Original Article

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Comparison of Preoperative Acupressure, Incentive Spirometry, and Nebulisation with Lignocaine in Reducing Fentany-induced Cough: A Randomised Controlled Study

Anaesthesia Section

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ABSTRACT

Introduction: Fentanyl bolus during induction often leads to cough. It is usually benign, but in some cases, it can be explosive and life-threatening. The incidence of Fentany-induced Cough (FIC) varies from 18% to 65%.

Aim: To compare the effect of acupressure, incentive spirometry, and nebulisation with lignocaine on the incidence and severity of FIC.

Materials and Methods: This single blind randomised controlled study was conducted in Department of Anaesthesia, Himalayan Institute of Medical Sciences, HIMS, Dehradun, Uttarakhand, India over a period of nine months from May 2019 to February 2020. Four hundred patients, aged 18-60 years, of either sex, scheduled for elective surgery, were randomly assigned to four groups: acupressure group (A), incentive spirometry group (S), nebulisation with lignocaine group (N), and control group (C). All patients received undiluted fentanyl at a dose of 2 mcg/kg over five seconds. Episodes of cough within 60 seconds of fentanyl administration were classified as FIC, and the severity was graded based on the number of coughs (mild: 1-2, moderate: 3-4, severe: 5 or more). The time of onset of FIC was recorded. Hemodynamic changes and adverse effects due to fentanyl injection and the procedure were noted. The Kruskal-Wallis test, Mann-Whitney U test, and Chi-square test were used for statistical analysis.

Results: There were no differences among the four groups in terms of patients' characteristics and a American Society of Anaesthesiologist (ASA) status. The incidence of FIC was higher in Group C (37%) compared to Group A (8%), S (12%), and N (10%), which was statistically significant (p-value <0.001). There was no significant difference in the incidence of FIC between Groups A, S, and N. Severe cough were observed in nine patients in the control group, one patient in the nebulisation and spirometry group, and none in the acupressure group.

Conclusion: Non pharmacological methods such as acupressure and incentive spirometry were equally effective in reducing the incidence of FIC as the pharmacological methods and are more cost effective.

Keywords: Anaesthesia, Opoid, Spirometer

INTRODUCTION

Fentanyl is the most common opioid used as premedication because of its rapid onset, short duration, potent analgesia, and minimal histamine release [1]. Rapid intravenous administration of fentanyl can cause a self-limiting cough of varying severity [2-4]. While the cough is usually harmless, it can sometimes be troublesome. In rare cases, explosive coughing after intravenous fentanyl administration has even resulted in conjunctival and periorbital petechiae [5]. Serious complications such as increased intra-abdominal pressure, vomiting, aspiration, and pneumonia have been reported after fentanyl administration [3]. The incidence of Fentanyl-Induced Cough (FIC) ranges from 18% to 65% [6].

FIC should be avoided in patients with raised intracranial pressure, such as those with ruptured cerebral aneurysms, penetrating eye injuries, acute glaucoma, or those at risk of intracranial pressure elevation, such as patients with cerebral aneurysms or tumours [5]. Cough is a strong reflex irritation that can cause rapid changes in a patient's internal environment during perioperative anaesthesia. There have been reported cases where immediate tracheal intubation was required due to excessive coughing before the induction of general anaesthesia. Factors associated with FIC include high drug dose and concentration, injection speed, and route of administration [5,7,8].

Numerous pharmacological and non pharmacological methods have been used to reduce the incidence of cough. While many studies have investigated pharmacological agents, limited research has been conducted on non pharmacological methods [1,4,7]. Non pharmacological approaches include slowing down fentanyl injection, using a mechanical dropper for administration, performing the huffing maneuver, swallowing before fentanyl injection, acupressure at specific sites, and incentive spirometry. Non pharmacological methods are less expensive and have fewer side effects compared to pharmacological approaches [7]. Authors hypothesised that preoperative non pharmacological methods would yield better results in reducing FIC compared to pharmacological methods. The primary objective of present study was to compare the effects of acupressure at the K-27 point, incentive spirometry, and nebulisation with lignocaine prior to fentanyl administration in reducing the occurrence of FIC. The secondary objective was to compare the groups for any side effects or complications.

MATERIALS AND METHODS

This single-blind randomised controlled study was conducted at the Himalayan Institute of Medical Sciences, SRHU, Dehradun, Uttarakhand, India, over a nine-month period from May 2019 to February 2020. The study received Institutional Ethical approval (Reg. No. ECR/483HnstruK/2013/RR-16), and written informed consent from 400 patients were obtained.

