Comparative Analysis of Patient Satisfaction and Sedation Outcomes in Bronchoscopy: Fentanyl/Chlorpheniramine vs. Ketamine/Chlorpheniramine

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Received: 20 Apr. 2023; Accepted: 21 Aug. 2023

Abstract- This randomized clinical trial aimed to assess and compare patient satisfaction and sedation outcomes in bronchoscopy procedures using two distinct sedation protocols: fentanyl/chlorpheniramine (FC) and ketamine/chlorpheniramine (KC). Ninety patients undergoing simple bronchoscopy and bronchoalveolar lavage were randomly assigned to receive either FC (1 µg/kg fentanyl and 10 mg chlorpheniramine) or KC (0.5 mg/kg ketamine and 10 mg chlorpheniramine). Lidocaine was also administered during bronchoscopy. Primary outcomes included patient satisfaction scores, while secondary outcomes encompassed sedation levels, bronchoscopist satisfaction, cough rates, lidocaine usage, and physiological parameters. Patients in the FC group exhibited significantly higher satisfaction levels compared to the KC group (P=0.002). Bronchoscopist satisfaction was also superior in the FC group (P=0.001). Although cough rates did not differ significantly, severe persistent coughs were more prevalent in the KC group. Physiological parameters such as oxygen saturation were comparable, but the KC group demonstrated higher increases in systolic blood pressure and heart rate. The use of fentanyl/chlorpheniramine resulted in higher patient and bronchoscopist satisfaction during simple bronchoscopy and bronchoalveolar lavage compared to ketamine/chlorpheniramine. This study suggests that the combination of fentanyl and chlorpheniramine may be a preferable sedation choice for bronchoscopy procedures.

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Acta Med Iran 2023;61(9):513-518.

Keywords: Bronchoscopy; Fentanyl; Ketamine; Chlorpheniramine; Sedation; Patient satisfaction

Introduction

The American College of Chest Physicians (ACCP) suggests that all physicians performing bronchoscopy should consider topical anesthesia as well as analgesic and sedative agents, when feasible (1). A combination of benzodiazepine and an opioid is the most used combination, and it seems to be safe for this purpose (2).

Many anesthetic drugs such as propofol, ketamine, lidocaine, benzodiazepines, and opioids have been commonly used to induce sedation during fiberoptic bronchoscopy (3-6). Airway secretion and coughing during bronchoscopy are the two most important problems that increase the time of the procedure and decrease the satisfaction of both the patient and the bronchoscopist (7). Apnea and hypoxemia are other concerns that may jeopardize the process of bronchoscopy while using sedative drugs.

Histamine is a stimulatory neurotransmitter in the brain. Chlorpheniramine is an antihistaminic drug that has anticholinergic and sedative activity although it lacks analgesia (8). Antihistaminic drugs in combination with opioids also have antitussive effects (9). On the other hand, too much sedation causes some adverse events and may disrupt patient cooperation during the procedure (10-12). It is hypothesized that the sedative effects attributed to antihistamines as well as their antitussive effects if combined with an analgesic may

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make them a favorable choice during bronchoscopy. This study is designed to compare the level of satisfaction in patients who undergo sedation for bronchoscopy provided by a combination of fentanyl/chlorpheniramine versus ketamine/chlorpheniramine.

Materials and Methods

This study was a randomized, parallel, two-armed, controlled, phase 3 clinical trial, which was conducted at Sina Hospital, Tehran, Iran from September 2018 to July 2019.

This clinical trial was approved by the Research Ethics Committee of Tehran University of Medical Sciences (approval number: IR.TUMS.MEDICINE.REC.1396.3784) and was authorized by the Iranian Registry of Clinical Trials (registration code: IRCT20140409017198N2).

Before the participant's enrollment, the freely informed written consent was taken from all eligible participants.

Study population

Patients age18 or more, were candidates for_simple fiberoptic bronchoscopy and bronchoalveolar lavage (BAL) were included in the study.

on the other hand, exclusion criteria were having a positive history of sleep apnea, opium addiction, epilepsy, psychological disorders and hemodynamic instability, and history of sensitivity to anesthetic drugs.

