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ORIGINAL ARTICLE

Passiflora incarnata Linneaus as an anxiolytic before spinal anesthesia

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Abstract
Purpose Patients who undergo regional anesthesia experience anxiety in the preoperative period. *Passiflora incarnata* Linneaus is a plant that has traditionally been used as an anxiolytic and sedative. We aimed to investigate the effect of preoperative oral administration of *Passiflora incarnata* Linneaus on anxiety, psychomotor functions, sedation, and hemodynamics in patients undergoing spinal anesthesia.
Methods Under local ethics committee approval, 60 patients who were aged 25–55 years and ASAI–II and who were scheduled for spinal anesthesia were enrolled in this prospective, randomized, double-blind and placebo-controlled study. Thirty minutes before spinal anesthesia, baseline hemodynamic parameters, State-Trait Anxiety Inventory (STAI) score, sedation score, and psychomotor function test results were measured, then patients were randomly assigned to two groups: oral *Passiflora incarnata* Linneaus extract or placebo was given to the patients. Tests were repeated just before spinal anesthesia. Hemodynamics, sedation score, sensory-motor block and side effects were assessed during the operation. Psychomotor function tests were repeated at the end of the operation and 60 min after the operation.
Results There was a statistically significant difference between the two groups for the increase in State Anxiety Inventory (STAI-S) score obtained just before spinal anesthesia when compared to the baseline. There was no statistically significant difference in psychomotor function from the baseline for either group. A significant difference was not found between the two groups in demographics, psychomotor function, sedation score, hemodynamics, and side effects.
Conclusion Oral preoperative administration of *Passiflora incarnata* Linneaus suppresses the increase in anxiety before spinal anesthesia without changing psychomotor function test results, sedation level, or hemodynamics.

Keywords Anesthesia · Spinal · Anxiety · *Passiflora incarnata*

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Introduction

Regional anesthesia is popular and offers several benefits to the patient. On the other hand, some drawbacks are linked with regional anesthesia: pain at the puncture site, fear of needles, seeing the surgery, and recalling the procedure. Anxiolysis helps to achieve a calm and cooperative patient during placement of the block and decreases the response to needle puncture. Additionally, sedation usually reduces postoperative recall, which is important for many patients but can be undesirable [1].

Passiflora incarnata Linneaus is a plant that has traditionally been used as an anxiolytic and sedative throughout the world. The plant is widely used in phytotherapy due to its mild sedative and anxiolytic properties [2, 3]. Although some studies have demonstrated its anxiolytic properties [2, 4–9], two recent systematic reviews have emphasized that randomized controlled trials that compare the effectiveness of *Passiflora* with placebo or other types of

medication are needed [10, 11]. There is only one study in the literature that focuses on the anxiolytic effect of *Passiflora incarnata* Linneaus before general anesthesia [8], and there is no data on the preoperative oral administration of *Passiflora incarnata* Linneaus for anxiolysis before regional anesthesia.

We aimed to test the hypothesis that oral *Passiflora incarnata* Linneaus intake is an effective premedication before spinal anesthesia. The primary endpoint of the study was to investigate the effect of the preoperative oral administration of *Passiflora incarnata* Linneaus on anxiety levels of patients before spinal anesthesia. The other endpoints were to evaluate the level of sedation, psychomotor function, hemodynamics, and side effects in the *Passiflora* group and the placebo group.

Materials and methods

The study was approved by the appropriate Institutional Review Board, and written informed consent was obtained from all the patients. Sixty patients aged 25–55 years, ASA physical status I–II, who were scheduled for elective inguinal herniorrhaphy under spinal anesthesia were enrolled in this prospective, randomized, double-blinded and placebo-controlled study. Exclusion criteria included lack of cooperation, previous experience with surgery and spinal anesthesia, bronchial asthma, cigarette smoking habit, anxiety disorders, chronic consumption of alcohol or antidepressant, sedative, analgesic, antiepileptic, or anticoagulant drugs, and contraindications for spinal anesthesia.

