Preoperative Oral *Passiflora Incarnata* Reduces Anxiety in Ambulatory Surgery Patients: A Double-Blind, Placebo-Controlled Study

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BACKGROUND: Many patients have preoperative anxiety; therefore, the development of a strong anxiolytic with minimal psychomotor impairment for premedication may be desirable.

METHODS: In this study, 60 patients were randomized into two groups to receive either oral *Passiflora incarnata* (500 mg, Passipy™ IranDarouk) ($n = 30$) or placebo ($n = 30$) as premedication, 90 min before surgery. A numerical rating scale (NRS) was used for each patient to assess anxiety and sedation before, and 10, 30, 60, and 90 min after premedication. Psychomotor function was assessed with the Trieger Dot Test and the Digit-Symbol Substitution Test at arrival in the operating room, 30 and 90 min after tracheal extubation. The time interval between arrival in the postanesthesia care unit and discharge to home (discharge time) was recorded for each patient.

RESULTS: The demographic characteristics of patients, ASA physical status, duration of surgery, basal NRS score, sedation at the preset time intervals, and discharge time were similar in the two groups. The NRS anxiety scores were significantly lower in the passiflora group than in the control group ($P < 0.001$). There were no significant differences in psychological variables in the postanesthesia care unit and recovery of psychomotor function was comparable in both groups.

CONCLUSIONS: In outpatient surgery, administration of oral *Passiflora incarnata* as a premedication reduces anxiety without inducing sedation.

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Many patients have preoperative anxiety; therefore, it would be desirable to develop a drug (preferably given orally) for premedication that is a strong anxiolytic with minimal psychomotor impairment. Benzodiazepines are presently the most commonly used class of anxiolytics. Midazolam, because of its short duration of action, is the most popular; however, the oral formulation of midazolam is not approved in certain countries.[1–3] Herbal remedies are an increasingly popular form of therapy.[4] The genus *Passiflora*, comprising about 500 species, is the largest in the family passifloraceas (the passion flower family). The species of this genus are distributed in the warm temperature and tropical regions of North and South America; they are much rarer in Asia, Australia, and tropical Africa.[5] *Passiflora incarnata* Linnaeus is a plant, which has traditionally been used as an anxiolytic and sedative throughout the world.[6] Germany's Commission E (Appendix) approved the use of passion flower for nervous restlessness and the British Herbal Compendium indicates its use for sleep disorders, restlessness, nervous stress, and anxiety.[7–9] Basic science studies have demonstrated its anxiolytic properties for rats.[10,11]

To our knowledge, the use of *Passiflora incarnata* in anesthesia has never been evaluated. We thus hypothesized that oral *Passiflora incarnata* would be an effective anxiolytic with limited impact on anesthesia and recovery. This study was designed to compare the effect of oral *Passiflora incarnata* with placebo as a premedication. The anxiolytic and sedative effects, in addition to psychomotor performance and discharge time, were evaluated.

METHODS

The protocol was approved by the Institutional Ethics Committee and informed written consent was obtained from the patients. Sixty patients, 25–45 yr, classified as ASA physical status I and II who were undergoing inguinal herniorrhaphy, were enrolled in this randomized, double-blind, and placebo-controlled study. Patients with a history of anxiety disorders, those consuming sedative, analgesic, antidepressant,

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or antiepileptic drugs, and patients with verbal analog scale for anxiety <1, were excluded from the study.

At the preoperative visit, a trained investigator explained to the patient the study plan and the different scales used in the study. All drugs were prepared by an anesthesiologist who was not involved in anesthesia administration or in patient observation; thus, both the anesthesiologist and the patients were blinded to group assignment. Patients were randomly assigned into two groups control (group C, $n = 30$) or passiflora (group P, $n = 30$) using a computer-generated randomization list.

Approximately 2 h before surgery, patients were transported to an isolated quiet room in the operating suite. All patients were monitored with an electrocardiogram, noninvasive arterial blood pressure, and pulse oximetry. Patients in group C received placebo and those in group P received *Passiflora incarnata* (500 mg, Passipy™ IranDarouk) orally 90 min before surgery. Each tablet contains 1.01 mg benzoflavone (BZF). The placebo and active form of drug were identical in appearance.

