Academic Journal of Medical Sciences
ISSN: 2708-2725
ORIGINAL ARTICLE

Effect of Nebulized Ketamine in Prevention of Postoperative Pharyngeal Pain

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Funding information
Self-funded

Conflict of interest
None declared by author

ABSTRACT

Background: *Postoperative pharyngeal pain (POPP) is a frequent complication characterized by the presence of odynophagia. It is a subjective experience that consists of the sensation of discomfort or pain in the pharynx after endotracheal intubation.*

Objective: *To assess the effect of nebulized ketamine in prevention of postoperative pharyngeal pain*

Patients and methods: *A prospective case control study carried in our hospital for six months duration (from the first of Feb 2022-to the end of July 2022). A sample size of 61 patients in Ketamine group and 56 patients in placebo group was estimated, for a total of 117 patients. These two groups was (group A: were given preoperative nebulized ketamine in a dose of 50 mg: 1 mL of ketamine + 2 mL of saline solution 0.9%) and (group B: placebo in which patients undergo nebulization of 3 mL saline solution 0.9% only).*

Results: *The use of nebulized ketamine does not represent a statistically significant difference compared to placebo for postoperative Pharyngeal pain. The incidence of postoperative Pharyngeal pain in the current study was of 59.29%.*

Conclusions: *further research were needed to assess the effect of nebulized ketamine with large sample size to find the correct treatment of POPP.*

Received *: April, 2023*
Published*: June, 2023*

Keywords: ***Ketamine; nebulized; nebulization; postoperative sore throat; prophylaxis; satisfaction***

1. INTRODUCTION

Postoperative pharyngeal pain (POPP) is a frequent complication characterized by the presence of odynophagia. It is a subjective experience that consists of the sensation of discomfort or pain in the pharynx after endotracheal intubation. The world bibliography reports a frequency of between 20 and 70% , although the latest systematic reviews in this regard conclude a frequency of 40%. POPP generally self-limits in less than 96 hours; however, there are reports stating that up to 10% of patients with POPP may have a longer duration (1,2). It is considered a significant morbidity in the postoperative period, since it causes an increase in the length of stay in the Post-Anesthesia Care Unit, with the subsequent increase in costs and risks (3). In addition, it is currently considered worldwide as a marker of quality in medical care, since patients have rated POFP as one of the 10 most uncomfortable conditions they presented, and it has been defined as one of the most important reasons for patient dissatisfaction (4). The drugs most frequently described in the world literature for the prevention of POPP include: Tramadol, Dexamethasone (RR 0.68) , Budesonide, Lidocaine, Betamethasone, Aspirin, Benzydamine (RR 0.42), Magnesium Sulfate Fluticasone and Ketamine ; in different doses and routes of administration. On the other hand, the non-pharmacological measures described include: use of smaller endotracheal tubes, endotracheal tube lubrication, use of humidifiers in the circuit, effective neuromuscular relaxation, gentle suctioning, balloon pressure less than 25 cm H 2 O, avoid coughing at the time of extubation, complete deflation of the balloon prior to extubation, and avoid as much as possible changing the head position such as rotation, extension and flexion (5). Ketamine has multiple pharmacological properties including: analgesic, and anti -inflammatory, and bronchodilator. Several studies have validated its use by different routes of administration (nasal, oral, rectal, nebulized), to obtain local effects. The mechanism of action is through the non-competitive antagonism of NMDA receptors, which are found in the CNS, in peripheral nerves and the cells adjacent to these. For this reason, NMDA receptor blockade has antinociceptive and anti-inflammatory effects, which prevent exaggerated responses from the immune system (4,5).