At the preoperative visit, an investigator informed the patients about the tests used in the study. Forty-five minutes before spinal anesthesia, patients were brought to the premedication room in the operating suite. All patients were monitored with an electrocardiogram, pulse oximetry, and for noninvasive arterial blood pressure. No premedication was given to the patients. All patients were requested to complete both parts of the State-Trait Anxiety Inventory (STAI) questionnaire. The STAI consists of two distinct forms, the Trait Anxiety Inventory (STAI-T) and the State Anxiety Inventory (STAI-S) scores. The former measures basic anxiety, and the latter evaluates anxiety that can be induced or modified by changes in the environment [12]. Sedation level was measured using the Observer's Assessment of Alertness/Sedation (OAA/S) score [1]. Patient psychomotor function was assessed with the perceptive accuracy test (PAT) and the finger tapping test (FTT). Patients were asked to state the two or three digits number displayed on a calculator. The number of correct answers provided during a period of 2 min was recorded in PAT. The patients were asked to tap on the keyboard of the calculator. The number of times that the patient tapped on the keyboard in a 30 s period was taken as the finger tap score [13]. After the completion of the tests (STAI-S_1, STAI-T_1, PAT_1 and FTT_1), 30 min before spinal anesthesia, baseline hemodynamic parameters [heart rate (HR) and the systolic, diastolic, and mean arterial pressures (SAP, DAP and MAP)] were measured, and then patients were randomly assigned to two groups according to the numbers inserted into sealed envelopes: *Passiflora incarnata* Linneaus 700 mg/5 ml aqueous extract (*Passiflora* Syrup, Sandoz, Kocaeli, Turkey) was given to the patients in group P ($n = 30$), and the same volume (5 ml) of drinking water with mineral was given in group C ($n = 30$). Hemodynamic parameters, oxygen saturation (SpO_2), and the OAA/S score were noted every 10 min before spinal anesthesia. 8 ml/kg of sodium chloride 0.9% solution were infused intravenously during this period. Thirty minutes after drug administration, the patients were transported to the operating room and prepared for spinal anesthesia. All of the tests were repeated (STAI-S_2, STAI-T_2, PAT_2, and FTT_2) just before spinal anesthesia in the operating room. Tests were performed by an anesthesiologist who was unaware of the group in which the patient was involved. Spinal anesthesia was then performed with the patient in the sitting position, using a 25 G Quincke needle in the $L_{4–5}$ interspace and a midline approach. Three milliliters of 0.5% hyperbaric bupivacaine were given via intrathecal injection. Hemodynamic parameters, SpO_2 value, sensory and motor blocks were assessed at 1, 3, 5, 7, and 10 min after the injection of the local anesthetic solution and then every 5 min. Sensory block was assessed using a pin-prick test. Motor block was assessed using modified Bromage scale (0 = no motor block, 1 = inability to raise extended legs, 2 = inability to flex knees, 3 = inability to flex ankle joints). The time to achieve a sensory block of T_{10}, the highest level of sensory block, the time to two-segment regression of the sensory block and the maximum degree of motor block were recorded. A 30% decrease from baseline SAP or SAP <90 mmHg was treated using incremental boluses of intravenous ephedrine 5 mg. Bradycardia was treated using intravenous atropine 0.5 mg. In the case of a failed spinal block, general anesthesia would be performed, and in the event of the need for sedation/analgesia, the patient would be discharged from the study. A decrease in SpO_2 to <93% in room air was defined as hypoxemia and treated with supplemental oxygen via a face mask.

Psychomotor function tests were repeated at the end of the operation (PAT_3, FTT_3) and 60 min after the end of the operation (PAT_4, FTT_4). In the postoperative care unit (PACU), patients received oxygen via a nasal cannula (4 l/min). Nausea and vomiting were treated with 10 mg metoclopramide intravenously. Patients were discharged from the PACU after the motor block was completely resolved. Paracetamol 1 g was given with a 15 min

infusion when the patient complained of pain in the postoperative period. The time to first analgesic requirement, time to discharge, and side effects were also noted. The patients were contacted at 24, 48, 72, and 168 h and asked to report backache, headache, or any transient neurological symptoms following the surgery.