Sample size calculation

According to Li's study (10), assuming a confidence level of 0.05 a margin of error of 80%, and a dropout of 10%, the sample size was calculated to be 45 people in each group.

Randomization

Eligible patients are evenly divided into two groups using the block randomization technique and computerized algorithms.

Intervention

In the anesthetic room, standard monitors including ECG, NIBP and SPO2 were established for all patients and baseline systolic blood pressure and heart rate were recorded.

Afterwards, an I.V. line was inserted, and normal saline was titrated slowly. All patients received supplemental O2 around 6 L/min through nasal prongs throughout the procedure.

The first group received ketamine /chlorpheniramine (KC) in the form of bolus injection of ketamine 0.5mg/kg plus chlorpheniramine 10 mg intravenously just three minutes before bronchoscopy. The second group (FC) received 1 µg/kg fentanyl plus 10mg chlorpheniramine similar to the first group.

Outcomes

Patients' satisfaction score was recorded as the primary outcome.

The bronchoscopist's satisfaction score, the highest systolic blood pressure changes above the baseline, the highest heart rates, and the highest oxygen saturation change during the procedure were also recorded as the secondary outcome.

Outcome assessment

Sedation level was evaluated three minutes after injections using the Sedation-Agitation Scale (SAS) based on the following scoring system: 1, patient unarousable, no response to noxious stimuli; 2, patient very sedated, rouses to stimuli; 3, sedated, obeys simple commands; 4, calm and cooperative, obeys commands; 5, agitated, attempts to sit up but calms down to verbal instructions; 6, very agitated, does not calm down, requires restraints.

For both groups, only when the SAS score was four or less, was the fiberoptic bronchoscopy procedure allowed to take place. If the SAS score was more than four, an additional bolus of the same sedatives was injected, and this event was recorded. The patients and the bronchoscopist as well as outcome evaluator were blind to the type of drug combinations. After passage of the bronchoscope (FB-55CR-1; Olympus Medical Systems Corp., Tokyo, Japan) via the nasal cavity of patients, the vocal cords and the tracheobronchial tree were anesthetized using a 5 ml aliquot of 1% lidocaine solution (lidocaine hydrochloride 2%; Pharmaceutical co, Rasht, Iran). It was sprayed through the airway by a spray-as-you-go technique.

Patients' satisfaction score in the recovery room is evaluated as the primary outcome. The Patients' satisfaction is classified according to a Likert's five-item scoring system as follows:

1=Not at all satisfied, 2=low, 3=medium, 4=high, 5=very highly satisfied

The patient's cough rate is graded as follows:

1=no cough, 2=some cough, 3=sustained severe cough

The length of the procedure and the amount of lidocaine used during procedure were recorded. All patients were monitored in the recovery room to gain full consciousness and then released to their wards.

Statistical analysis

To describe and compare the qualitative data of the study, the frequency (percent) is used, and for quantitative variables, the mean (standard deviation) is used. Categorical variables were expressed as frequencies and percentages. A chi squared test is used to examine the relationship between interval variables. Fisher's exact test was used to examine the relationship between categorical variables. A *P* less than 0.05 is regarded as significant difference.

A sample size of forty cases in each group is calculated to have at least 80% power to detect 30% difference in satisfaction scores (effect size) between the two treatment protocols It is assumed that any treatment that can increase the level of satisfaction more than 30% in comparison to the other group is considered statistically significant.

Results

The study included 90 patients, with each group containing forty-five individuals (Figure 1). The average age of the patients was 52.5±12.8 years, ranging from 20 to 69 years. Table 1 displays the demographic data, mean time of procedures, and amount of lidocaine utilized.