Other sites of action of ketamine are: on opioid receptors (μ, κ, δ) at concentrations greater than 30 μM, on monoamine transporters (norepinephrine, dopamine, serotonin) at more than 60 μM, on D2 receptors at 0.5 μM and in 5-HT 2 receptors at 15 μM. It also has a blocking effect on various receptors such as nicotinic and muscarinic receptors at plasma concentrations of 10-80 μM and on calcium-sodium, sodium-potassium, and calcium-potassium channels at higher concentrations (over 50 μM) (6,7). Regarding POFP, because the pathophysiology is due, on the one hand, to direct trauma to the mucosa that causes inflammation and edema, and, on the other hand, to the excessive muscle contracture exerted by the tube , Several studies have used ketamine locally, due to its already described anti-inflammatory properties, without presenting adverse effects due to its local and non-systemic effect. Such is the case of ketamine used as a mouthwash for 30 to 40 seconds, which has been shown in multiple studies to reduce the frequency of this complication 1 reaching a plasma concentration of 16 mg/mL. (6-8) The objective of the study: To evaluate if nebulized ketamine in the preoperative period is effective as a prophylaxis for the reduction of postoperative pharyngeal pain in elective surgery under general anesthesia, in adults from 18 to 80 years old, compared with placebo.

2. METHODOLOGY

Study design: A prospective case control study carried in our hospital for six months duration (from the first of Feb 2022-to the end of July 2022).

With prior authorization from the local Research and Ethics Committee of Our Hospital and once the informed consent of the patient was obtained, a prospective, study was carried out in which POPP was evaluated. It was carried out within the service of the operating theater facilities and the corresponding rooms of the medical city, Baghdad, Iraq.

Study population

All patients scheduled for surgery within the period of the study within the inclusion criteria were considered eligible.

Inclusion criteria: adult patients between 18 and 80 years of age, of any gender, physical status I or II according to the American Society of Anesthesiologists (ASA), with preoperative evaluation that specifies that it will be used: general anesthesia, for scheduled surgery and whose scheduled anesthesiologist agreed with the standardized management for the study.

Exclusion criteria: patients with previous lung disease, upper respiratory tract infection, known allergy to ketamine, congenital or acquired airway deformities, state of consciousness that prevented them from understanding the explanations, inability to understand the numerical scale to pain assessment,

Material

Two identical vials: one with ketamine and the other with 0.9% saline solution, jet nebulizer, oxygen intake in the preoperative area, non-invasive monitoring (pulse oximetry, blood pressure, and ECG) before the operation.

Methods

Ethical considerations

Prior approval was carried out by both the ethics committee and the Hospital Committee, and with the informed consent of the patients.

This protocol has been designed based on ethical principles for medical research in humans. There are no ethical conflicts for carrying out this study since despite being an experimental study, the maneuver evaluated does not deprive the patient of any treatment; on the contrary, it represents another possibility for optimization in perioperative management.

Sample size

A sample size of 61 patients in Ketamine group and 56 patients in placebo group was estimated, for a total of 117 patients. A first observer in the preoperative area assigned the patients to each group according to the corresponding randomization, recording only those people who met the study inclusion criteria.

An anesthesiologist administered nebulization at 5 L/m for 5 minutes preoperatively according to envelope assignment. If the envelope read “A”, one milliliter from bottle A plus 2 milliliters of saline was nebulized. On the other hand, if the envelope said "B", one milliliter from bottle B was nebulized plus 2 milliliters of saline solution. Therefore, two groups were

obtained: group K: nebulized ketamine (50 mg: 1 mL of ketamine + 2 mL of 0.9% saline solution) and group P: placebo (nebulized 3 mL of 0.9% saline solution).

Subsequently, laryngoscopy and intubation were performed. The first observer made sure that, once the patient arrived at the Post-Anesthesia Care Unit area, intubation and anesthetic management had been carried out in accordance with the study criteria and also verified that the patient did not present elimination criteria. .

