

Preoperative Oral *Passiflora Incarnata* Reduces Coughing Following Extubation: A Double Blind, Placebo-Controlled Study

Alireza Saliminia¹, Omid Azimaraghi¹, Maryam Ghadimi², Naieemeh Kafi Kang², Ali Movafegh^{1*}

Background: The incidence of coughing following extubation can result in a number of undesirable side effects. Therefore, the development of antitussive premedication may be desirable.

Methods: In this study, 138 patients were randomized into two groups to receive either oral *Passiflora incarnata* (500 mg, PassipyTM IranDarouk) (n = 69) or placebo (n = 69) as premedication, 120 min before surgery. After extubation, all patients were observed to record the incidence of coughing during a 15 minute period. Hemodynamic variables were recorded before induction of anesthesia, 1 minute following intubation, and 5 minutes after extubation.

Results: The demographic characteristics of patients, ASA physical status, duration of surgery, hemodynamic variables were similar in the two groups. The incidence of cough following extubation was significantly lower in the *passiflora* group compared to the control group (P <0.001).

Conclusion: In outpatient surgery, administration of oral *Passiflora incarnata* as a premedication reduces incidence of coughing following extubation.

Keywords: cough; tracheal extubation; *passiflora incarnata*

The incidence of coughing on emergence from general anesthesia in the presence of an endotracheal tube (ETT) has been estimated to be between 38% and 96% [1-2].

Coughing on emergence can result in a number of undesirable side effects including hypertension, tachycardia, tachyarrhythmia, myocardial ischemia, surgical bleeding, bronchospasm, increased intracranial pressure and raised intraocular pressure [3-4].

Techniques that have been used to diminish coughing during emergence include "deep" extubation, administration of intravenous (IV) opioids, or administration of IV lidocaine prior to emergence, since systemic narcotics and lidocaine have antitussive properties [5-7]. Concerns about the use of these techniques include delayed emergence from anesthesia, aspiration in the presence of an unprotected airway. Spraying the endotracheal tube with lidocaine, ketamine, application of betamethasone gel on the tracheal tube and endotracheal tube cuff decreases the incidence and severity of cough after extubation, but the effect of the drugs that are used topically is short lived [8-10].

Herbal remedies are a popular form of therapy. *Passiflora incarnata* is a plant, which has traditionally been used as an anxiolytic and sedative throughout the world [11-12].

Previous studies have approved the use of passionflower for some respiratory tract diseases with chronic cough such as whooping cough, asthma and bronchitis.

Basic science studies have demonstrated antitussive and antiasthmatic activity of the methanol extract of *Passiflora incarnata* leaves in experimental animals [13-15].

We thus hypothesized that oral *Passiflora incarnata* would be effective in reducing cough on extubation after general anesthesia. This study was designed to compare the effect of oral *Passiflora incarnata* with placebo as a premedication before general anesthesia.

Methods

Institutional Ethics Committee approved the study protocol and the study was registered at the Iranian registry of clinical trials (IRCT registration number: IRCT201301075140N8) and informed written consent was obtained from all the patients. One hundred and thirty-eight, non-smoker patients aged 18–60 years, classified as ASA physical status class I and II, who were scheduled to undergo elective inguinal herniorrhaphy lasting less than 2 hours were enrolled in this randomized, double-blind, and placebo-controlled study.

Patients with a history of surgery on larynx or trachea, smokers, those with active upper respiratory tract infection, sore throat, bronchial asthma, chronic obstructive pulmonary disease, those consuming beta blockers, steroids and drugs that have interactions with *passiflora* (benzodiazepines, tricyclic anti-depressant, anti-histamine, anti-platelet, anticoagulant and monoamine oxidase inhibitor) were not

From the ¹Department of Anesthesiology, Pain and Critical Care, Dr. Ali Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran.

²Research Development Center, Dr. Ali Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran.

Received: 8 March 2017, Revised: 30 March 2017, Accepted: 15 April 2017

The authors declare no conflicts of interest.