Statistical analysis

It was calculated that a sample size of 30 patients per group was required to detect at least a five-score difference in STAI-S between the two groups with a power of 80% and $\alpha = 0.05$, based on a pilot study. Sample size was estimated using NCSS and the PASS (Hintze J., 2001, Number Cruncher Statistical Systems, Kaysville, UT, USA) statistical package program. All of the data were analyzed using SPSS 11.5 (SPSS Inc., Chicago, IL, USA) software. The Shapiro–Wilk test was used to test the normality of the distribution for continuous variables. Data are presented as mean ± SD, median (range), or number (incidence) as appropriate. Statistical analyses were performed using Student's *t* test for parametric data and the Mann–Whitney *U* test for nonparametric data. Fisher's exact test or chi-square test was used for categorical comparisons. Repeated measurements in groups were compared using a repeated measurements of variance analysis or the Friedman test, where applicable. The data for STAI-S and STAI-T scores and OAA/S scores were analyzed using the Wilcoxon signed-rank test. Statistical significance was set at the $p < 0.05$ level. Bonferroni adjustment was applied to control type I error in all possible multiple comparisons.

Results

Patient demographics are presented in Table 1. Spinal anesthesia was accomplished successfully in all patients.

Table 1 Demographic data

	Group P ($n = 30$)	Group C ($n = 30$)	*p*
Age (years)	50 (26–55)	44 (25–55)	0.434
Gender (F/M)	5/25	3/27	0.706
Weight (kg)	74.1 ± 11.4	75.6 ± 10.8	0.605
Height (cm)	169.2 ± 7.0	170.4 ± 8.3	0.538
BMI (kg m^{-2})	25.7 ± 3.4	26.4 ± 3.8	0.457
ASA I/II	19/11	18/12	0.791
Duration of operation (min)	62.8 ± 16.9	61.0 ± 20.4	0.480

Values are expressed as mean ± SD, median (minimum–maximum), or number of patients

BMI body mass index, *P Passiflora incarnata*, *C* control

Intraoperative sedation/analgesia was not administered. STAI-S_1 and STAI-T_1 scores were similar in both groups ($p = 0.728$ for STAI-S_1 and $p = 0.141$ for STAI-T_1). There was a statistically significant increase in STAI-S and STAI-T scores just before spinal anesthesia in group C (Table 2). A statistically significant difference from the baseline was found for the two groups in terms of the increase in STAI-S score obtained just before spinal anesthesia ($p = 0.004$ for STAI-S and $p = 0.293$ for STAI-T). PAT and FTT scores were similar in both groups ($p = 0.723$ and $p = 0.096$, respectively). There was no statistically significant difference from the baseline for either group in terms of the PAT and FTT scores (Table 3). The OAA/S scores for the groups were not significantly different during the study period (Mann–Whitney *U* test, $p > 0.05$). There was no statistically significant difference from the baseline for either group in terms of the OAA/S score (Wilcoxon signed-rank test $p > 0.05$ in each group) (Fig. 1). There was no statistically significant difference between the groups in terms of the characteristics of the sensory and motor blocks, the time to first analgesic requirement, the time to discharge (Table 4), and side effects. Nausea, vomiting, respiratory depression, shivering, or postoperative complications were not observed in any patient. The incidence of intraoperative hypotension was 3.3% (one patient) in group P and 10% (three patients) in group C ($p = 0.612$). The incidence of intraoperative bradycardia was 10% (three patients) in group P and 6.7% (two patients) in group C ($p = 1.00$). Hemodynamic parameters and SpO_2 values were similar in both groups during the study period.

Discussion

The results of the study demonstrate that preoperative oral administration of *Passiflora incarnata* Linneaus 700 mg/5 ml aqueous extract suppresses the increase in anxiety before spinal anesthesia, and *Passiflora incarnata* Linneaus is a safe and effective anxiolytic remedy.

We used the STAI scale and OAA/S scale to evaluate patients' anxiety and sedation levels, respectively. STAI is a well-established instrument for self-reporting anxiety [12], and the OAA/S scale may be the best choice if precise assessment of sedation is required [1]. Age, ASA physical status >III, history of smoking, and type of operation are important factors that affect preoperative anxiety [14]. We paid attention to these criteria before patient selection. Nonsmokers were enrolled in the study. Patients who chronically consume alcohol or antidepressant, sedative, analgesic, or antiepileptic drugs are prone to anxiety disorders, so we excluded these patients from the study.