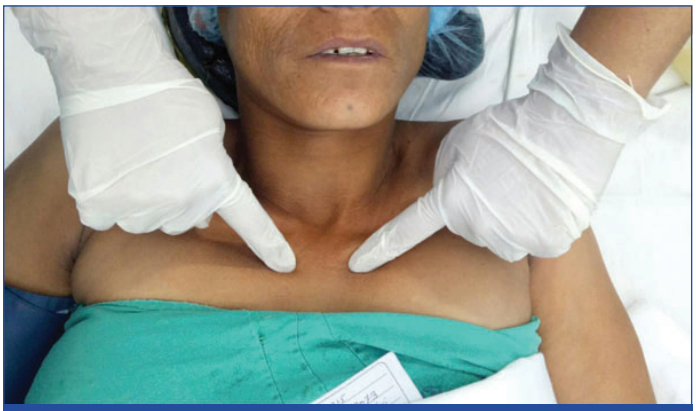
Inclusion criteria: Patients presented for elective surgery under general anaesthesia requiring endotracheal intubation were included in the study. All patients included in the study were of American Society of Anaesthesiology physical status 1 and 2, aged 18-60 years included.

Exclusion criteria: The present study excluded patients with pre-existing respiratory and cardiac diseases, impaired kidney or liver function, a history of Upper Respiratory Tract Infection (URTI) in the past four weeks, a history of smoking, pregnant patients, patients taking antipsychotics or Angiotensin Converting Enzyme (ACE) inhibitors in the last year, and those with allergies to the study drug were excluded.

Sample size calculation: The required sample size was 388 patients, but to account for potential dropouts, a total of 400 patients were enrolled. The sample size was estimated based on a previous study by Goyal VK et al., where the occurrence of FIC was found in 32% of the population [9]. It was calculated using the formula n=(Z1-α/2/ε)2, where n is the required sample size, Z is 1.96 at a 0.05 level of significance, and ε is a 20% relative error.

Study Procedure

Patients were randomly assigned to one of four groups using random table numbers generated by a computer, with 100 patients in each group. In Group A, patients were informed about the nature and location of acupressure. The K-27 point, located just below the medial end of the clavicle on either side of the sternum, was palpated using the index fingers of each hand simultaneously. Patients were instructed to take slow and deep breaths while the K-27 point was held for 30 seconds [Table/Fig-1] [10]. The pressure applied was tolerable for the patient. After this, undiluted fentanyl at a dose of 2 µg/kg was administered over five seconds, and pressure was continued at the same point for another one minute. The occurrence of cough was noted for one minute.



[Table/Fig-1]: Compression point in acupressure (K-27 point).

In Group S, participants were asked to sit in a straight posture with their chin slightly tilted up and mouth open. They were instructed to perform incentive spirometry ten times, aiming to lift a minimum of two balls with a four-second gap between inspirations. After this, fentanyl at a dose of 2 µg/kg was administered over five seconds, and cough was observed for one minute.

Group N patients received nebulisation with 4% lignocaine at a dose of 2 mg/kg, ten minutes before induction. Group C served as the control group.

In the operating theatre, all patients received undiluted fentanyl at a dose of 2 µg/kg, and the occurrence of FIC was recorded for one minute. Patients were not premedicated and were kept fasting. Standard monitors, including Non-Invasive Arterial Pressure (NIBP), Pulse Rate (PR), Electrocardiogram (ECG), and Pulse Oximeter (SpO_2), were attached. No preoxygenation or other medication was administered before the fentanyl bolus. Standard anaesthesia and surgical techniques were followed according to institutional protocols. All patients received undiluted fentanyl at a concentration of 50 µg/mL and a dose of 2 µg/kg. The primary endpoint was the incidence and severity of FIC.

An anaesthesiologist who was blinded to the method used recorded the occurrence of FIC. Coughing within 60 seconds of fentanyl administration was classified as FIC, and severity was graded based on the number of coughs (mild: 1-2, moderate: 3-4, severe: 5 or more) [11]. The time of cough onset was recorded in seconds after fentanyl administration. Secondary endpoints included any changes in Mean Arterial Pressure (MAP) and Heart Rate (HR) observed before and after the study procedures. The incidence of truncal rigidity, apnea, and desaturation were also recorded.