*Corresponding author: Ali Movafegh, MD. Department of Anesthesiology, Pain and Critical Care, Dr. Ali Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran. E-mail: Movafegh@sina.tums.ac.ir

Copyright © 2017 Tehran University of Medical Sciences

included in the study. In case of two or more failed intubation attempts and patients that their surgery lasted more than 2 hours were excluded from the study.

During the preoperative visit, the study plan was explained to the patients thoroughly by a trained investigator. An anesthesiologist who was not involved in anesthesia administration or patient observation prepared all drugs; thus, both the anesthesiologist and the patients were blinded to group assignment. Using a computer-generated randomization list patients were randomly assigned into two groups control (group C, n = 69) or passiflora (group P, n=69).

Patients' in-group C received placebo and those in-group P received Passiflora incarnata (500 mg, Passipy™ IranDarouk) orally 120 min before surgery. Each tablet contains 1.1 mg benzoflavone (BZF). The placebo and active form of drug were identical in appearance.

In the operating room, an infusion of lactated Ringer's solution (7 cc per kg) was commenced.

Anesthesia was induced with alfentanil and propofol; the trachea was intubated after administration of cisatracurium. After tracheal intubation, anesthesia was maintained with propofol and alfentanil. Ventilation was adjusted to maintain normocapnia. 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 and extubated when they opened their eyes on command.

After extubation, during a 15-minute period, an investigator who was blinded to the study groups observed the patients for recording any coughs. Hemodynamic variables including systolic (SBP) and diastolic blood pressures (DBP), and heart rate (HR) were recorded before induction of general anesthesia, one minute after tracheal intubation, and 5 minutes following extubation.

Based on a pilot study on 10 patients whom had received Passiflora incarnate, 25% incidence of post-extubation cough was reached. It was estimated that 62 patients in each group were needed to have 80% power to detect 20%

difference in incidence of cough at a significant level of 0.05. This number was raised to 69 to allow predicted drop-out of 10%.

Statistical analysis was performed using SPSS package (SPSS Inc., Chicago, IL), version 17. The distribution of age, weight, surgery time, heart rate(HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) were checked by the Kolmogorov-Smirnov test. They followed a normal distribution. Age, weight, surgery time, HR, SBP, and DBP were compared between two groups by independent sample t-test.

To compare the incidence of cough between groups, chi square and Fisher's exact tests were used.

The sex and ASA physical status class were compared with χ^2 tests. Two-tailed $P < 0.05$ was taken as significant.

Results

One hundred and thirty-eight patients were included in the study. No patient was excluded from data analysis. Patient's characteristics and duration of surgery were the same in both groups (Table 1).

The incidence of coughing after tracheal extubation was significantly higher in the Passiflora group compared with the control group (78.3% vs 52.2% of patients, respectively; $P < 0.001$) (Figure 1).

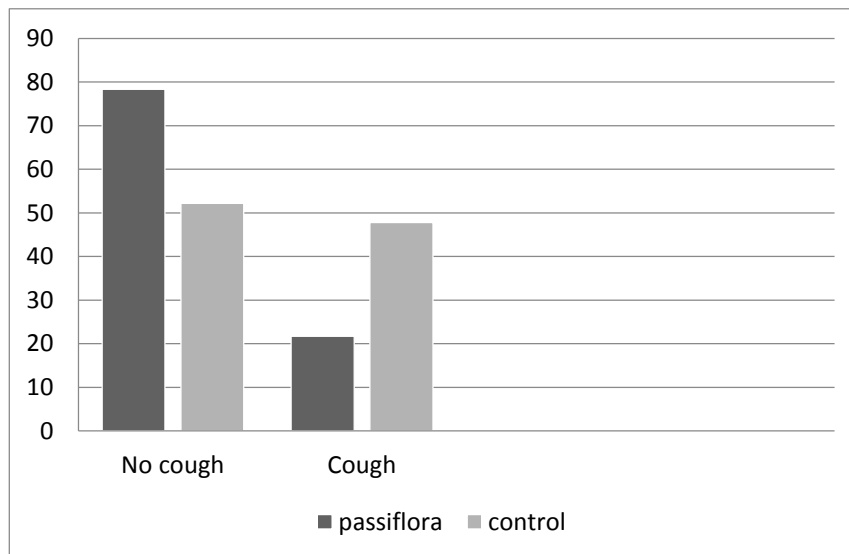
There were no clinically significant differences in post-extubation HR, SBP or DBP, between the two groups (Table 2).