Anesthetic management

All patients received the same anesthetic management, which consisted of the following: upon arrival of the patient in the operating room, the presence of a permeable peripheral venous line was verified. Non-invasive monitoring was placed (consisting of five-lead ECG, non-invasive blood pressure measurement, pulse oximetry, and End-tidal carbon dioxide (ETCO2)). Baseline signs were taken upon arrival in the operating room and it was verified that they were similar to the baselines reported in the nursing sheet. Anesthetic management had to adhere to the following drugs: for induction fentanyl 3-5 µg/kg, steroidal neuromuscular relaxant (rocuronium 0.6 mg/kg, vecuronium 0.15 mg/kg), propofol (2-2.5 mg/kg). Laryngoscopy was performed with a curved blade 3 or 4, at the discretion of the anesthesiologist, and the use of Glide Scope was taken into account if necessary . endotracheal tubes were used.

Analgesic prophylaxis with paracetamol and NSAIDs was used. Antiemetic prophylaxis with 5-HT 3 inhibitors 30 minutes prior to emersion (ondansetron) and dexamethasone at the start of anesthesia. Maintenance at the choice of the anesthesiologist in charge of the case, either with inhalation or with total intravenous anesthesia, subsequent doses at the choice of the anesthesiologist in charge.

Statistical analysis

The analysis of the information was carried out by means of descriptive statistics, measures of central tendency and dispersion. The systematization of the information was carried out with the SPSS package version 25 for Windows and the accepted level of statistical significance was set as a value of $p < 0.05$.

3. RESULTS

117 patients were selected to participate in this study. The other patients did not meet the inclusion criteria as detailed in method . The patients were scheduled for otolaryngology surgery, general surgery, and orthopedics. The selected patients were divided into two groups, so that group K was made up of 61 patients and group P was made up of 56. Normality tests were performed in which it was concluded that the sample does not follow a normal distribution, so the data was analyzed with Kolmogorov-Smirnov and Shapiro-Wilk. Being measurement scales and therefore ordinal quantitative variables, the mean and standard deviation was measures. The demographic characteristics of both groups are detailed in (**Table 1**). The characteristics of the groups according to the post-nebulization conditions are detailed in (**Table 2**). Five patients were eliminated after the nebulization was administered. The results obtained show that there is no statistically significant difference between the use of ketamine and placebo at hour 1 or hour 4 postoperatively, as detailed in (**Tables 3 & Table 4**). A frequency of postoperative pharyngeal pain was obtained in the population of Hospital, 39.4% in the first postoperative hour and 42.3% in the fourth hour. With no significant difference found between the studied group (P>0.05). No adverse effects such as dissociation, nystagmus, increased heart rate or blood pressure were observed upon arrival in the operating room. Dizziness was only observed in four patients (3.53%) after nebulization. In none of these patients did dizziness persist postoperatively. On the other hand, the frequency was also obtained according to gender, where we found that in the female it was 54.83% and for the male it was 60.86%, with an odds ratio of 0.502 (CI 0.199-1.268) and with a difference between genders of 6.03%. Other risk factors were analyzed according to those reported in the literature. Our results report that the main risk factors for the appearance of POPP in our population are the use of a metal guide (OR 1.56 IC 1.30-1.87) and previous smoking (OR 3.778 IC 1.227-11.631). Other historically reported factors such as Trendelenburg position, use of intravenous anesthesia against balanced general anesthesia and use of Glide Scope (OR 0.947 CI 0.263-3.406), They did not turn out to be significant in our study. In the Mann-Whitney U analysis, it was observed that the ketamine dose according to weight was 0.761 mg/kg (0.34-1.0). We observed that there is a frequency of 15.17% of postoperative hoarseness. Of the 16 patients who presented it, nine (56.25%)

belonged to the ketamine group and seven (43.75%) to the placebo group; however, the difference was not statistically significant either (p = 0.699) (**Figure 1**).

Table 1. Demographic characteristics.

