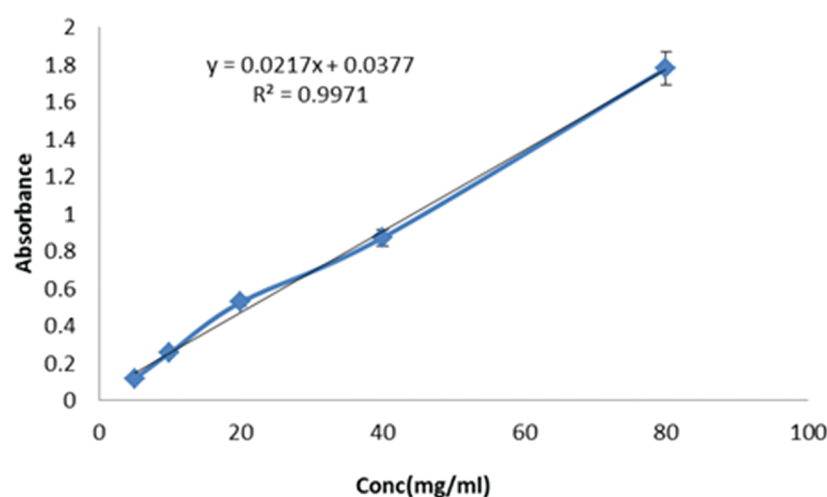


Figure 3: Calibration curve of trigonelline in different concentrations at maximum wavelength ($\lambda_{\max}= 270$ nm)

Demographic characteristics of enrolled patients have been shown in Table 1. The mean age of participants was 43.0 ± 11.0 , 44.8 ± 10.5 and 44.2 ± 13.5 for FDP, DP and placebo group, respectively. Among the patients, 2 (6.9%), 1 (4.16%) and 1 (4.17%) were female and the average weight was 82.11 ± 1.60 , 81.23 ± 1.61 and 78.93 ± 2.51 for FDP, DP and placebo patients (Table 1). There was no significant difference between enrolled groups from the point of age, sex and weight ($p>0.05$).

Table 1: Demographic characteristics of patients involved in the trial in three groups of fenugreek dermal patch, diclofenac dermal patch and placebo.

Variable	FDP ^a	DP ^b	Placebo	p Value ^c
Sex	2 (6.90 %)	1 (4.16 %)	1 (4.17 %)	Not significant
Female (%)	27 (93.10 %)	23 (95.83 %)	25 (96.15 %)	Not significant
Male (%)				
Age (years)	43.0±11.0	44.8±10.5	44.2±13.5	Not significant
Weight (kg)	82.11±1.60	81.23±1.61	78.93±2.51	Not significant

^aFenugreek dermal patch, ^bDiclofenac dermal patch, ^cBased on Chi-square.

Pain intensity score has been shown in Table 2. As shown, the patients who were treated with FDP reported significantly less pain 1 h ($p<0.005$) and 6 h ($p<0.001$) after operation in comparison with those in placebo and DP groups (Table 2). Pain score was significantly different in FDP group up to 24 h in comparison to placebo too. Patients in DP group also reported pain relief in comparison to placebo from 6 h to 24 h post-operation ($p<0.05$) (Table 2).

Table 2: Pain intensity using visual analogue score (VAS) in different intervals after inguinal hernia surgery in patients treated with fenugreek dermal patch (FDP), diclofenac dermal patch (DP) and placebo.

Time (h)	FDP ^a	DP ^b	Placebo
After 1 h	2.4±0.54 ^{ab}	4.49±1.20	5.55±1.02
After 6 h	3.92±0.47 ^{ab}	5.17±0.51 ^a	6.88±0.91
After 12 h	3.75±0.96 ^a	2.93±1.21 ^a	4.26±0.45
After 18 h	1.77±0.21 ^a	1.6±0.32 ^a	2.08±0.24
After 24 h	1.23±0.53 ^a	1.55±0.12 ^a	2.01±0.37
After 48 h	1.1±0.33	1.3±0.40	1.5±0.26

^aSignificantly different from placebo, ^bSignificantly different from diclofenac patch based on Chi-square ($p<0.05$).

Morphine consumption in patients treated with fenugreek dermal patch (FDP), diclofenac patch (DP) and placebo in the first 24 h after operation has been shown in Table 3. Average of morphine injection significantly was decreased in patients who received FDP (5.63±2.38) and DP (5.83±2.73) in comparison to placebo group (9.33±3.21) ($p=0.003$), but no significant difference was considered between FDP and DP treated patients ($p=0.016$).

Table 3: Morphine consumption, demand for diclofenac suppository and side effects severity in patients treated with fenugreek dermal patch (FDP) in comparison to diclofenac patch (DP) and placebo.

Group	Mean of morphine consumption (mg/kg/h)	Mean of patients with diclofenac suppository Demand	Nausea and vomiting	Pruritus
Placebo	9.33±3.21	10±3	12±3	6 %
FDP	5.63±2.38 ^a	7±1 ^{ab}	8±1	0 %
DP	5.83±2.73 ^b	17±3	7±1	0 %

Pain severity measured using a visual analogue scale, values are given as mean±SD unless otherwise indicated. ^aSignificantly different from placebo ($p<0.05$), ^bSignificantly different from diclofenac gel ($p<0.05$).

Mean of diclofenac suppository demand was compared in different groups and the results indicated a significant decrease in FDP patients in comparison to DP group ($p=0.025$). No significant difference was observed between placebo and DP ($p>0.05$) (Table 3).

