

## BOTH ORAL *PASSIFLORA INCARNATA* AND OXAZEPAM CAN REDUCE PRE-OPERATIVE ANXIETY IN AMBULATORY SURGERY PATIENTS: A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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### ABSTRACT

**Objectives:** Pre-operative anxiety control without increased post-operative psychomotor dysfunction is an anesthesia concern especially in ambulatory surgery; so, the development of a strong anxiolytic with minimal psychomotor impairment for premedication is desirable. In this study, it was hypothesized that *Passiflora incarnata* decreases pre-operative anxiety (PAN) similar to oxazepam.

**Methods:** In this double-blinded placebo controlled study, 128 patients were randomized into *Passiflora* group (n=68) who received oral *P. incarnata* and oxazepam group (n=60) who received oxazepam (10 mg) as premedication, 90 minutes before surgery. A numerical rating scale (NRS) was used for each patient to assess anxiety before, and 90 minutes following premedication. Psychomotor function was assessed with the trigger dot test (TDT) and the digit-symbol substitution test at arrival in the operating room, and 90 minutes after tracheal extubation.

**Results:** The 90<sup>th</sup> minutes NRS anxiety scores were significantly lower in the *Passiflora* group compared with oxazepam group (p<0.001). There were no significant differences in psychological variables, in groups, in the postanesthesia care unit.

**Conclusion:** In outpatient surgery, administration of oral *P. incarnata* as a premedication reduces PAN with similar psychomotor function impairment compared with pre-operative oral oxazepam.

**Keywords:** Anesthesia, Anxiety, *Passiflora incarnata*, Oxazepam, Psychomotor performance.

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### INTRODUCTION

The prevalence of pre-operative anxiety (PAN) has been reported to be up to 80% among adult patients [1,2]. PAN may be associated either with abnormal intraoperative hemodynamic profiles or an altered pharmacokinetics of anesthetic drugs, which may increase intraoperative anesthetic requirements [3].

PAN results in sympathetic neural activation and leads to increased heart rate, blood pressure, cardiac irritability [4], increased plasma epinephrine levels, and impaired balance of serum electrolytes [5]. There is also an association between high levels of pre-operative levels of anxiety and post-operative pain [6].

A variety of methods has been proposed for perioperative anxiety reduction. Pre-operative visit by the anesthesiologist can be a good way to reduce PAN [7,8]; medical interventions were considered in several studies, and benzodiazepines (BZD) was administered as the most commonly used PAN killer [9-11]. Meantime, scientists accept some herbal treatments nowadays and many people in different socioeconomic levels, are exploring herbal and other natural remedies for the treatment of their psychological conditions. The previous studies have reported the good effects of extracts of Passionflower or kava and combinations of L-lysine and L-arginine as a treatment for anxiety disorders [12].

In general, *Passiflora incarnata* may be regarded as a well characterized plant-derived agent with anxiolytic properties without negative sedative and cognition-attenuating side effects.

BZD are widely used by ambulatory surgery centers as painkillers; however, there are some concerns about prolongation of the recovery time.

To our knowledge, the use of *Passiflora incarnata* compared with a BZD in anesthesia has never been evaluated. In this study, it was hypothesized that oral *P. incarnata* would be an effective anxiolytic similar to oxazepam with limited impact on psychomotor function. The numerical rating scale (NRS) for anxiety 90 minutes after premedication was considered as the primary outcome of this study, and trigger dot test (TDT) and digit-symbol substitution test (DSST) were considered as secondary outcomes.

### METHODS

The Institutional Ethics Review Board approved the study protocol, and an informed written consent was obtained from all the patients. Patients classified as the American Society of Anesthesiologists (ASA) physical Status I or II, aged 18-60, whom were candidates for outpatient inguinal herniorrhaphy, were enrolled in this double-blind, randomized and parallel group trial. The patients with a history of anxiety disorders and consuming sedatives, analgesics, antidepressants, or antiepileptic drugs, addict patients and patients with any contraindications to the study drugs and patients with NRS for anxiety <1 and anyone who received any other drugs except study protocol drugs perioperatively, were not enrolled in the study. An anesthesiology technician who was not involved in anesthesia administration or inpatient observation prepared all drugs; so, both the anesthesiologist and the patients were blinded to group assignment. At the pre-operative visit, a trained

anesthesiology resident explained the study plan and three scales were used in the study for all the included patients. Based on computerized program patients were randomly divided into oxazepam (group O, n=60) or Passiflora (group P, n=68) group.