Table 1- Patient's demographic data and surgery time

	Passiflora (n=69)	Control (n=69)
Age (years)	37.1±0.3	35.6±0.3
Weight (Kg)	74.8±0.3	72.9±0.4
Sex (Female/Male)	33/36	30/39
ASA class(I/II)	30/39	28/41
Surgery time (minutes)	70±20.1	75±21.6

*There is no significant differences between groups

Figure 1- Incidence of cough following extubation in the two groups.



* $P < 0.05$

Table 2- SBP, DBP and HR changes

		Passiflora Group (n=69)	Control Group (n=69)
SBP(mmHg)	Before induction	106±18	110±20
	After intubation	118±21	113±24
	After extubation	125±31	130±36
DBP(mmHg)	Before induction	84±12	80±14
	After induction	86±20	80±22
	After extubation	84±16	90±26
HR(B/minute)	Before induction	80±23	93±20
	After induction	75±18	78±16
	After extubation	90±21	95±14

*There are no significant differences between the two groups

Discussion

The results of this study show a decrease in the incidence of early post-extubation cough in patients emerging from general anesthesia which have received *Passiflora incarnata* 500 mg (Passipy™, IranDarouk) as premedication 120 min before surgery compared to patients who have received placebo drug.

Thus, our study demonstrates that the administration of *Passiflora incarnata* as a premedication provides antitussive activity without impairing vital signs or delaying discharge.

Coughing on emergence can result in a number of undesirable side effects. Many techniques such as “deep” extubation, administration of intravenous narcotics, or administration of IV Lidocaine, endotracheal spraying with Lidocaine application of betamethasone gel on the tracheal tube and endotracheal tube cuff lidocaine have been used as antitussive, some of them associated with undesirable side-effects [7-10].

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. In many countries extracts from passion fruit have been used widely in folk medicine and herbal medicine to treat anxiety, insomnia, bronchitis, and asthma [16,13].

Contrary to main cough-suppressants such as opioids and anti-histamines, addiction liabilities of *P. incarnata* have not been reported yet. Opioids and anti-histamines produce some other adverse effect such CNS depression, mouth dryness, blurred vision, GI effects and urinary retention.

Earlier researchers have highlighted the role of the methanol extract of leaves of *P. incarnata* as a reason of its antitussive effects [12-16].

Kamaldeep Dhawan and Anupam Sharma examined the suppression of SO₂-induced cough in mice using the methanol extract of the leaves of *P. incarnata*. These results corroborate to folklore claims on the effectiveness of the plant in managing ‘tough’ cough conditions [12].

In a double blind, randomized, controlled trial, asthmatic patients received PFP extract (150 mg/d) or placebo pills orally. Most clinical symptoms of the PFP extract-treated group were suppressed moderately in comparison to the control group. The prevalence of wheeze, cough, as well as shortness of breath was reduced significantly in the group treated with PFP extract. The authors concluded that The PFP extract might be safely offered to asthmatic subjects as an alternative treatment option to reduce clinical symptoms

[14].

As noted previously, to our knowledge, the use of *Passiflora incarnata* for reduction of cough after extubation has not been described previously.

Herbal medicines may have significant adverse effects, which are not suspected or recognized. There are few reports of toxicity associated with *passiflora* ingestion. Yet, these adverse effects occurred only after chronic usage.

Hypersensitivity with cutaneous vasculitis and urticaria has been reported after ingestion of tablets containing *passiflora* [16].

Furthermore, the BZF concentrations of commercially available tablets are variable. There might be differences in constituents or efficacy between 500 mg tablet used in this study from other 500 mg tablet. The acceptable range of BZF of each 500 mg tablet is 0.9–1.1 mg, the BZF concentration of our tablet was 1.01 mg.

There are a few potential limitations to this study. The first limitation of the study was the relatively small sample size, which may limit the generalizability of the findings. However, the most notable limitation of our study is related to the short observation period. More powered studies are needed to define accurately the effect of *passiflora* on cough reflex.

