Original Article

Preoperative Oral Valiflore Reduces Anxiety in Laparoscopic Cholecystectomy: a Double Blind, Placebo Controlled Study

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Abstract

Background: Many patients undergoing surgical procedures experience preoperative anxiety. Therefore; develop a drug as a premedication with strong anxiolytic effect and minimal psychomotor impairment is desirable.

Materials and Methods: Under ethics committee approval, eighty patients, who met the inclusion criteria, were randomly assigned to two groups to receive either oral Valiflore (600 mg, Niak) or placebo as a premedication, 90 minutes before surgery. A numerical rating scale (NRS) for anxiety and the Ramsay sedation scale were measured at baseline, and 15, 30, 60, 90 minutes after premedication. Psychomotor function recovery was assessed using the Digit Symbol Substitution Test and the Trieger Dot Test on arrival in the operating room, 30 and 90 minutes after tracheal extubation. The duration of anesthesia, surgery and recovery time were recorded for each patient.

Results: There were no significant differences in the patients' demographic characteristics, ASA physical status, basal NRS score, the sedation level at different time intervals, duration of anesthesia, surgery and recovery time in the two groups ($p>0.05$). The NRS anxiety scores were significantly lower in the Valiflore group in comparison with the control group ($p<0.001$). There was no significant difference in psychomotor function test in both groups.

Conclusion: Oral administration of Valiflore as a premedication reduces anxiety before surgery without inducing sedation.

Keywords: Anxiety, Herbal medicine, Premedication, Preoperative anxiety, Valiflore

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Introduction

Patients undergoing surgical procedures often experience high levels of anxiety (1, 2). This anxiety may induce adverse effects resulting in unfavorable physiological changes, including elevated blood cortisol levels and sympathetic hyperactivity leading to slower wound healing, decrease immune response and increase risk of infection. High anxiety may also adversely impact patients' experience of the surgery and intrude treatment process (2-4).

To reduce patient anxiety, anxiolytic premedications are highly recommended (2). Benzodiazepines are the most commonly used anxiolytic in reducing preoperative anxiety. These drugs are frequently accompanied by side effects,

such as drowsiness, respiratory suppression and may interact with anesthetic agents to prolonged recovery and discharge of the patient (3, 5). Therefore, safe alternative treatments are considered.

Phytotherapeutic products have been administered increasingly to control anxiety (6, 7). Valiflore is an herbal medication containing combined extracts of *Passiflora incarnata Linneaus* and *Valeriana* officinalis.

Passiflora incarnata L. (Passion Flower) is a plant in the family of *Passifloraceae* that has traditionally been used as an anxiolytic and sedative worldwide since ancient times (8, 9). *Valeriana officinalis* (Valerian root) is a traditional herbal supplement from the *Valerianaceae* family, which has been widely used to reduce anxiety, restlessness, somatic arousal, as well as improve sleep disorders (10-13).

The therapeutic efficacy of valerian has been confirmed by the European Medicines Evaluation Agency in an actual monograph (Committee on Herbal Medicinal Products (HMPC/ EMEA) (11).

To our knowledge, the use of Valiflore on anxiety before inducing anesthesia has never been evaluated. In this double-blinded, placebo-controlled clinical trial, we hypothesized that the use of Valiflore as a premedication alleviates preoperative anxiety with limited impact on anesthesia and recovery. The primary outcome of the present study was to investigate the efficacy of preoperative oral administration of Valiflore on anxiety levels of patients during the preoperative period. The sedative effects, psychomotor function, anesthesia duration, surgery duration and the recovery period were assessed as secondary outcomes.

Methods

The study protocol was approved by the Tehran University of Medical Sciences Ethics Committee and written informed consent was obtained from all patients. The trial is registered at the Iranian Registry of Clinical Trials (IRCT.ir) with the registration number IRCT201404115175N13.

Eighty patients aged 20–55 years, classified as American Society of Anesthesiologists (ASA) physical status I and II, who were undergoing elective surgical laparoscopic cholecystectomy were enrolled in this randomized, double-blinded, placebo-controlled study. Patients with a history of chronic diseases, anxiety and other mental and psychological disorders, those consuming any medication chronically, including anti-depressant, sedative, analgesic and antiepileptic drugs, patients with pre-operative numerical rating scale for anxiety less than one were excluded from the study.