Approximately, 2 hrs before surgery, all patients were transferred to an isolated quiet room. All patients were monitored with an electrocardiogram, noninvasive blood pressure, and pulse oximetry. The patients in group O received premedication of oxazepam 10 mg, and those in group P received premedication of *P. incarnata* (500 mg, PassipyTM IranDarouk) orally 120 minutes before surgery.

An NRS scale was used to evaluate anxiety, where 0=No anxiety and 10=The worst possible anxiety. The NRS scores were measured at baseline and 90 minutes after administration of premedication. The psychomotor function was assessed with the TDT and the DSST, at arrival in the operating room, and 90 minutes after tracheal extubation. The TDT is a variation of Bender-Gestalt test in which the patient is asked to connect a series of dots arranged in a specific pattern [13]. Points are subtracted for missing how many of dots. The DSST is a subtest of 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 seconds.

In the operating room, an infusion of 7 mL/kg/hrs isotonic saline (N/S) was administered. Anesthesia was induced with fentanyl 2 µg/kg, propofol 2.5 mg/kg, and the tracheal intubation was facilitated by administration of cisatracurium 0.2 mg/kg. Anesthesia was maintained with propofol (100 µg/kg/minutes). Ventilation was adjusted to maintain normocapnia (end-tidal carbon dioxide partial pressure 4.7-5.3 kPa). The patients were actively warmed to keep normothermic based on core temperature (esophageal).

When skin suturing was started, anesthetic drug infusion was stopped and neuromuscular blockade was antagonized by intravenous administration of 0.04 mg/kg of neostigmine and 0.02 mg/kg atropine. They were considered awake and were tracheally extubated when they opened their eyes on command or after gentle tactile stimulation. In the postanesthesia care unit (PACU), patients received continuous oxygen via a nasal cannula (4 L/minutes). Post-operative pain was treated with 3 mg/kg tramadol that was infused over 10 minutes. Post-operative nausea and vomiting was treated with 4 mg intravenous ondansetron. PACU discharge criteria included being awake and oriented, able to breathe deeply and cough freely, arterial blood pressure within 20% of pre-operative values, temperature >36°, absence of shivering, minimal pain, and minimal tolerable nausea. The time interval between arrival to PACU to discharge home (discharge time) was recorded for every patient. Patients were discharged from hospital when they met the minimum requirements based on the hospital discharge criteria.

Statistical analysis was performed using SPSS package (SPSS, Chicago, Illinois, USA), version 20. The distribution of age, weight, surgery duration, 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 in two groups by independent sample t-test. The paired t-test was used to assess the differences of NRS for anxiety, over the time in each group. The sedation scores were an ordinal scale measurement. To compare the sedation scores in groups in each measurement times,  $\chi^2$  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  $\chi^2$ -test. Statistical significance was noted for  $p < 0.05$ . Data are expressed as mean±standard deviation (SD) and 95% confidence interval (95% confidence interval [CI]). We determined that a sample size of 60 in each group would be sufficient to detect a difference of three scores in the mean of anxiety score, estimating a SD of 3, a power of 95%, and a significance level of 5%; this

number was increased to 65 per group, to allow for a predicted drop-out from treatment of around 10%.

## RESULTS

A total of 128 patients were enrolled in the study; there were no study protocol violations and all the data were analyzed. The study consisted of 68 patients in P group and 60 patients in O group. Age range of subjects was 18-59 years. Demographic data, duration of surgery, and ASA physical status were similar in between the two groups (Table 1).

Baseline NRS anxiety score was similar P (7.6±0.9) and O groups (6.6±1.0). There was a significant difference in 90<sup>th</sup> minutes NRS anxiety score of group P (4.4±1.2) and the group O (6.1±1.3) ( $p < 0.001$ , CI: -2.0 to -1.1).