Variable		Group K (n = 61)		Group P (n = 56)		P. value
		No.	%	No.	%	
Sex	Female (n = 70)	33	47.1	37	52.8	0.8 Ns
	Male (n = 47)	28	59.6	19	40.4	
Age (years)		48.1± 16.6		46.9± 15,4		0.9 Ns
ASA 1 (n = 65)		32	49.2	33	50.8	0.8 Ns
ASA 2 (n = 52)		29	55.8	23	44.2	
BMI		29.4± 3.6		28.9± 2.9		0.6 Ns
Smoking (n = 29)		18	62.1	11	37.9	0.2 Ns
surgery specialty	General Surgery: 79	35	44.3	44	55.7	0.01 S
	Otorhinolaryngology: 18	10	55.6	8	44.4	
	Orthopedics: 20	16	80.0	4	20.0	

Group K = ketamine group; P group: placebo group; ASA = *American Society of Anesthesiologists*.

Table 2: Post-nebulization characteristics.

Variables		Group K (n = 58)		Group P (n = 54)		P value
		No.	%	No.	%	
Mean Time between nebulization and intubation minutes		30 ± 23.55		30± 11.88		0.4 Ns
Endotracheal tube number mean± SD		7.5 ± 0.57		7.5 ± 0.48		0.8 Ns
Number of laryngoscopies mean		1.26 ± 0.548		1.17 ± 0.505		0.2 Ns
Mean Cormack lehane grading		1.9 ± 0.83		1 ± 0.8		0.2 Ns
Type of anesthesia	Balanced overall	41	70.7	38	66.7	0.6 Ns
	Total intravenous	17	29.3	18	33.3	
Neuromuscular relaxant	Rocuronium	48	82.8	48	88.9	0.2 Ns
	Vecuronium	10	17.2	6	11.2	
Mean opioid rate		2.4 ± 1.9		2.3 ± 2.05		0.6 Ns
Prone position		5	8.6	8	14.8	0.04 S
Trendelenburg position		8	13.8	12	22.2	0.2 Ns
Changes in the patient's position during surgery		11	19	9	16.7	0.7 Ns
Use of metallic guide		10	17.2	12	22.2	0.5 Ns
Mean Dexamethasone dose mg		8 ± 5.6		8± 7.9		0.9 Ns
Mean total minutes of anesthesia		120± 66.659		132.50± 72.09		0.4 Ns

Table 3: Pain in the first postoperative hour.

Intensity		Group K (n = 58)		Group P (n = 54)		P. value
		No.	%	No.	%	
Without pain (n=68, 60.7%)		34	58.6	34	63	0.1 Ns
With pain (n=44, 39.4%)	Mild: 28	19	67.9	9	32.1	0.1 Ns
	Moderate: 11	4	36.4	7	63.6	
	Severe: 5	1	20.0	4	80.0	

Mild pain considered as 1-3, moderate 4-6, severe 7-10 on the ENA scale.

Table 4: Pain in the fourth postoperative hour.

Intensity		Group K (n = 58)		Group P (n = 54)		P. value
		No.	%	No.	%	
Without pain		35	60.3	29	53.7	0.7 Ns
With pain (n=48, 42.3%)	Mild	16	27.6	15	27.8	0.3 Ns
	Moderate	6	10.34	8	14.81	
	Severe	1	1.7	2	3.7	