At the preoperative visit, all patients received an explanation of the study plan and the different scales used in the study by a trained investigator. An anesthesiologist who was not involved in anesthesia administration or in patient allocation prepared all drugs; thus, patients and investigators were blinded to group assignment. Patients were randomly allocated into two groups, control (group C, n=40) and intervention (group V, n=40) using a computer generated randomization list.

Approximately 2 hours before surgery, patients were transferred to a quiet room in the operating suite. All patients were assessed by monitoring with an electrocardiogram, noninvasive arterial blood pressure, and pulse oximetry on arrival to the operating room.

The patients' level of anxiety was evaluated using a Numeric Rating Scale (NRS); a 0–10 scale, where 0= no anxiety and 10=the worst possible anxiety. Patients' level of sedation was assessed using the Ramsay sedation scale where 1=agitated, anxious or restless; 2=cooperative, oriented and tranquil; 3=responds to commands only, 4=asleep, brisk response to light glabellar tap or auditory stimulus; 5=asleep, sluggish response to light glabellar tap or auditory stimulus; 6=asleep, no response (14).

Instantly prior to receiving the premedication or placebo, each patient was assessed for their baseline anxiety score using a Numeric Rating Scale and their baseline sedation level using the Ramsay sedation scale.

Patients in the control group received a placebo tablet and patients in the intervention group received a Valiflore tablet orally 90 minutes before surgery. The placebo and the active forms of drugs were identical in appearance.

The NRS score and Ramsay sedation score were repeated at 15, 30, 60 and 90 (immediately before induction of anesthesia) minutes after drug

taken.

Psychomotor function was assessed using Trieger Dot Test (TDT) and Digit-Symbol Substitution Test (DSST) at preoperative baseline, 30 and 90 minutes after tracheal extubation. The TDT is a variation of the Bender-Gestalt test in which the patients were required to arrange a series of dots connected in a specific pattern. Points are subtracted for missing a dot. TDT deviation represents the cumulative distance (in millimeters) between the drawn line and missed dots. The DSST is a subtest of the Wechsler Adult Intelligence Scale. It is a timed paper and pencil test in which patients are asked to appropriately match numbers and symbols. The number of correct symbols matches during 90 seconds is the score (6).

In the operating room, a standard general anesthesia method was used in all patients. Anesthesia was induced with Alfentanil 15 µg/kg and Propofol 2.5mg/kg. Cisatracurium 0.2 mg/kg was administrated to facilitate orotracheal intubation. Anesthesia was maintained with Propofol 60-100µg/kg/min and 1 µg/kg/min Alfentanil.

Mechanical ventilation was adjusted to maintain end-tidal carbon dioxide (ETCO2) pressure at 35-40mmHg level. Patients were actively warmed to maintain body core temperature (esophageal normothermic). At the end of the surgery, neuromuscular block was resolved by the administration of neostigmine 2.5mg and atropine 1mg. The duration of anesthesia, surgery and recovery were assessed and recorded for all patients.

At the post-anesthesia care unit (PACU), patients received supplemental oxygen via a nasal cannula at 4 liters/minute-1. Postoperative pain was treated with 3mg/kg-1 Tramadol during 10 minutes infusion. Postoperative nausea and vomiting were treated with 4mg Ondansetron intravenously.

Patients were discharged from the PACU when they were awake and oriented, and were able to breathe deeply and cough freely, their arterial blood pressure was within 20% of preoperative values, their body temperature>36°C, and there was no shivering, minimal pain, and minimal nausea (15).

Based on the pilot study of 10 patients, 63% of patients experienced moderate to severe anxiety (score 4 to 10) before surgery (at 90 minutes). For a predicted 50% reduction in the percentages of patients experienced anxiety and bringing it to 32 was calculated that a sample size of 40 patients in each group would be sufficient to detect a three score difference in the mean of anxiety score between the two groups considering a power of 80%, and a significance level of α=0.05.

Statistical analyses were performed using SPSS software (SPSS Inc., Chicago, IL, USA), version 20. To compare demographic data, ASA physical status, the basal NRS anxiety score, the duration of anesthesia, surgery and recovery time between the two groups, independent sample t-test was performed.

The repeated measures analysis of variance (ANOVA) was utilized to assess the changes in NRS for anxiety between groups and the changes over time in each group.

To compare the sedation scores between groups at each measurement time, the Fisher's exact test was used and to compare the sedation scores in groups within time, the Friedman test was used.

Data are presented as mean ± standard deviation (SD), median (range), or number (incidence) as appropriate. Statistical significance was considered significant when P value<0.05.