There were no significant differences between the two groups, in the measured psychomotor function scores, in the PACU. Recovery of psychomotor function scores was comparable in both groups, and the psychomotor function scores reached baseline values 90 minutes after extubation in both groups (Table 2).

Discharge time was similar between the two groups (Table 1).

## DISCUSSION

This study demonstrated that patients who received oral Passiflora tablets, as premedication experienced less PAN than those who received pre-operative oxazepam, while the effect of both drugs on post-operative psychomotor function was the same. Therefore, Passiflora is a safe and stronger candidate for PAN reduction in comparison to oxazepam. The recovery time was alike in both groups.

Movafegh *et al.* [8] conducted a study on the effects of the oral *P. incarnata* on PAN and reported good anxiolytic effects with limited effects on anesthesia drugs and recovery time compared to placebo. In this study, a similar study design was used to compare pre-operative anxiolysis effects of *P. incarnata* and oxazepam.

**Table 1: Demographic data of the patients (value are expressed as mean±SD)**

| Variables                 | Passiflora group (n=68) | Oxazepam group (n=60) | p value |
|---------------------------|-------------------------|-----------------------|---------|
| Age (year)                | 37.2±8.6                | 36.3±7.2              | 0.52    |
| Sex (male/female)         | 38/30                   | 36/24                 | 0.63    |
| Weight (kg)               | 74.8±10.2               | 73.3±12.2             | 0.46    |
| Duration of surgery (min) | 162.2±32.6              | 167±34.4              | 0.42    |
| ASA Class (I/II)          | 58/8                    | 55/5                  |         |
| Home discharge (minutes)  | 283.3±36.1              | 291.7±38.6            | 0.65    |

SD: Standard deviation, ASA: American Society of Anesthesiologists

**Table 2: Recovery of psychomotor function in PACU (90 minutes after extubation)**

| Variables        | Pre-operative baseline | 90 minutes after extubation | p value |
|------------------|------------------------|-----------------------------|---------|
| TDTmm            |                        |                             |         |
| Passiflora group | 0.9±0.2                | 1.2±0.4                     | 0.79    |
| Oxazepam group   | 0.8±0.2                | 1.1±0.3                     | 0.56    |
| TDTnr            |                        |                             |         |
| Passiflora group | 0.8±0.8                | 1.0±0.9                     | 0.66    |
| Oxazepam group   | 0.9±0.7                | 1.2±1.0                     | 0.47    |
| DSST             |                        |                             |         |
| Passiflora group | 31.1±5.1               | 28.6±5.0                    | 0.75    |
| Oxazepam group   | 30.8±5.0               | 29.1±4.8                    | 0.54    |

TDTmm: Trieger dot test millimeter missed, TDTnr: Trieger dot test number missed, DSST: Digital-symbol substitution test, PACU: Postanesthesia care unit

The genus *Passiflora* consist of about 500 species, it is the largest family among the Passifloraceae (Passion Flower family). Species of these apices grow in areas with warm temperatures and tropical weather and are distributed in North and South America. Extracts of *Passiflora* species are scarce in Asia, Africa, Australia and the tropics. Its indication for sleep disorders, restlessness, nervous stress, and anxiety has confirmed by various authentic institutions: British herbal compendium (Passion Flower Herb, England) [14], German commission standard licenses (*Passiflora incarnata*, Germany) [15].

*P. incarnata* as a species of these large genuses was studied as PAN killer herbs, in a few studies [16,17].

The mechanism of action is still unclear and several studies were done to discuss about that. The effects of *P. incarnata* coming extracts, petroleum ether, chloroform, methanol and water have been investigated about anxiolytic properties, in mice. Methanol extract from the leaves, stems, flowers, and whole plants had anxiolytic effect. Furthermore, Dhawan *et al.* observed that the roots and flowers of *Passiflora incarnata* neutralize, anxiolytic effects of other parts of the plant naturally and cause to increasing the effective dose, therefore, should be separate during processing [6].