The least occurrence of vomiting and nausea was due to DP-treated patients (7±1) followed by FDP (8±1) and placebo (12±3) without any statistically significant difference ($p=0.22$). None of the patients experienced pruritus as the one of common side effects of morphine (Table 3).

Discussion

In this study, FDP 10% was applied topically in IH post-operative patients twice daily and the pain score was compared to ones in the patients treated with diclofenac patch 1% and placebo group using VAS. This method of measurement is a simple and quick way for acute pain assessment, but might be affected by different parameters such as cognitive status, education and age. A total of 90 patients were enrolled in the study (of them 79 patients stayed in the trial), of which 95.6% of them were male due to more incidence of IH. Patients were not significantly different with respect to sex, weight and age (Table 1) ($p > 0.05$). The participants who treated with FDP, reported a gradual but significant pain reduction during the first 6 h after operation up to 24 h ($p < 0.005$) (Table 2). Both FDP and DP decreased post-operative pain and caused a slight reduction in the average of demand of analgesic dose. The mean of pain score in FDP-treated patients was significantly lower than patients in DP and placebo groups 1 h ($p = 0.001$) and 6 h ($p = 0.005$) after operation (Table 2). The average of 24 h morphine consumption was significantly lower in FDP-treated patients in comparison to placebo group ($p = 0.003$) but was not significantly different from DP patients ($p > 0.05$). Demand for diclofenac suppository was significantly lower in FDP group in comparison to placebo and DP group ($p = 0.024$) (Table 3). The least occurrence of vomiting and nausea was observed in patients treated with DP and FDP respectively. Pruritus also was rarely common in three groups of patients. No other severe reaction and or side effects was observed in the patients which might be due to the short time of study that did not exceed more than 48 h. This trial is the first clinical study for assessing the analgesic effect of fenugreek. Our previous studies confirmed *in vivo* analgesic effect of this plant in animals too [19, 20]. The results of the present study demonstrated that FDP reduced the pain score especially up to 24 h post-operation (Table 2 and Table Table 3). Fenugreek seeds contain about 1.6 mg trigonelline/g dry extract which has a low molecular weight ($MW = 137$) and readily soluble in intracellular fluids. This compound can diffuse through the skin barriers and enters the blood stream and so can be efficient in the state of chronic pains which occurs in some post-operative patients. Oral consumption of 40 mg/kg fenugreek seeds has shown antinociceptive effect in comparison to diclofenac (5 mg/kg) and pentazocin (5 mg/kg) [21]. In post-operative pain, tendency has been attracted focus for using of multimodal analgesia and development of new routes for drug administration especially in topical form. Topical use of antinociceptive medications can overcome problems such as absorption and bioavailability challenges through GI and safety profile [22]. This route of use can block peripheral locations of pain and maximize the drug delivery to the site of pain with the least systemic effects. Direct application of drug in the site of the pain is more interested even if the pain results from another location. The skin is permeable to many foreign matters especially the small and lipophilic ones [23] and formulations with such medication molecules can partly transfer through the skin. Different mechanisms have been proposed for the plant antinociception effect, e. g. involvement of endogenous opioids and the presence of some steroids which act through inflammation suppression [24]. Clinical experience and some animal data indicate that at least a part of post-operative pain is due to neuropathic pains which happen acutely due to nerve injury. For example after cancer surgery, acute neuropathic pain was reported in the first week of post-operation in about 10% of patients [25]. Acute neuropathic pain can increase the risk of chronic pains [26]. On the other hand, chronic pain is the most significant complication after IH surgery. This pain progresses promptly and continues for at least 2 months [27]. The source of pain mostly is attributed to tissue inflammation and local nerve injury or entrapment [28]. In addition, several studies indicate that in the early days after surgery in post-operative patients, high pain sense is due to peripheral sensitization and primary afferent activation, and there are relations between pain location and sensory trouble. So pathophysiological mechanisms of pain might be related to the direct injury of intraoperative nerve or inflammation response that laed to nerve damage [26]. Antioxidants can be involved in the nociceptive process through scavenging of reactive oxygen and nitrogen species. Nitric oxide (NO), a signaling molecule, which is synthesized in the brain and can generate highly reactive peroxynitrite radical (ONOO⁻), is the primary component of nitroxidative stress [29]. However, the accurate mechanism of action of fenugreek has not been known, and alkaloids, flavonoids like apigenin and rutin as well as plant saponins might be responsible for antinociception effect [30, 31].

Transdermal patches have different advantages such as the ease of application, lack of hepatic first pass and best patient acceptance [32]. Different herbal and chemical patches have been reported for topical analgesic purposes such as the use of lidocaine patch for local use in patients with osteoarthritis [33], topical use of capsaicin for chronic pains [34], fentanyl patch for control of chronic pains [32] and single dose and multiple doses of cannabis extract for postpartum nociception [35]. Our data indicated that topical patch of fenugreek is an effective formulation for decreasing pain in IH post-operative patients; however the data used in this study were limited to a relatively small sample of patients and a short period (48 h) after the surgical interventions.

In conclusion, in the present work, topical use of fenugreek dermal patch significantly decreased the pain score in IH post-operative patients. This treatment was safe and free from allergic and/or severe early side effects. Fenugreek patch is a new option for topical purposes which can be a helpful way for overwhelming the pain and minimizing the side effects of antinociceptive drugs. There were some limitations in the present

work which was due to short-time analgesic therapy and quick discharge of patients from hospital obstruct. It is needed to do this clinical study in larger populations of patient and the other surgical techniques to get more logical results. In addition, further studies are necessary to verify the safety and effectiveness of FDP for extended use. Separation of active phytochemicals might lead to access new therapeutic agent which is being carried out.

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