A numeric rating scale (NRS) was used to evaluate anxiety, where 0 = no anxiety and 10 = the worst possible anxiety. The NRS score and sedation score (1 = awake; 2 = drowsy; 3 = asleep, but arousable; 4 = asleep, but not arousable) were measured before, and 10, 30, 60, 90 min after administration of premedication.

Psychomotor function was assessed with the Trieger Dot Test (TDT) and the Digit-Symbol Substitution Test (DSST)[1] at arrival in the operating room, 30 and 90 min after tracheal extubation. The TDT is a variation of the Bender-Gestalt test in which the patient is asked to connect a series of dots arranged 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 pen-and-paper test in which patients are required to appropriately match numbers and symbols. The score is the number of symbols correctly matched during 90 s.

In the operating room, an infusion of lactated Ringer's solution was commenced. Anesthesia was induced with alfentanil 15 μg/kg, propofol 2.5 mg/kg; the trachea intubated after administration of cisatracurium 0.2 mg/kg, and ketorolac 0.5 mg/kg (maximum 30 mg) given for postoperative analgesia. After tracheal intubation, anesthesia was maintained with propofol (100 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and alfentanil (1 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Ventilation was adjusted to maintain normocapnia (end-tidal carbon dioxide partial pressure 4.7–5.3 kPa). Patients were actively warmed to keep core temperature (esophageal) normothermic. At the beginning of skin suturing, drug infusion was stopped and neuromuscular block was antagonized by IV administration of 2.5 mg of neostigmine along with 1.0 mg atropine. Patients were considered awake when they opened their eyes on command or after gentle tactile stimulation; they were tracheally extubated soon thereafter.

In the postanesthetic care unit (PACU), patients received oxygen via a nasal cannula (4 L/min). Postoperative pain was treated with 3 mg/kg tramadol that was infused over 10 min. Postoperative nausea and vomiting were treated with ondansetron 4 mg IV. PACU discharge criteria included being awake and oriented, able to breath deeply and cough freely, arterial blood pressure within 20% of preoperative values, temperature >36 degrees, absence of shivering, minimal pain, and minimal nausea. The time interval between arrival to PACU to discharge home (discharge time) was recorded for every patient.

On the basis of a pilot study of 10 patients (5 in each group), we determined that a sample size of 27 in each group would be sufficient to detect a difference of three scores in the mean of anxiety score, estimating a standard deviation of 3, a power of 95%, and a significance level of 5%; this number was increased to 30 per group, to allow for a predicted drop-out from treatment of around 10%. Statistical analysis was performed using SPSS package (SPSS Inc., Chicago, IL), version 11.5. The distribution of age, weight, surgery time, home discharge, psychological variables, and NRS anxiety score was checked by the Kolmogorov-Smirnov test. They followed a normal distribution. Age, weight, surgery time, home discharge, the basal psychological variables, and the basal NRS anxiety score were compared between two groups by independent sample t-test. The repeated measures ANOVA was used to assess the differences of NRS for anxiety and psychological variables between groups and the changes over time in each group. The sedation scores were an ordinal scale measurement. To compare the sedation scores between groups in each measurement time, χ^2 and Fisher's exact tests (when appropriate) were used. To compare the sedation scores within groups against time, the Friedman test was used. The sex and ASA physical status class were compared with χ^2 test. Two-tailed $P < 0.05$ was taken as significant.

RESULTS

We randomized 60 patients. There were no protocol violations, and all patients were included in the analysis.

Demographic characteristics, ASA physical status, and the duration of surgery were similar in the two groups (Table 1).

The basal NRS anxiety scores (mean ± SD) were similar in the passiflora group (4.6 ± 1.7) and in the control group (5.1 ± 2) ($P < 0.05$).