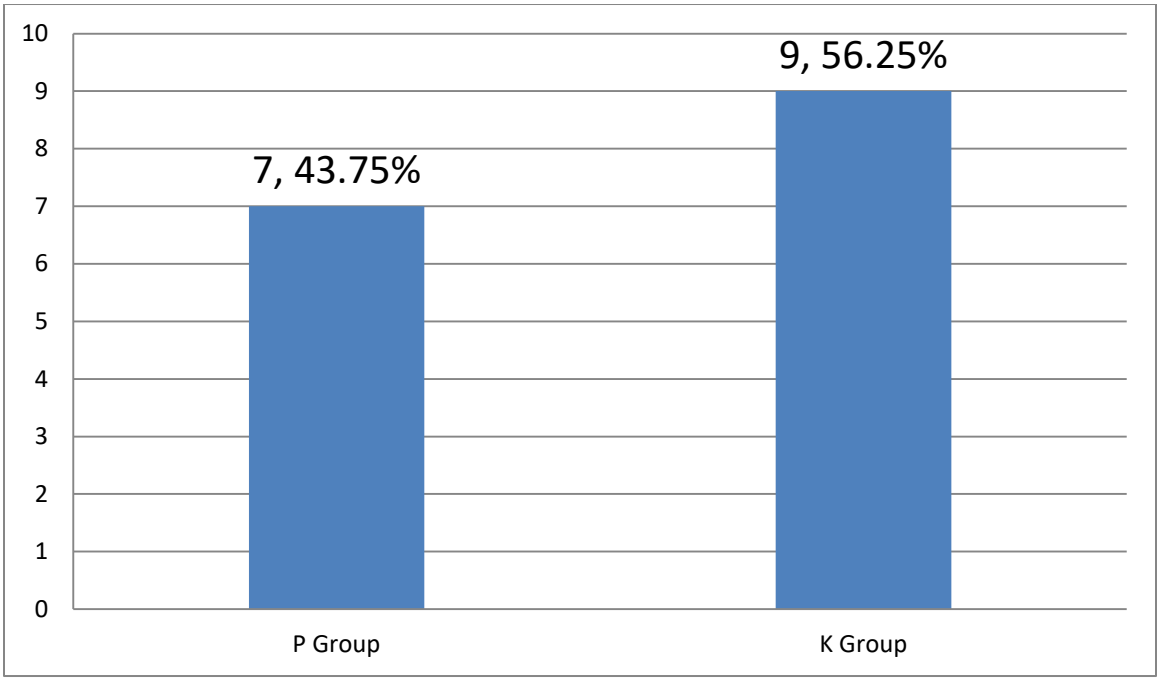

Figure 1. Postoperative hoarseness

4. DISCUSSION

The validity and importance of our study lies in the fact that it is the first study in our country in which nebulized ketamine is used for the prevention of POPP; however, we consider that there are several improvements that should be made for subsequent studies. It is worth remembering that pain is a highly personal experience, involving not only what the patient is feeling physically, but also physiological changes and the way in which the patient interprets pain, given their previous experiences and their state of mind. This may be one of the reasons why, despite the many methodological similarities with the study by Ahuja et al., when dealing with two culturally and geographically different populations, the results they have found do not coincide with ours (9). We did not find that nebulized ketamine represents an advantage in the treatment for the prevention of POPP. We believe that this negative result may be due to several factors: the first is that the dose we used was a standard dose of 50 mg for all patients, without considering the weight of each one. Our mean rate used was 0.7 mg/kg of weight. The only other study in the literature that reports the use of nebulized ketamine for the same purpose is the study by Ahuja et al. (10). They use the same standardized dose of 50 mg; however, they do not report the rate per kilogram

of weight. Given the differences in BMI that we can find between our population and the Indian population, we consider that their results on the usefulness of ketamine for the prevention of POPP cannot really be extrapolated to our population; Therefore, in future studies, a dose per kilogram of weight should be considered and not a standard one; as well as the use of plasma ketamine measurements. The second possible explanation for the difference in the results obtained in both studies is the volume and time of nebulization used in each one. Ahuja et al. (10) used 5 mL (50 mg volumetric) nebulized for 15 minutes, while we used 3 mL (50 mg volumetric) nebulized for five minutes. We are aware that this methodological difference may have made the results less extrapolable between one study and another; however, given the nature of our population and being a private hospital with the same sociodemographic characteristics as ours, spending more than five minutes in the preoperative area is not common, so this time was standardized for all patients, to thus being able to compare one group against another within our same population. The third explanation we found is that when conducting a review of the literature on drug metabolism reports in general in the Indian population, we found some studies that show that the South Indian population has genetic variations in metabolism, due to to a polymorphism of the CYP2C19 enzyme. This variation causes them to metabolize slowly certain drugs such as sertraline and omeprazole. Some authors such as Hijazi studied the influence of this enzyme on the N-demethylation activity of ketamine, concluding that there is a 15% decrease in the conversion to nor ketamine. It would be worth considering that these differences in metabolism between the two populations could explain why the same dose of drug in them had a greater effect than in us, since they are considered "slow metabolizers" for certain drugs (11,12). It would also be important to consider that the diameter of the microparticles obtained with the different types of nebulizers varies: with the jet type, these particles measure from 10 to 25 micrometers, of which it is considered that one to two are lost in the environment. thirds of the administered dose and that manage to be deposited only in the mouth and in the upper airway. In contrast, ultrasonic nebulizers obtain smaller particles (5 to 10 micrometers in diameter) that are capable of covering a larger territory of the airway (13).