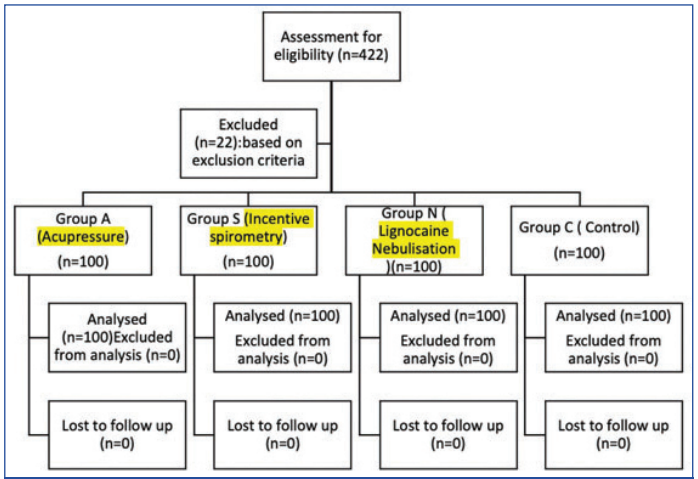
STATISTICAL ANALYSIS

The data was collected and entered into MS Excel 2010. Different statistical analyses were performed using IBM Statistical Packages for Social Sciences (SPSS) Statistics base version 22.0 (SPSS South Asia Pvt., Ltd., Bengaluru, India).

Continuous variables were presented as mean±SD, while categorical variables were presented as absolute numbers and percentages. Normally distributed continuous variables were compared using Analysis of Variance (ANOVA). The Kruskal-Wallis test was used for variables that were not normally distributed, and further comparisons were made using the Mann-Whitney U test. Categorical variables were analysed using the Chi-square test. A p-value of less than 0.05 was considered to indicate a significant difference.

RESULTS

Out of the 422 patients assessed for eligibility criteria, 22 patients were excluded from the study based on exclusion criteria. Therefore, a total of 100 patients in each group participated in the study and underwent further statistical analysis [Table/Fig-2]. There were no differences among the four groups in terms of patients' characteristics and ASA status [Table/Fig-3]. Out of the 400 patients enrolled in the study, 67 (16.7%) patients experienced FIC. The incidence of FIC was significantly higher in Group C (37%) compared to Groups A (8%), S (12%), and N (10%) (p-value <0.001) [Table/Fig-4]. There was no significant difference in the incidence of FIC between Group A, S, and N. Severe cough was observed in nine patients in the control group, one patient in the nebulisation and spirometry group, and none in the acupressure group.



[Table/Fig-2]: CONSORT (Consolidated Standards of Reporting Trials) diagram depicting the flow of study patients.

	Group A (n=100)	Group S (n=100)	Group N (n=100)	Group C (n=100)	*p-value
Age (years) (mean±SD)	38.80±12.83	40.63±13.58	38.69±13.86	40.81±14.09	0.549
Weight (kg) (mean±SD)	60.14±10.17	60.07±10.27	59.87±9.63	59.64±10.47	0.986
Gender M:F	43/57	41/59	41/59	35/65	0.682
ASA I:II	80/20	81/19	82/18	75/25	0.593

[Table/Fig-3]: Demographic data (N=400).
*ANOVA, data is expressed as numbers or percentage and mean±standard deviation
SD: Standard deviation; M: Male; F: Female; ASA: American society of anaesthesiologist

Parameters	Group A	Group S	Group N	Group C	*p-value
Incidence of cough (no. of patients and percentage)	8 (8%)	12 (12%)	10 (10%)	37 (37%)	
Severity of cough in numbers					
Mild	6	9	6	18	0.293
Moderate	2	2	3	10	0.885
Severe	0	1	1	9	0.247
Time of onset of FIC (median)	10	11.50	10	12	0.057
Dose of fentanyl (mcg/kg)	120.80±20.45	119.85±20.10	120.45±19.34	117.95±20.26	0.752
Comparison of incidence of FIC among all groups	A vs C	C vs N	S vs C	A vs N	A vs S	N vs S
*p-value	0.001**	0.001**	0.001**	0.624	0.347	0.652

[Table/Fig-4]: Incidence and severity of FIC, time of onset of FIC, total dose of fentanyl and comparison of incidence of FIC among groups.
*ANOVA, Chi-square test, Mann-Whitney U test
**p-value <0.01 (highly significant)