There was a significant difference in the mean NRS anxiety scores measured over time between the two groups (repeated-measures ANOVA, between-subjects effects, $P < 0.001$) (Fig. 1). The changes in NRS anxiety

Table 1. Patient Characteristics

	Passiflora group (n = 30)	Control group (n = 30)
Age (yr)	32.0 ± 4.6	31.7 ± 5.1
Sex (F/M)	14/16	16/14
Surgery time (min)	68 ± 25.6	74 ± 23.2
ASA class (I/II)	20/10	17/13
Weight (kg)	68.3 ± 7.5	70.1 ± 10.4
Home discharge (min)	212 ± 69	221 ± 73

Values are expressed as mean ± SD.

* There were significant differences between groups.

scores over time were significant in each group (repeated-measures ANOVA, tests of within-subjects effects, with significant interaction between NRS and group, $P < 0.001$) (Fig. 1).

There was no significant difference between groups in the level of sedation at 10, 30, 60, and 90 min (Fisher's exact test, $P > 0.05$) (Table 2). Sedation scores increased significantly in both the passiflora and control groups with time (Friedman test, $P < 0.001$ and $P = 0.009$, respectively).

There were no significant differences in the measured psychological variables in the PACU. Recovery of psychomotor function was comparable in both groups, although the psychomotor function scores were significantly reduced 30 min after tracheal extubation; they reached baseline values 90 min after extubation (Table 3).

There was no significant difference in discharge time between the two groups (Table 1).

Table 2. Sedation in Groups

	Passiflora group (n = 30)	Control group (n = 30)
Before premedication		
Awake	26 (86.7)	25 (83.3)
Drowsy	4 (13.3)	5 (16.7)
Asleep, but arousable	0 (0)	0 (0)
Asleep, but not arousable	0 (0)	0 (0)
10 min after premedication		
Awake	13 (43.3)	17 (56.7)
Drowsy	16 (53.3)	11 (36.7)
Asleep, but arousable	1 (3.3)	2 (6.7)
Asleep, but not arousable	0 (0)	0 (0)
30 min after premedication		
Awake	12 (40.0)	17 (56.7)
Drowsy	14 (46.7)	10 (33.3)
Asleep, but arousable	4 (13.3)	3 (10)
Asleep, but not arousable	0 (0)	0 (0)
60 min after premedication		
Awake	12 (20.0)	17 (56.7)
Drowsy	13 (43.3)	9 (30)
Asleep, but arousable	5 (16.7)	4 (13.3)
Asleep, but not arousable	0 (0)	0 (0)
90 min after premedication		
Awake	12 (20.0)	17 (56.7)
Drowsy	13 (43.3)	9 (30.0)
Asleep, but arousable	5 (16.7)	4 (13.3)
Asleep, but not arousable	0 (0)	0 (0)

* There was no significant difference between groups.

DISCUSSION

The current study demonstrates that patients who received oral premedication with *Passiflora incarnata*