We believe that in subsequent studies an attempt could be made to use a more effective type of nebulization than the one used by both Ahuja et al. like us (10). In this study, an attempt was made to generalize the results and obtain a broad overview of the POPP in our hospital, so that the results were applicable to our population. For this reason, it was decided to include the five surgical specialties with the highest number of interventions per year in our hospital (General Surgery, Otolaryngology, and Orthopedics), with a different percentage of participation of each one and with a different number of procedures. surgical, which may affect heterogeneity in some of the analyses; however, this allows the results to be applicable to a larger sector. The distribution of ketamine and placebo was not uniform in some of the specialties (Orthopedics, Neurosurgery and Otorhinolaryngology), as well as in the use of the prone position, so we initially considered that this could represent a bias. To verify this, two analyzes were carried out, one considering this and the other ruling out these three specialties. The results we found were the same in both cases. Even so, we consider that the use of a larger population sample could avoid this conflict. Regarding the most important risk factors for presenting POPP, the published evidence is controversial. In the logistic regression analysis of the systematic review by El-Boghdadly et al. it was established that the main risk factors are: female gender (OR 1.66), previous lung disease (OR 3.12), duration of anesthesia (OR 1.27) and presence of blood in the tube (OR 4.81) (14). Unlike them, in our study we found that the main risk factors for POPP are the use of a metal guide wire and previous smoking. Biro P et al. also found that smoking is one of the main risk factors, as well as female gender, previous lung disease, duration of anesthesia, postoperative nausea, and presence of blood in the tube (15). Regarding gender as a risk factor, other studies, have shown that reducing the size of the tube can reduce the risk, so the female gender is no longer considered by some as a risk factor (16). No significant differences were found between the use of nebulized ketamine or placebo at the first postoperative hour or at the fourth hour, so the null hypothesis is verified, as in the study by Park SY et al. used intravenous ketamine to avoid POPP. There is a slight non-statistically significant difference in frequency that favors nebulized ketamine by 0.66% (13). We observed that there is a frequency of 15.17% of postoperative hoarseness. Of the 16 patients who presented hoarseness in the postoperative period, 56.25% belonged to the ketamine

group and 37.5% to the placebo group. This frequency was also higher than that of Kumar M et al., who reported 10% (17). However, the difference between groups in our study was also not statistically significant (p = 0.699). Regarding the adverse effect of dizziness during nebulization, we observed that the rate of ketamine was similar in all the patients who presented dizziness, in addition to being close to the group average (0.7), so we conclude that there are other predisposing factors that should be analyzed in a subsequent study.

5. CONCLUSIONS

further research were needed to assess the effect of nebulized ketamine with large sample size to find the correct treatment of POPP.

Ethical Approval:

All ethical issues were approved by the author. Data collection and patients enrollment were in accordance with Declaration of Helsinki of World Medical Association , 2013 for the ethical principles of researches involving human. Signed informed consent was obtained from each participant and data were kept confidentially.

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Citation:

Almashhadani M.M, Abd Janabi A.H, Kareem M.A Effect of nebulized ketamine in prevention of postoperative pharyngeal pain. AJMS 2023; 9 (2): 230-43