Results

We randomized 80 patients. No patients dropped out and all patients were included in the data analysis. A flow diagram of conduct of the trial is presented in figure 1.

Patients' characteristics, ASA physical status, the duration of anesthesia, surgery and recovery time were similar in the two groups (Table 1).

The basal NRS anxiety scores were similar in the Valiflore group (5.62±0.89) and in the control group (5.87±1.06) (p>0.05). A significant difference in the mean NRS anxiety scores from the baseline was found in the Valiflore group over time (p<0.001) (Figure 2).

Based on Ramsay sedation scores, the sedation levels of the patients were similar over time within and between groups (Fisher's exact test, p>0.05; Friedman test, p>0.05) (Table 2).

Psychomotor function scores were similar in both groups. The psychomotor function scores were

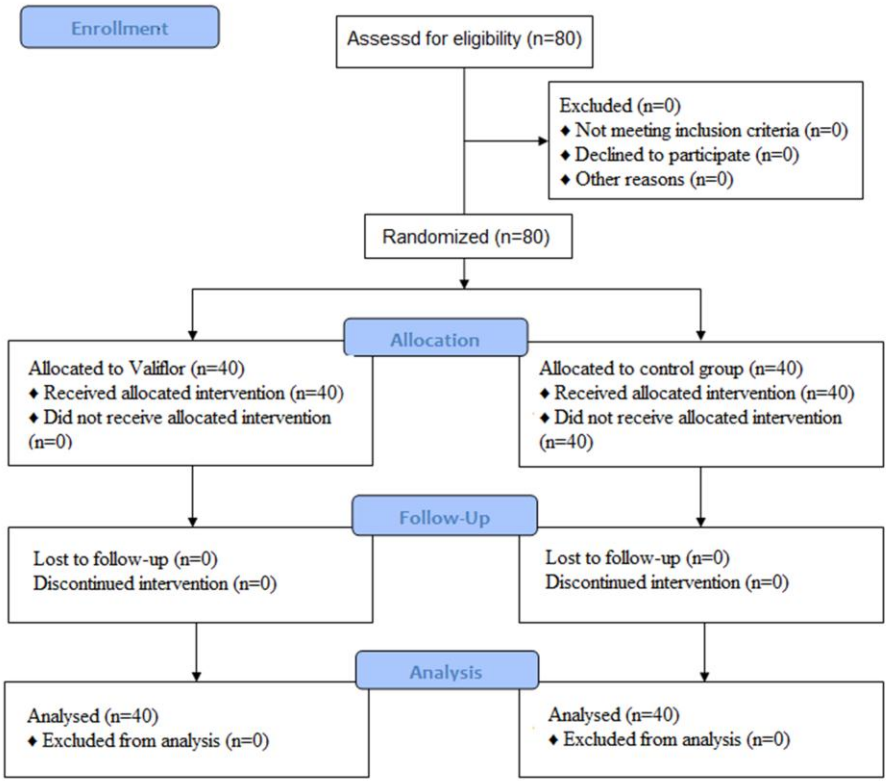

Figure 1. Flow diagram according to CONSORT statement.

Table 1: Patient Characteristics. There was no significant difference between groups.

	Valiflore group (n=40)	**Control group (n=40)**
Age (years)	37.1±8.7	39.5±6.3
Weight (kg)	64.4±9.4	67.0±10.0
ASA I/II	21/19	19/21
Anesthesia duration (min)	118.6±5.9	118.0±7.6
Surgery duration (min)	86.4±6.0	87.0±7.1
Recovery duration (min)	29.3±4.9	28.8±5.7

significantly reduced 30 minutes after tracheal extubation in both groups; however, within 90 minutes after extubation they reached baseline values (Table 3).

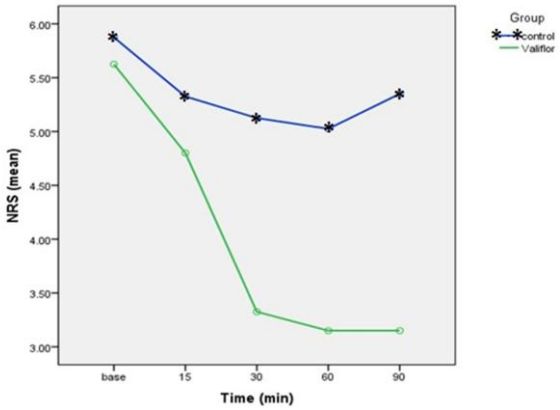

Figure 2. Numeric Rating Scale (NRS) of anxiety at different time intervals.