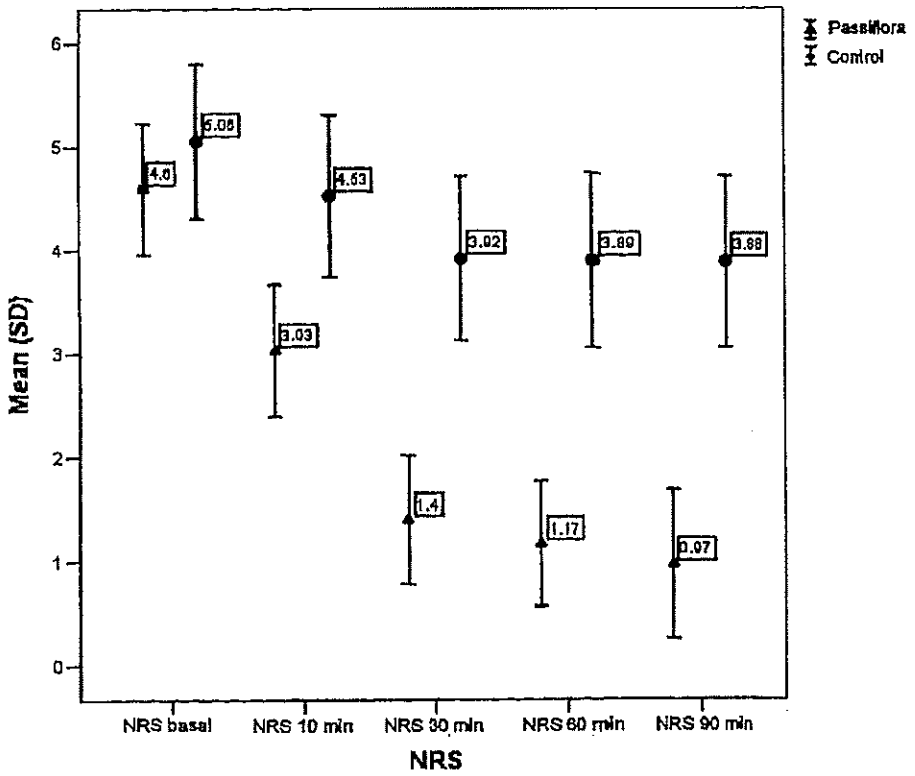

Figure 1. Numeric Rating Scale (NRS) anxiety scores at different time intervals.

Table 3. Recovery of Psychomotor Function

	Preoperative baseline	30 min after extubation	90 min after extubation
TDTmm			
Passiflora group*†	0.7 ± 1.1	1.8 ± 1.0	0.7 ± 0.2
Control group*	0.6 ± 1.0	1.6 ± 0.9	0.6 ± 0.3
TDTnr			
Passiflora group*	0.7 ± 0.62	1 ± 1.80	8 ± 0.5
Control group*	0.8 ± 0.9	2.2 ± 1.6	0.9 ± 0.8
DSST			
Passiflora group*	23.6 ± 7.2	18.1 ± 6.8	22.4 ± 6.5
Control group*	24.3 ± 6.2	17.2 ± 7.1	21.5 ± 7.1

Values are expressed as mean ± SD.

TDTmm = Trieger Dot Test millimeter missed; TDTnr = Trieger Dot Test number missed; DSST = Digital Symbol Substitution Test.

* $P < 0.05$, within groups, within-subjects effect.

† There were no significant differences between groups, between-subjects effect.

500 mg (Passipy, IranDarouk) had a significant decrease in anxiety levels compared with patients who received placebo.

The onset and peak effect of passiflora's anxiolytic activity were noted at 10 and 30 min, respectively, after oral administration.

After surgery, patients in both groups had performance impairment on the DSST and TDT test at 30 min, but there were no significant differences in psychomotor function at 90 min after tracheal extubation. Also, the recovery time was similar in both groups. Thus, our study demonstrates that the administration of *Passiflora incarnata* as a premedication provides anxiolytic activity without impairing psychomotor function or delaying discharge to home compared with placebo.

Previous studies showed that up to 80% of outpatients expressed a preference for a combination of anxiety-reducing and hypnotic premedication before surgery.[3]

Passiflora incarnata is a climbing plant with white, blue, purple, or red flowers and yellow ovoid fruit. The main constituents of the extract are flavonoids. Aerial parts have been used for sedative, anxiolytic, and antispasmodic purposes. The whole plant has also been used for insomnia, anxiety, and other central nervous system (CNS) disorders. The methanol extract of the aerial parts has been shown to possess significant anxiolytic activity.[11]

Despite a long history of use, supported by the well-documented phytochemical reports on *Passiflora incarnata*, the exact mode of its antianxiety effects and the phytoconstituents responsible for the much acclaimed CNS effects have not been described clearly. Earlier researchers have postulated different theories on the bioactive phytomoieties of *Passiflora incarnata* and there has been no consensus regarding the exact mode of the pharmacological activity of *Passiflora incarnata*. Other researchers have highlighted the role of the flavonoid chrysin and even the pyrone derivative maltol to be responsible for the CNS effects of the plant.[12] Recently, the sedative and anxiolytic activities in *Passiflora incarnata* have been attributed to the benzodiazepine and γ-aminobutyric acid receptors-mediated biochemical processes in the body.[13,14] Contrary to all these reports, the exhaustive pharmacological studies on *Passiflora incarnata* by Soulimani et al. have excluded the role of any of the known phytoconstituents being responsible for the well-established anxiolytic and sedative activity of *Passiflora incarnata*.[15]