Table 2 Anxiety scores in the two groups

	STAI-S_1	STAI-S_2	p	STAI-T_1	STAI-T_2	p
Group P ($n = 30$)	36.4 ± 10.9	35.7 ± 10.8	0.311	32.5 ± 9.5	33.4 ± 8.7	0.421
Group C ($n = 30$)	34.8 ± 8.4	36.6 ± 7.6	<0.001*	35.3 ± 8.3	38.1 ± 9.2	0.004†

Values are expressed as mean ± SD

STAI-S_1 Baseline State Anxiety Inventory score, *STAI-S_2* State Anxiety Inventory score obtained just before spinal anesthesia, *STAI-T_1* Baseline Trait Anxiety Inventory score, *STAI-T_2* Trait Anxiety Inventory score obtained just before spinal anesthesia

* $p < 0.001$ indicates a significant difference from the baseline score

† $p < 0.01$ indicates a significant difference from the baseline score

Table 3 The perceptive accuracy test (PAT) and the finger tapping test (FTT) scores in both groups

	Group P ($n = 30$)	Group C ($n = 30$)		Group P ($n = 30$)	Group C ($n = 30$)
PAT_1	98.0 ± 2.6	95.2 ± 16.4	FTT_1	67.4 ± 18.9	72.3 ± 14.1
PAT_2	98.0 ± 2.9	98.6 ± 2.3	FTT_2	68.1 ± 19.8	70.9 ± 13.0
PAT_3	98.6 ± 2.1	98.9 ± 2.4	FTT_3	67.4 ± 19.7	71.6 ± 12.6
PAT_4	99.1 ± 1.7	99.1 ± 1.4	FTT_4	67.6 ± 19.8	72.3 ± 13.1
p	0.138	0.565	p	0.151	0.172

Values are expressed as mean ± SD

PAT_1, *FTT_1* baseline score, *PAT_2*, *FTT_2* score obtained just before spinal anesthesia, *PAT_3*, *FTT_3* score obtained at the end of the operation, *PAT_4*, *FTT_4* score obtained 60 min after the end of the operation

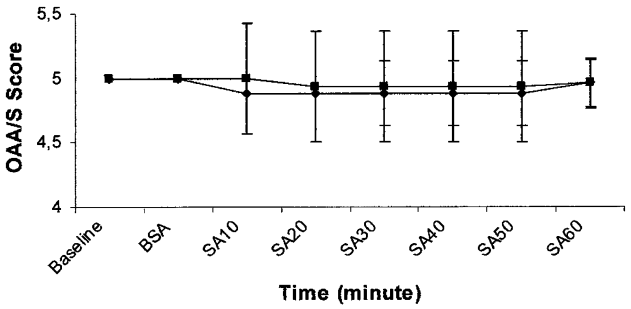

Fig. 1 Observer's Assessment of Alertness/Sedation (OAA/S) scores at different time intervals in the *Passiflora* group (*filled diamonds*) and in the control group (*filled squares*). *BSA* before spinal anesthesia, *SA10* 10 min after spinal anesthesia, *Group P Passiflora incarnata*, *Group C* control

Anxiolytic drugs and sedatives are administered before surgery for the purpose of calming patients. On the other hand, sedation involves some risks, especially the induction of respiratory depression, hemodynamic instability, or uncontrolled movements [1]. Using a safe and cheap herbal remedy with an anxiolytic effect as an alternative to conventional anxiolytic–sedative drugs for alleviating patient anxiety levels before regional anesthesia may seem worthwhile.

Amongst the 500 species of the genus *Passiflora*, *Passiflora incarnata* Linneaus is the one used most extensively for clinical applications throughout the world. *Passiflora incarnata* Linneaus is included in the nine plants for which there is considerable evidence of therapeutic effect, and is marketed in Western countries [15]. The sedative and anxiolytic activities of *Passiflora incarnata* Linneaus have been attributed to benzodiazepine and γ-aminobutyric acid receptor-mediated biochemical processes in the body [16, 17]. There are many different preparations of *Passiflora incarnata* Linneaus that vary considerably in their constituents. Although the compounds responsible for the therapeutic activity of *Passiflora incarnata* Linneaus are yet to be identified, phytomedicines should be made using plant material characterized by the typical flavonoid profile [18]. We used the aqueous extract of *Passiflora incarnata* Linneaus that contained 2.8 mg benzoflavone per 5 ml extract. The therapeutic dose of *Passiflora incarnata* Linneaus is 500–1000 mg three times daily [19]. We used the anxiolytic dose (700 mg/5 ml) that is suggested for adults in the prospectus. The peak anxiolytic activity of *Passiflora incarnata* Linneaus was noted to occur at 30 min after oral administration [8]. *Passiflora incarnata* Linneaus was given to the patients 30 min before spinal anesthesia in the study.