Discussion

This study demonstrates that patients who received oral premedication with Valiflore experienced lower preoperative anxiety compared with patients who received placebo.

Table 2: Sedation in Groups. There was no significant difference.

	Valiflore group (n=40)	**Control group (n=40)**
Before premedication		
Agitated, anxious or restless	0	0
Cooperative, oriented and tranquil	40 (100%)	40 (100%)
Responds to commands only	0	0
Brisk response to light glabellar tap or auditory stimulus	0	0
Sluggish response to light glabellar tap or auditory stimulus	0	0
No response	0	0
15 min after premedication		
Agitated, anxious or restless	0	0
Cooperative, oriented and tranquil	40 (100%)	40 (100%)
Responds to commands only	0	0
Brisk response to light glabellar tap or auditory stimulus	0	0
Sluggish response to light glabellar tap or auditory stimulus	0	0
No response	0	0
30 min after premedication		
Agitated, anxious or restless	0	0
Cooperative, oriented and tranquil	40 (100%)	40 (100%)
Responds to commands only	0	0
Brisk response to light glabellar tap or auditory stimulus	0	0
Sluggish response to light glabellar tap or auditory stimulus	0	0
No response	0	0
60 min after premedication		
Agitated, anxious or restless	0	1 (2.5%)
Cooperative, oriented and tranquil	40 (100%)	39 (97.5%)

Responds to commands only	0	0
Brisk response to light glabellar tap or auditory stimulus	0	0
Sluggish response to light glabellar tap or auditory stimulus	0	0
No response	0	0
90 min after premedication		
Agitated, anxious or restless	0	0
Cooperative, oriented and tranquil	40 (100%)	40 (100%)
Responds to commands only	0	0
Brisk response to light glabellar tap or auditory stimulus	0	0
Sluggish response to light glabellar tap or auditory stimulus	0	0
No response	0	0

The onset and the peak effects of Valiflore's anxiolytic activity were observed at 15 and 60 minutes following oral administration. It was notable that the single dose of the Valiflore tablet led to 43% decrease in the level of anxiety.

In both groups, psychomotor impairment occurred 30 minutes after surgery; although, they returned to the basic levels after 90 minutes.

Also, the recovery time was similar in both groups which present that the administration of Valiflore as a premedication does not affect psychomotor function or discharge time to home. Preoperative Anxiety has been reported in 11–80% of adult patients, which can lead to unfavorable health outcomes result in longer recovery time and hospital stays. Prevention of preoperative anxiety, improves surgical outcome and decreases inpatient stay (3, 16).

Passiflora incarnata and Valerian root are popular medicinal plants for the treatment of anxiety with a long history of usage in the world (10, 17, 18). In Iran, compound drug has been introduced to the market with the trade name ''Valiflore'' (Niak R). In the present study, the effect of this almost new herbal combination on preoperative anxiety was evaluated.

Passiflora incarnata's anxiolytic effects have been supported in many well-documented studies, though; the active phytoconstituents and the exact mechanism of action responsible for the therapeutic properties have not been identified yet (19).

The anxiolytic activity of *Passiflora incarnata* has been attributed to mediate via benzodiazepine and γ-aminobutyric acid receptors (6, 17). Flavonoids are considered for the most probable active ingredient; they have anxiolytic properties similar to benzodiazepines, and modulate or inhibit GABAA and GABAC receptor currents. Chrysin has been shown to act as a partial agonist of benzodiazepine receptors and GABA was found to be a prominent ingredient of Passiflora extract (20, 21).

The evidences also support the *Valeriana officinalis*'s efficacy and clinical safety in the treatment of anxiety with no effect on psychomotor performance, alertness or concentration (7, 22). *Valeriana officinalis* was the most reported product (19.4%) among herbal products which is used in preoperative patients (23). The main active constituents of *Valeriana officinalis* are valerenic acid and valepotriates (24). The presence of the anxiolytic flavone 6-methylapigenin (MA) in *Valeriana officinalis* also has been reported (13). The exact mechanism of action of *Valeriana officinalis* has remained unknown. Neurobiological studies showed that valerenic acid interacts within the GABAA-ergic system, similarly to a mechanism of action of the benzodiazepine drugs, by binding to specific subunits of the GABAA receptor complex, result in opening of chloride channels and producing neural inhibition. Valerenic acid also has been attributed to work via

Table 3: Psychomotor Function tests.