Although *Passiflora incarnata* has been successfully used for relief of anxiety, systemic reviews concluded that there was insufficient evidence to show that *Passiflora* has anxiolytic properties.[16]

In a double-blind, randomized, controlled trial (RCT), 32 patients with generalized anxiety disorder were randomized to receive 45 drops of a passion flower tincture or 30 mg oxazepam per day.[17] After 4 days of treatment, no significant differences in anxiety levels were noted. Patients treated with passion flower reported fewer adverse effects than those receiving the synthetic anxiolytic. The authors concluded that *Passiflora* is effective. However, they were inconclusive about equivalent efficacy as the trial was not designed as an equivalence study.[16]

In another systemic review, two studies with 198 participants were found eligible for inclusion. The reviewers concluded that RCTs examining the effectiveness of *Passiflora* for anxiety are too few to permit any conclusions to be drawn. RCTs with larger samples that compare the effectiveness of *Passiflora* with placebo and other types of medication, including antidepressants, are needed.[18]

As noted previously, to our knowledge, the use of *Passiflora incarnata* in anesthesia has not been described in any studies. There are few reports of toxicity associated with *Passiflora* ingestion. In one report, a 34-yr-old woman developed nausea, vomiting, prolonged QT, and ventricular arrhythmias after 2 days self-administration of an herbal remedy containing *Passiflora incarnata*.[4] However, no acute toxicity was observed after intraperitoneal injection in mice of doses larger than 900 mg/kg.[4] In humans, a case of hypersensitivity with cutaneous vasculitis and urticara after ingestion of tablets containing *Passiflora* extract has been reported.[19] *Passiflora* is associated with IgE-mediated occupational asthma and rhinitis.[20] Also, *Passiflora* may induce uterine contraction and hence its use is contraindicated during pregnancy. However, these adverse effects are very rare and only occurred after chronic usage.[4]

The challenge for standardization of plant-derived medicines is the need to identify, select, and use only those plant parts which possess the maximum therapeutic efficacy.[11]Roots of *Passiflora incarnata*, being

devoid of anxiolytic effects, act as natural adulterants and should be separated from the aerial parts. The presence of flowers along with leaves and stems is also undesirable.[10] Therefore, separation of these parts is recommended before any pharmacological, phytochemical and standardization studies of *Passiflora incarnata*.

Furthermore, the constituents of commercially available tablets are variable. Therefore, the 500 mg tablet used in this study may differ from other 500 mg tablet in constituents or efficacy. The acceptable range of BZF of each 500 mg tablet is 0.9–1.1 mg, and as noted previously, the BZF concentration of our tablet was 1.01 mg.

The therapeutic dose of *Passiflora incarnata* is 500–1000 mg three times daily.[7]

Administration of oral *Passiflora incarnata* as a premedication to relieve preoperative anxiety has not been evaluated. We used the minimum dose that previous researches indicated was safe in adults.[7]

During the present study, we did not observe any evidence of side effects, although this was a very small sample size.

Our findings demonstrate that in the outpatient population, oral premedication with *Passiflora incarnata* 500 mg reduces preoperative anxiety without inducing sedation or changing psychomotor function.

APPENDIX

The German Commission E is a governmental regulatory agency that was established in 1978. It is composed of scientists, toxicologists, physicians, and pharmacists. It evaluated the usefulness of 300 herbs, studied the literature, clinical studies, case studies, field studies, and then prepared monographs. Published monographs list uses, side effects, and any known drug/herb interactions. It found 200 herbs as useful, and rejected the rest. The American Botanical Council based in Austin, Texas, published an English translation of the Commission E monograph text. It can be compared with the United States Food and Drug Administration.

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