Parameters	Group A	p-value	Group S	p value	Group N	p-value	Group C	p-value
MAP pre post	101.27±15.60	0.001**	100.25±14.36	0.081	99.61±16.49	0.201	96.65±17.94	0.278
	97.05±15.29		96.33±19.81		96.40±14.60		94.74±16.50	
HR pre post	81.37±15.14	0.006**	82.88±16.77	0.045	79.24±14.31	0.805	82.76±14.78	0.058
	78.90±14.20		79.68±14.40		78.97±13.02		80.30±14.55	

[Table/Fig-5]: Comparison of Mean Arterial Blood Pressure (MAP) and Heart Rate (HR) in all the groups pre and post-procedure.
Paired T-test; *p-value <0.05 (significant) **p-value <0.01 (highly significant)

The onset time of FIC in all groups was between 10 and 12 seconds [Table/Fig-4]. The dose of fentanyl administered was comparable between patients who experienced FIC and those who did not. Significant differences were observed in MAP and HR before and after acupressure [Table/Fig-5]. Three patients experienced rashes at the injection site, but there were no incidences of other adverse effects such as rigidity, apnea, and desaturation after fentanyl administration.

DISCUSSION

In the present study, the results demonstrated that the incidence of FIC could be significantly reduced by acupressure (8%), incentive spirometry (12%), and nebulisation with lignocaine (10%). When fentanyl was administered via a peripheral intravenous cannula within five seconds, it provoked cough in 16% of patients. The observed occurrence of FIC in Group C (37%) was similar to a previous report (18%-65%) [6]. Another study by Bohrer et al., reported a much higher occurrence of cough (45%) when fentanyl was administered in doses as high as 7 µg/kg via a central line [12].

Literature has shown that age, ethnicity, and smoking have varying degrees of effects on the incidence of FIC. Infants and children have a higher incidence of FIC even with small doses (1 µg/kg), which is attributed to an increase in irritant cough receptors [6,12,13]. Similarly, evidence shows that the Asian population has a higher incidence of FIC than the European population [13]. Light smoking (<10 cigarettes/day) may have a protective factor against FIC. It is postulated that nicotine has an inhibitory effect on C-fibers present in the smooth muscles of the trachea and bronchi. These receptors are abolished in chronic smokers [13].

Various hypotheses regarding the mechanism of cough induced by opioids have been implicated. "Cough is a pulmonary chemoreflex, mediated by either irritant receptors (rapidly adapting receptors) present on the mucosa of proximal tracheobronchial airways or by J-receptors (vagal C-fiber receptors)" that are close to pulmonary vessels [3]. These receptors are very sensitive to chemical irritants like citrate present in fentanyl and release neuropeptides bradykinins and tachykinins, which cause cough [13]. Moreover, FIC is also related to vocal cord spasm and vagally mediated bronchoconstriction [2].

In the present study, we observed a lower incidence (8%) and severity (mild/moderate/severe: 6/2/0) of cough in the acupressure group compared to the control group (37%) (mild/moderate/severe: 18/10/9). Solanki SL et al., have also emphasised the role of acupressure at the K-27 point in significantly reducing the incidence of FIC (1.3% versus 12.7%, p-value=0.008) and the severity of cough [Table/Fig-6] [2,9,11,14-18]. They found an overall lower incidence of FIC (12.7%) in female cancer patients [11]. Acupressure, according to traditional Chinese medicine, has a role not only in relieving cough but also in postoperative nausea and vomiting [19]. Five important pressure points have been described in the literature, but we used the K-27 point, which is an effective point for relieving chest congestion, throat spasms, coughing, sore throat, and back pain [10]. Although the mechanism of action is not clear, it is suggested that the pressure at this point (K-27) opens the ability to breathe deeply, which relieves pain by releasing endorphins [11].

Incentive spirometry has an established role in preventing and treating postoperative lung complications. It is a widely used device to improve lung compliance after abdominal and thoracic surgeries [20]. In the present study, preoperative incentive spirometry proved to be of great benefit in decreasing the incidence of FIC (12%) and its severity (mild/moderate/severe: 9,2,1). Goyal VK et al., also observed a lower incidence of FIC (6%) in the spirometry group compared to the control group (26%) [9]. As the patient breathes slowly and deeply into the device and holds their breath for 3-5 seconds, a back pressure is created which opens up the alveoli, improves the cough reflex, and helps clean the airways. Incentive spirometry reduces the pulmonary cough reflex, which is a cause of FIC. Thus, it acts by preconditioning the lungs for FIC [9,21].