There is only one study in the literature on the use of *Passiflora incarnata* Linneaus before general anesthesia for its anxiolytic effect [8]. Movafegh et al. have used a tablet form of *Passiflora incarnata* Linneaus extract (500 mg) 90 min before general anesthesia [8]. Unlike in their study, we used a liquid extract of the plant 30 min before spinal anesthesia, and we investigated the effects of the extract in awake patients under spinal anesthesia. Movafegh et al. [8] suggested that oral administration of *Passiflora incarnata* Linneaus significantly reduces preoperative anxiety levels,

Table 4 Characteristics of spinal anesthesia in the two groups

	Group P ($n = 30$)	Group C ($n = 30$)	p
Time to T_{10} (min)	10.8 ± 6.1	9.6 ± 5.0	0.709
Highest level (dermatome)	T_7 (T_{10}–T_3)	T_7 (T_{10}–T_6)	0.221
Time to two-segment regression (min)	78.6 ± 27.6	83.5 ± 24.0	0.310
Maximum motor block degree (n) (Bromage 2/3)	2/28	1/29	1.000
Time to first analgesic requirement (min)	92.0 ± 53.7	88.0 ± 57.8	0.714
Time to discharge (min)	316.0 ± 58.8	319.0 ± 67.9	0.694

Values are expressed as mean ± SD, median (minimum–maximum), or number of patients

but does not affect the preoperative sedation level, recovery time, or psychomotor function test results after extubation. They found that psychomotor function test results were impaired 30 min after extubation but reached their preoperative values 90 min after extubation in both groups. In our study, we did not find any impairment in psychomotor function test results during the study period. We observed that *Passiflora incarnata* Linneaus does not affect discharge after spinal anesthesia.

It was stated that there is a significant relationship between the maximum extent of sensory block and the level of sedation during spinal anesthesia [20]. In our study, maximum sensory block levels were similar in both groups, and hence the maximum level of sensory block did not affect the results for the sedation levels.

There are a few reports of side effects of *Passiflora incarnata* Linneaus ingestion. Side effects include cutaneous vasculitis, urticaria, asthma, and rhinitis [21, 22]. These side effects are very rare, and only occurred after chronic usage [22]. Many herbal remedies influence platelet activity. It was suggested that aqueous extract of *Passiflora incarnata* Linneaus inhibits human platelet aggregation by only 1.3% in platelet-rich plasma induced by ADP. The maximum inhibitory effect (90%) was observed with garlic, followed by alfalfa (73%), onion (71%), fresh nettle (65%), and chamomile (60%) [23]. We used a single dose of aqueous extract before spinal anesthesia, and no side effect was seen after the procedure. Hemodynamic parameters did not change after the administration of *Passiflora incarnata* Linneaus when compared to those of the placebo. Lack of intraoperative sedation and respiratory depression is an another advantage of this plant. According to our results, *Passiflora incarnata* Linneaus is a safe and effective anxiolytic remedy that can be used before spinal anesthesia.

One limitation of this study is that there are statistically significant but small differences in STAI scores. Subsequent investigations of the clinical usefulness of *Passiflora incarnata* Linneaus may be useful to support our findings. Another limitation is that it is difficult to produce a placebo with the same color and taste as *Passiflora incarnata* Linneaus. To exclude this limitation, the drug or the placebo was given to the patient in a dark colored glass. The patients were asked whether they noticed the group in which they were enrolled. In the event of a patient being aware of which group they were in, they would have been excluded from the study. However, none of the patients noticed the group in which they were enrolled.

It was concluded that preoperative oral administration of 700 mg/5 ml of *Passiflora incarnata* Linneaus aqueous extract suppresses the increase in anxiety levels of patients before spinal anesthesia without changing their sedation level, psychomotor function test results, or hemodynamics.

Conflict of interest No conflict of interest exists.

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