	Valiflore group (n=40)	**Control group (n=40)**
TDTmm	0.8 ± 0.5	0.8 ± 0.3
Preoperative baseline		
TDTmm	1.8 ± 1.0	2.0 ± 1.0
30 min after extubation [a]		
TDTmm	0.6 ± 0.2	0.7 ± 0.2
90 min after extubation		
TDTnr	0.8 ± 0.3	0.8 ± 0.2
Preoperative baseline		
TDTnr	1.9 ± 1.1	1.8 ± 0.8
30 min after extubation [a]		
TDTnr	2.8 ± 0.3	0.9 ± 0.5
90 min after extubation		
DSST	25.1 ± 7.2	24.0 ± 6.3
Preoperative baseline		
DSST	18.1 ± 7.2	18.2 ± 6.6
30 min after extubation [a]		
DSST	21.4 ± 6.2	22.1 ± 6.6
90 min after extubation		

a There was a significant difference

modulation of the serotonergic system, adenosine receptors or melatonergic effects (10, 25).

In a double-blinded, randomized, controlled trial (RCT) 60 patients who were scheduled for spinal anesthesia were randomly allocated into two groups to receive oral *Passiflora incarnata* aqueous extract 700 mg 5 ml-1 or placebo. The result of this study showed that preoperative oral administration of *Passiflora incarnata* extract suppresses the increase in anxiety levels of patients before spinal anesthesia without changing in sedation level, psychomotor function test results, or hemodynamics (17).

In another study *Passiflora incarnata* extract was administered as a premedication to control presurgical anxiety in patients undergoing elective surgery under general anesthesia. A total of 60 patients was randomized into two groups to receive a *Passiflora incarnata* or a placebo tablet as a premedication, 90 minutes before surgery (n=30 for each group). The results revealed a significant reduction of preoperative anxiety in Passiflora group compared with placebo without inducing sedation or changing psychomotor function (6).

Contrary to all these reports, the study by Elsas and colleagues; in 2010 showed that Passiflora extracts have anxiogenic effects instead of the expected anxiolytic effects. The unexpected anxiogenic activity of Passiflora extracts may attributed to some conditions, such as dosage changes in flavonoids, which act as weak agonists to weak antagonists at specific GABAA receptor subtypes (20).

There are a few reports of adverse effects associated with *Passiflora incarnata* consumption (26), there are no such reports about *Valeriana officinalis*. Nausea, vomiting, prolonged QT, and ventricular arrhythmias developed following self-administration of *Passiflora incarnata* in a 34 year-old female patient (27). Hypersensitivity with cutaneous vasculitis, urticaria, asthma, and rhinitis after ingestion of tablets containing Passiflora extract has also been reported (6). Furthermore, Passiflora has been attributed to induce uterine contraction so its use is contraindicated during pregnancy (6, 17, 27). Altered consciousness has been reported after taking an herbal compound containing *Passiflora incarnata*. It was recommended not to take *Passiflora incarnata* with CNS depressants or stimulants to minimize possible adverse effects on CNS (27) although; these side effects are sporadic, and only occurred after chronic usage.

In the study, we used the 600 mg Valiflore tablet introduced by Niak pharmaceutical company-Iran, which may differ from other products in constituents or efficacy. It consists of dry extracts from Passion flower (30mg) and Valerian (100mg).

Valeriana officinalis extract ratio of 33% and *Passiflora incarnata* extract ratio of 9.9% is prepared.

The therapeutic dose of Valiflore for anxiety is 1-2 tablet/s once or twice a day. As Oral administration of Valiflore to reduce preoperative anxiety has not been evaluated, we used the minimum effective dose, a single dose of tablet (600 mg) to minimize few possible side effects. At the end of surgery, Valiflore presented a better effect than placebo. In this study, the patients were not required to complete side effect questionnaires, but they were asked to verbally report if they experienced any side effects both during and at the end of the day and no evidence of side effects were reported.

One limitation of this study was that we evaluated the psychological stress with subjective assessment tools which are not reliable parameters to assess anxiety as they are patient dependent. Therefore more physiological parameters such as stress biomarkers may have been able to assess subtle effects of the medication on the patients' level of anxiety. This would be an interesting consideration for future studies.

Conclusion

In conclusion, preoperative oral administration of Valiflore tablet was effective in reducing anxiety without changing in the sedation level or impairing psychomotor function compared with placebo. As this trial was the first study on the issue, more trials are required.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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