In a study sought to isolate and identify the bioactive component of *P. incarnata* by chromatographic procedures, a fraction, which is obtained from the methanol extract of *P. incarnata*, showed a significant anxiolytic activity with a dose of 10 mg/kg in mice. This fraction consisted of two main components that were seen turquoise and blue while colored by fluorescent at wavelength of 366 nm of ultraviolet light maybe the bioactive component of *P. incarnata* is benzoflavone nucleus [17]. It is being recognized that dysfunction of the  $\gamma$ -aminobutyric acid (GABA) system is implicated in anxiety. Appel *et al.* investigated the *in vitro* effects of *P. incarnata* on GABA system of rats. The [3H]-GABA uptake into cortical synaptosomes of rat was inhibited by *Passiflora*, but *Passiflora* had no effect on GABA release and GABA transaminase activity. The ethanol-and the benzodiazepine-sites of the GABA A-receptor were not affected by *Passiflora*, and finally, this study classified the *Passiflora*, as an antagonist of the GABA B-receptor [18].

BZD is routinely used as a premedication to decrease PAN [10,19]. Two drugs from BZD group, chlordiazepoxide and diazepam as a single pretreatment dose, were studied on women's PAN. The findings of this study were compared with those who received the previous consumed agents, such as opioids and phenothiazine products. The ability of these two drugs is documented to reduce PAN and chlordiazepoxide showed very mild sedative effects also [9]. Diazepam was used along with belladonna, before surgery in 40 neurosurgery patients. Two other pretreatment, belladonna without sedative drug, and belladonna with hydroxyzine were used in 78 similar patients. Sedative effect of diazepam was stronger than hydroxyzine and has not autonomic unwanted effects and seemed to be as safe as a simple drug such as belladonna [20]. However, diazepam has unwanted central sedative and muscle relaxant effects also.

Anxiolytic, and amnesic properties of low dose of BZD have been used in outpatient surgeries. Oral diazepam, 60-90 minutes before surgery reduces the level of stress hormones in the days after the surgery. Most commonly used BZD is diazepam, however, midazolam can be the better choice due to a shorter lifespan, lack of specific adverse events, and better recovery profile after ambulatory surgery.

In our center, oxazepam has been used routinely as a PAN killer, so it was chosen to compare it with *Passiflora incarnata*. Previously, *Passiflora incarnata* was used for the treatment of generalized anxiety disorders (GAD). In a randomized controlled study, 32 patients with GAD divided into *Passiflora* group receiving 45 drops of tincture of *Passiflora* and Oxazepam group which received 30 mg oxazepam, daily. 4 days following treatment, the difference in groups was observed in the level of anxiety. Adverse reactions reported in patients treated

with the *Passiflora* was lesser than oxazepam and therefore, ultimately, the authors concluded that the *P. incarnata* is an affective antianxiety agent and has fewer side effects comparing the synthetic antianxiety agents [21].

Akhondzadeh *et al.* [22] compared Passionflower (*P. incarnata*) with oxazepam in the treatment of GAD and reported *Passiflora* extract as an effective drug for curing GAD, and also this study confirmed the lower incidence of impairment, in job performance with *Passiflora* extract compared with oxazepam.

Extracts from *Passiflora* possess potential antidepressant effects which could be of therapeutic interest for using in the treatment of patients with depressive disorders [23]. It is very interesting that it has been proposed that the co-administration of *Passiflora* and BZD such as diazepam prevents the development of diazepam-dependence and the subsequent appearance of withdrawal effects [24].

The therapeutic dose of *P. incarnata* is 500-1000 mg three times daily [25]. However, the lowest approved treatment dosage of *Passiflora* for the PAN relief was 500 mg, 2 hrs before surgery, which were studied in Movafegh *et al.* study [8]. Furthermore, the minimum dose of *Passiflora* was used, in this study, which was reported safe in previous researches on adults [25].

Reducing levels of PAN will lead to decreased PAN and lesser post-operative analgesic requirements, in pediatrics also [26] and it is valuable to evaluate the beneficial effects of *P. incarnata* and its minimum effective dose in pediatric patients with ambulatory surgery.

## CONCLUSION

In conclusion, pre-operative administrations of oral *Passiflora incarnata* in outpatient patients decreases PAN more than oxazepam without recovery prolongation of psychomotor function impairment.

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