Intravenous lignocaine is effective in suppressing FIC, regardless of dosage. However, high doses of lignocaine before induction may not be justified due to its arrhythmogenic effect and increased vasodilatory effect caused by induction agents [22,23]. Therefore, in the present study, we used nebulised lignocaine 4% at a dose of 2 mg/kg, which did not exceed 200 mg of lidocaine. Blood lignocaine concentrations after nebulisation are much lower compared to the intravenous route and thus do not cause cardiac side effects [24,25]. The mechanism of action of nebulised lignocaine is both peripheral and central. Peripherally, it anaesthetises the cough receptors in the trachea, inhibiting sensory afferent nerves involved in the cough reflex. The central effect involves the direct depression of brain stem function responsible for cough suppression [25,26]. We found a decrease in the incidence and severity of FIC in Group N (10%) (mild/moderate/severe: 6/3/1) compared to the control group (37%). Golmohammadi M et al., conducted a

study and administered 1 mcg/kg of intravenous lignocaine before fentanyl and found a significant reduction in the incidence and severity of cough [Table/Fig-6] [2,9,11,14-18]. When comparing different methods of reducing FIC as mentioned in the table above, it was observed that these methods significantly reduced not only the incidence but also the severity of cough. Most of the episodes were of mild grade compared to the control group. The present study also showed a decrease in the severity of cough in Groups A, S, and N compared to the control group [Table/Fig-6].

The time of onset of FIC did not have any significant relation to the different groups. It was found to be less than 15 seconds in all groups. There was no statistically significant difference between the patients who coughed (n=67) and those who did not cough (n=333) regarding age, weight, sex, and dose of fentanyl. There was a significant decrease in mean arterial pressure and heart rate after applying acupressure. The acupressure point at K-27 releases endorphins, which decreases anxiety and apprehension [11]. The decrease in patient anxiety would have lowered blood