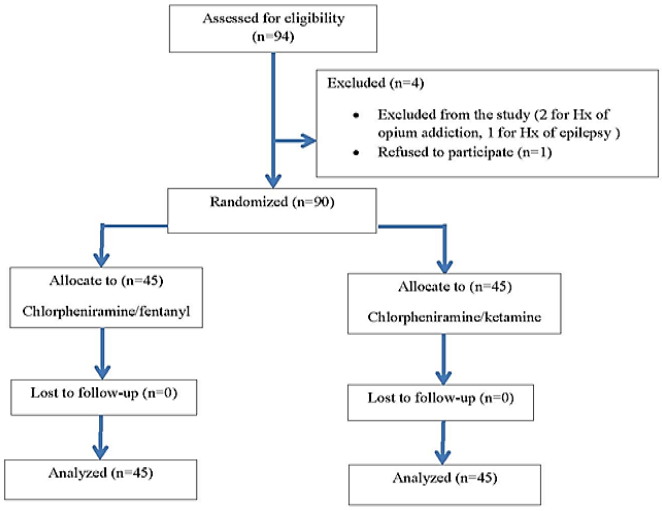

Figure 1. Diagram flowchart of study/Abbreviations: Hx: history

Table 2 shows the comparison of the patients' satisfaction score, bronchoscopist's satisfaction score, cough rate, and SAS scores.

No case in either group, as shown in Table 2, exceeded the four SAS scores, indicating that no further sedative reuse was necessary. Also, table 2 demonstrate that there were more patients in the KC group than in the FC group who had a sedation score of two or less (over-relaxing).

Table 1. Characteristics of patients, duration of procedures, and amount of used lidocaine

Variables	FC group N=45	KC group N=45	*P**
Age (mean±SD)	52.8±13.67	51.1± 12.17	0.78
Sex (Male/Female)	23/22	30/15	0.13
Smoking, n(%)	14(31)	18(40)	0.09
Duration of procedure (min), (mean±SD)	11.4±2.91	12.3±2.58	0.13
amount of used lidocaine (mg) (mean±SD)	185±42	208±41	0.10

*Results of chi square test
FC, fentanyl/chlorpheniramine; KC, ketamine/ chlorpheniramine; SD, standard deviation

Table 2. Comparison of patients and bronchoscopist satisfaction, SAS scores, and severity of cough

Variables		FC group N=45	KC group N=45	*P**
Patients satisfaction N (%)	Very low	2 (4.4%)	5(11.1%)	0.002
	low	3(6.6%)	17(37.7%)	
	moderate	19(42.2%)	15(33.3%)	
	high	17(37.7%)	6(13.3%)	
	Very high	4(8.8%)	2(4.4%)	
Bronchoscopist satisfaction N (%)	Very low	3(6.6%)	13(28.8%)	0.001
	low	2 (4.4%)	10(22.2%)	
	moderate	15(33.3%)	11(24.4%)	
	high	19(42.2%)	7(15.5%)	
	Very high	6(13.3%)	4(8.8%)	
SAS N(%)	1-unarousable	0 (0%)	1 (2.2%)	0.058
	2-very sedated	2 (4.4%)	7 (15.5%0	
	3-sedated	11 (24.4%)	16 (35.5%)	
	4-calm and cooperative	32 (71.1%)	21 (46.6%)	
	5-agitated	0 (0%)	0 (0%)	
	6-very agitated	0 (0%)	0 (0%)	
Severity of cough N(%)	No cough	3(6.6%)	1(2.2%)	0.121
	some cough	39(86.6%)	35(77.8%)	
	Sustained severe cough	3 (6.6%)	9(20.0%)	

*Results of chi square test
FC, fentanyl/chlorpheniramine; KC, ketamine/chlorpheniramine; SAS, sedation agitation score

When comparing the KC group to the FC group, there was a substantial increase in both heart rate and systolic blood pressure. The study did not find a statistically significant difference in oxygen saturation across the groups, as shown in table 3.

In the KC group, there was one case of apnea that necessitated the use of mask ventilation for a duration of seven minutes until spontaneous respiration resumed.

Table 3. Comparison of the changes in the oxygen saturation, heart rate, and systolic blood pressure

Variables	FC group N=45	KC group N=45	*P**
SPO_2 at the baseline (%) (mean±SD)	96.04±3.48	96.7±3.09	0.45
SPO_2 changes compared to the baseline at minute 3 from intervention (%) (mean±SD)	-0.4±23.09	1.31±2.55	0.21
Heart rate at minute 3 from intervention (beats/min) (mean±SD)	85.88± 13	93.26 ±16	0.02
Amount of increase in systolic blood pressure at minute 3 from intervention (mmHg) (mean±SD)	12.6±4.8	24.4±10.9	0.001

*Results of chi square test
SD, standard deviation; SpO2, saturation pressure of oxygen

Discussion

The passage of the bronchoscope through the upper airways almost always causes discomfort. We know that histamine acts as a stimulatory neurotransmitter in the brain that is crucial for wakefulness, motivation, and goal-directed behaviors (8).