The therapeutic dose of *Passiflora incarnata* is 500–1000 mg three times daily. We used the minimum dose that previous studies demonstrated safe in adults [17].

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

In conclusion, results of present study demonstrate that oral premedication with *Passiflora incarnata* 500 mg reduces coughing following tracheal extubation.

References

1. Fagan C, Frizelle HP, Laffey J, Hannon V, Carey M. The effects of intracuff lidocaine on endotracheal-tube-induced emergence phenomena after general anesthesia. *Anesth Analg*. 2000; 91(1):201-5.
2. Gonzalez RM, Bjerke RJ, Drobycki T, Stapelfeldt WH, Green JM, Janowitz MJ, et al. Prevention of endotracheal tube-induced coughing during emergence from general anesthesia. *Anesth Analg*. 1994; 79(4):792-5.
3. Lowrie A, Johnston PL, Fell D, Robinson SL. Cardiovascular and plasma catecholamine responses at tracheal extubation. *British journal of anaesthesia*. 1992; 68(3):261-3.
4. Leech P, Barker J, Fitch W. Changes in intracranial pressure and systemic arterial pressure during the termination of anaesthesia. *Br J Anaesth*. 1974; 46(4):315-6.
5. Bidwai AV, Bidwai VA, Rogers CR, Stanley TH. Blood-pressure and pulse-rate responses to endotracheal extubation with and

- without prior injection of lidocaine. *Anesthesiology* 1979; 51:171-3
6. Steinhaus JE, Gaskin I. A study of intravenous lidocaine as a suppressant of cough reflex. *Anesthesiology*. 1963; 24:285-90
 7. Gefke K, Andersen LW, Friesel E. Lidocaine given intravenously as a suppressant of cough and laryngospasm in connection with extubation after tonsillectomy. *Acta Anaesthesiol Scand*. 1983; 27(2):111-2.
 8. Sumathi P A, Shenoy T, Ambareesha M, Krishna M. controlled comparison between betamethasone gel and lidocaine jelly applied over tracheal tube to reduce postoperative sore throat, cough, and hoarseness of voice. *Br J Anaesth*. 2008; 100(2):215-8.
 9. Minogue SC, Ralph J, Lampa MJ. Laryngotracheal topicalization with lidocaine before intubation decreases the incidence of coughing on emergence from general anesthesia. *Anesth Analg*. 2004; 99(4):1253-7.
 10. Hosseini L, Yazarlu K, Eslami B, Marzony SG. The Relation between Ketamine Spraying on the Endotracheal Tube Cuff and Reduced Postoperative Sore Throat, Cough and Hoarseness in Parturient Patients. *Archives of Anesthesiology and Critical Care*. 2015;1(1):8-12.
 11. Fisher AA, Purcell P, Le Couteur DG. Toxicity of *Passiflora incarnata* L. *J Toxicol Clin Toxicol*. 2000; 38(1):63-6.
 12. Dhawan K, Sharma A. Antitussive activity of the methanol extract of *passiflora incarnata* leaves. *Fitoterapia*. 2002; 73(5):397-9.
 13. Watson RR, Zibadi S, Rafatpanah H, Jabbari F, Ghasemi R, Ghafari J, et al. Oral administration of the purple passion fruit peel extract reduces wheeze and cough and improves shortness of breath in adults with asthma. *Nutr Res*. 2008; 28(3):166-71.
 14. Dhawan K, Kumar S, Sharma A. Antiasthmatic activity of the methanol extract of leaves of *passiflora incarnata*. *Phytother Res*. 2003; 17(7):821-2.
 15. Zibadi S, Watson RR. Passion fruit (*Passiflora edulis*): composition, efficacy and safety (Review). *Evid Based Integrative Med*. 2004; 1(3): 183-7.
 16. Smith GW, Chalmers TM, Nuki G. Vasculitis associated with herbal preparation containing *Passiflora* extract. *Brit J Rheumat*. 1993; 32(1):87-8.
 17. Blumenthal M. *The Complete German Commission E Monographs. Therapeutic Guide to Herbal Medicines*. Austin: American Botanical council, 1998.