S. No.	Author and year/ study	Sample size	Age/sex	Details	Incidence of FIC	Severity of cough	Limitation(s)
1.	Present study; Comparison of acupressure (A), incentive spirometer (S), nebulisation with lignocaine (N) and control group (C)	400 patients	18-60 years/ Both sex	In Group A-K-27 point was held with constant pressure for 1 min seconds. Group S-performed incentive spirometry ten times to lift a minimum of two balls with a gap of 4 seconds between for inspiration. After this, fentanyl in a dose of 2 mcg/kg was given over 5 sec. Group N-nebulised with 4% lignocaine, 2 mcg/kg, 10 minutes before induction. Group C-control group.	Group A-8 patients Group S-12 patients Group N-10 patients Group C-37 patients	Mild; moderate; severe Group A 6;2;0 Group S-9;2;1 Group N-6;3;1 Group C-18 ;10; 9	Smoking was not considered.
2.	Ambesh SP et al., 2010; Huffing manoeuvre, immediately before induction of anaesthesia, prevents fentanyl-induced coughing	300 patients	18-60 years; Both sex	Group 1 patients breathed normally whereas Group 2 patients were asked to perform huffing manoeuvre just before the fentanyl injection.	Incidence of cough was 32% in the control group and 4% in the huffing manoeuvre group (p-value <0.00]	Mild; moderate; severe Control Group 30;12;6 Huffing Group 6;0;0	Blinding could not be done.
3.	Solanki SL et al., 2016 [11]; Acupressure verses dilution of fentanyl	225 patients	18-60 years/ all female patients	In control (C) group, patients received undiluted fentanyl at 3 mcg/kg IV in 3 seconds. In dilution group (D), patients received diluted fentanyl at 3 mcg/kg IV in 3 seconds. In acupressure group (A) Acupressure was continuous for 1 minute following administration of fentanyl.	In control Group 9 In undiluted Group 5 In acupressure Group 1	Mild; moderate; severe Group C 6;1;2 Group D 2;1;2 Group A-1;0;0	Sample size was based on a 35% reported incidence of FIC in previous studies, but the actual incidence in control group was 12.7%. All patients were female.
4.	Goyal VK et al., 2017 [9]; Preoperative incentive spirometry on fentanyl-induced cough	200 patients	18-60 years/ Both sex	Patients in the F+IS group performed incentive spirometry 10 times just before an intravenous bolus of 3 µg/kg fentanyl in the operating room Group F-control group.	Patients in the F+IS group had a significantly lower incidence of FIC than in the F group (6% vs. 26%)	Mild; moderate; severe Group F+IS=5;1;0 Group F=17;7;2 (p<0.05)	Administered oral alprazolam 2 hour before surgery although preoperative alprazolam may falsely decrease the incidence of FIC.
5.	Golmohammadi M et al., 2018 [14]; Comparison of the effects of pretreatment intravenous fentanyl or intravenous lidocaine on suppression of fentanyl-induced cough in children	100 patients	2-10 years/ Both sex	Group I received 1.0 mg/kg lidocaine (n=33), Group II received 0.5 µg/kg fentanyl (n=34) and Group III received normal saline as a control group (n=33).	Incidence of cough was found in the Group III (54.5%) versus 32.4% and 21.1% in Group II and Group I subsequently	Mild; Moderate; severe Group I=71.4%;14.3%;14.3% Group II=45.5%;27.3%;27.3% Group III=22.2%;27.8%;50%	Different dosages of lidocaine or fentanyl on FIC were not used.
6.	Lin W et al., 2019 [15]; A small dose of remifentanil pretreatment suppresses sufentanil-induced cough during general anesthesia induction	100 patients	20-70 years/ Both sex	Patients in the Remifentanil group (R group) received an intravenous infusion of remifentanil 0.3 µg/kg (diluted to 2 mL) 1 min before sufentanil injection; patients in the Control group (C group) received 2 mL of normal saline (NS) at the same time point.	The incidence in Group C was 31% and in group R was 4.8%	Mild; Moderate; severe Group C=7.1%;4.8%;19% Group R=2.4%;0;2.4%	Single dose of remifentanil was used.
7.	Gupta P et al., 2019 [16]; Role of pre-emptive Huff's manoeuvre and acupressure in reducing the incidence of fentany-induced cough	336 patients	18-60 years/ all female patients	Group A-The index finger of each hand was placed below the collarbone on either side and pressure at the point K27 was held for 1 minute. In Group B, patients were asked to take a deep breath and then hold breath for 2 or 3 seconds and exhale forcefully. In Group C, patients were explained about the FIC and reassured.	Incidence of FIC was 8%, 7.1%, and 25.9% in acupressure, Huff's and control group respectively	Mild; Moderate; severe Group A=5;4;0 Group B=3;5;0 Group C=15;12;0	Only female patients were included; ASA grade IV were not included.

8.	Liu M et al., 2019 [17]; Application via mechanical dropper alleviates sufentanil induce cough	200 patients	18-65 years/ Both sex	Administration of Sufentanil by mechanical dropper at 1 ml·s–1 (Group M); Control Group C.	Incidence Group M 2%; Group C 21%	Mild; Moderate; severe Group M=2,0,0 Group C=8;11;2	Slow, incredible, Infusion time was very long in group M.
9.	Malaithong W et al., 2022 [18]; Efficacy of Intravenous 0.25 mg/ kg Lidocaine (Group T) compared with 0.5 mg/ kg Lidocaine (Group C) for reducing fentanyl-induced cough	139 patients	18 to 60 years/Both sex	Lidocaine 0.5-1.5 mg·kg-1 given intravenously over 5 seconds, 1 min before administration of fentanyl.	13 (18.8%) patients in the 0.25% lidocaine group and 11 (15.7%) patients in the 0.5% lidocaine group experienced FIC	Mild; Moderate; severe Group T=10;2;1 Group C=8;2;1	Arrhythmia and depression.

[Table/Fig-6]: Comparison of different methods for reducing incidence of Fentany-induced Cough (FIC) [2,9,11,14-18].

pressure and heart rate in this group. Further research is needed on non pharmacological methods to reduce FIC, intraoperative hemodynamics, postoperative nausea and vomiting, and postoperative respiratory complications.

Limitation(s)

One limitation of present study is that smokers were not included, so we could not assess the effect of nicotine on FIC.

CONCLUSION(S)

The present study concluded that non pharmacological methods, such as acupressure and incentive spirometry, were equally effective in lowering the incidence and severity of FIC compared to pharmacological methods. Moreover, incorporating non pharmacological methods into daily practice is recommended as they are free of side effects and are cost-effective.

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