The result of the current study showed that antihistaminic drug can be used for induction of sedation in patients while preparing acceptable satisfaction for them.

Lin *et al*., through an animal study showed that the

use of antihistaminic drugs improves opioid-induced pain relief after electro-acupuncture via non-opioid receptors (13). The result of the current study shows that this concept may be true in humans.

A combination of an antihistaminic drug with dexamethasone and fentanyl, improved the control of postoperative pain, nausea and vomiting in bariatric surgical patients (14). The current study supports the concept which is conveyed in the above-mentioned study.

Ketamine as the principal hypnotic agent has been used in flexible bronchoscopy especially for pediatric patients (4). Ketamine has some adverse effects including visual and auditory hallucinations (psychoactive effects). Benzodiazepine is usually initially given to reduce these effects (15). Ketamine is used to satisfy the analgesic component in the KC group versus fentanyl in the other group. It should be noted that fentanyl, which is used for the preparation of analgesia in the FC group, doesn't cause such psychological effects. Significant difference in patients' satisfaction scores between groups may be partially due to the above issue.

Hwang *et al.*, evaluated a combination of propofol/alfentanil versus propofol/ketamine via a patient-controlled analgesia system in bronchoscopy patients. They used ketamine in one group to provide analgesia versus alfentanil in the other group and reported that ketamine is superior to alfentanil when combined with propofol (16). However, the current study shows that chlorpheniramine, as the hypnotic base, may not be an appropriate choice to be combined with ketamine. To explain afore-mentioned phenomenon we can suggest that propofol (like midazolam that works via the GABAergic system) might have mitigated the psychotomimetic effects of ketamine in Hwangs' study while chlorpheniramine couldn't have the same preventive effect on psychotomimetic effects of ketamine in the current study.

Dal *et al.*, got an equivocal result for ketamine/midazolam versus ketamine/propofol to induce sedation in ultrasound guided trans-bronchial needle aspiration. They reported that both protocols were similarly effective and provided good levels of satisfaction for patients and bronchoscopist without remarkable side effects (17). Their equivocal results might be explained by the preventive effect of both midazolam and propofol on psychotomimetic effects of ketamine. Retrospectively, it might be deduced that the GABAergic system might not be involved in the induction of hypnosis by chlorpheniramine. In addition, the rise in hemodynamic variables (heart rate and systolic blood pressure) was significantly higher in the KC group. The possible synergistic anticholinergic effect of ketamine with chlorpheniramine may explain above-mentioned findings. In addition, palpitation due to anticholinergic effects might have a negative impact on the feelings of patients during bronchoscopy in the KC group and that might lead to a less satisfaction score in the patients of the KC group.

Although the rate of cough was not significantly different between groups there were three patients with severe persistent cough in the FC group versus nine in the KC group which deserves attention. We can assume that severe persistent cough may affect the satisfaction of bronchoscopist.

There is just one case report in literature regarding intramuscular injection of chlorpheniramine that enhances the respiratory depressant effect of epidural fentanyl (18).

There is one case of long-lasting apnea in the KC group. Although it isn't statistically significant, even one case of apnea may be clinically significant when the airway is the site of intervention, and it is better to be avoided it. So, we can consider this event as a disadvantage for KC protocol.

Occurrence of too much sedation (SAS score less than 2) in the KC group (8 versus 2) might be another contributing factor for making less satisfaction of bronchoscopist with the KC group. It is obvious that too much sedated patient may not be able to swallow oral secretions and don't cooperate with bronchoscopist.

In conclusion, this study demonstrates that chlorpheniramine is an acceptable hypnotic drug to induce sedation but is not capable of mitigating psychotomimetic and hemodynamic effects of ketamine. In addition, when chlorpheniramine combined with fentanyl provides more satisfaction in both patients and bronchoscopist compared with chlorpheniramine/ ketamine during bronchoscopy.

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