An-Najah National University

Faculty of Graduate Studies

THE EFFECT OF PROPHYLACTIC PREOPERATIVENEBULIZED KETAMINE VS. NEBULIZED DEXAMETHASONE ON POSTOPERATIVE SORE THROAT IN PATIENTS UNDERGOING SURGERY UNDER GENERAL ANESTHESIA: A RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND TRIAL

By

Mohammad Moufeed Mahmoud

Supervisors

Dr. Aidah Abu El-Soud Al-Kaissi

Dr. Nouraldin Almasri

This Thesis is Submitted in Partial Fulfillment of the Requirements for the Degree of Master Nursing Anesthesia, Faculty of Graduate Studies, An-Najah National University, Nablus - Palestine.

2022

THE EFFECT OF PROPHYLACTIC PREOPERATIVE NEBULIZED KETAMINE VS. NEBULIZED DEXAMETHASONE ON POSTOPERATIVE SORE THROAT IN PATIENTS UNDERGOING SURGERY UNDER GENERAL ANESTHESIA: A RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND TRIAL.

By

Mohammad Moufeed Mahmoud

This Thesis was Defended Successfully on 18/8/2022 and approved by

Dr. AidahAl-Kaissi	
Supervisor	Signature
Dr. NouraldinAlmasri	
Co-Supervisor	Signature
Dr. ImadTaeym	
External Examiner	Signature
Dr.ImadThultheen	
Internal Examiner	Signature

Dedication

Dedicated to my father, may he rest in God's spacious gardens for eternity.

To my loving mother, may God protect her and bless her with a long life.

To my dear brothers and sisters.

To all my friends and colleagues, may God protect them all.

Acknowledgments

Thanks to God for allowing me to finish my master's thesis to earn my anaesthesia nursing degree and I ask him to help me be able to help others.

Then I would like to thank:

Dr. Aidah Abu El-Soud Al-Kaissi for her generosity of supervising this thesis and not sparing her efforts in guiding and instructing me. May God protect her and bless her long life.

Dr. Nouraldin Almasri, my supervisor, for his guidance and education during my training.

To the Honorable Committee members Dr. Imad Thultheen, the internal examiner and Dr. Imad Tayem, the external examiner.

To all the teachers and trainers at the university and hospital who have helped me with my education and training.

Declaration

I, the undersigned, declare that I submitted the thesis entitled:

THE EFFECT OF PROPHYLACTIC PREOPERATIVE NEBULIZED KETAMINE VS. NEBULIZED DEXAMETHASONE ON POSTOPERATIVE SORE THROAT IN PATIENTS UNDERGOING SURGERY UNDER GENERAL ANESTHESIA: A RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND TRIAL

I declare that the work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree or qualification.

Student's Name: _____

Signature: _____

Date: _____

List of Contents

List of Tables

List of Figures

List of Appendices

THE EFFECT OF PROPHYLACTIC PREOPERATIVE NEBULIZED KETAMINE VS. NEBULIZED DEXAMETHASONE ON POSTOPERATIVE SORE THROAT IN PATIENTS UNDERGOING SURGERY UNDER GENERAL ANESTHESIA: A RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND TRIAL

By

Mohammad Moufeed Mahmoud

Supervisors

Dr. Aidah Abu El-Soud Al-Kaissi

Dr. NouraldinAlmasri

ABSTRACT

Background: Postoperative sore throat is a minor undesirable complication following general anesthesia with endotracheal intubation, causing discomfort and decreasing satisfaction to the delivered anesthetic care. An injury related to direct tracheal mucosa trauma and decreased humidity because of the ETT cuff pressure are the main cause behind POST, which means it's almost unavoidable and therefore an appropriate prophylactic intervention is needed to decrease its incidence. Many studies proved promising results of ketamine and dexamethasone nebulizers to decrease and prevent the incidence and severity of POST with other laryngeal morbidities like cough and hoarseness.

Objectives: To determine if preoperative nebulization of ketamine or dexamethasone has a significant influence on POST and other laryngeal morbidities incidence and severity in patients undergoing elective surgeries under GA with ETT, and to determine if it has a significant effect on endotracheal intubation condition and hemodynamic response to laryngoscopy.

Methodology: Ninety nine patients allocated for surgeries under GA enrolled in thisprospective double-blind, randomized, placebo-controlled study. Every participant received a nebulizer for 15 minutes and just 15 minutes before the anesthesia induction as follows: 33 participants in the control group received 5 ml nebulizer of normal saline, 33 participants in the dexamethasone group received a nebulizer of 8 mg of

dexamethasone in volume of 5 ml and 33 participantsin ketamine group received a nebulizer of 50 mg of ketamine in volume of 5 ml.

Results: Ketamine and dexamethasone nebulizers were effective in preventing POST (p-value < 0.001) and hoarseness postoperatively with a maximum efficacy in the ketamine group. Ketamine nebulizer was effective in preventing cough and PONV, while dexamethasone wasn't. Also, patients in ketamine group were more satisfied in comparison to dexamethasone and saline groups (p-value < 0.001). There was a significant elevation in SBP and HR in ketamine group after nebulization but no serious systemic adverse effects were noted.

Conclusions: Nebulizing 50 mg of ketamine or 8 mg of dexamethasone is an effective way to prevent and to decrease the incidence of POST and other laryngeal morbidities with a maximum efficacy in the ketamine.

Keywords: Ketamine, Dexamethasone, Nebulizer, Sore Throat.

Chapter One

Introduction

Postoperative Sore Throat (POST) is a well-known minor subjective complication and cause of discomfort. It's clearly demonstrated that the occurrence of POST has an obvious impact on patient's satisfaction to the delivered anesthetic care. According to the American anesthesiologist, it is considered the 8th most unwanted outcome after general anesthesia (Macario et al., 1999). The incidence rate of POST is varying and overwhelming in many studies. In general, it ranges from 14.4% (Christensen et al., 1994) to 59.6% (Gemechu et al., 2017) with its peak incidence at 2-4th hours postoperatively (Monroe et al., 1990).

The incidence of other morbidities such as post-operative hoarseness, cough and dryness was 50.1%, 18.5% and 70.5% respectively (Christensen et al., 1994), while in another studies, it was 29% (Ahmed et al., 2007), and 19.7% (Chinachoti et al., 2017) for hoarseness of voice.

Higher cough rates are significantly associated with POST especially the cough at emergence. The cough rate was 66.4% for the group who suffered POST and 38.6% for the group who didn't suffer POST, and hoarseness at Post-Anesthesia Care Unit (PACU) was significantly associated with POST. The cough was defined as an abrupt, strong contraction in the abdomen, and hoarseness was defined as a harsh or disgraced voice assessed by patients (Lee et al., 2017).

Cough is a vital reflex to protect the airway. It is induced by a chemical or mechanical stimulus, which triggers the distributed sensory receptors all over the respiratory tract (Mazzone, 2005). Hoarseness is a result of vocal cords edema after endotracheal intubation, due to the mechanical contact, and scratch by the tube in the glottis zone (Liu et al., 2010).

It's obvious that POST is unavoidable undesirable outcome following general anesthesia with endotracheal intubation. A nonpharmacological intervention to decrease the incidence and severity of POST is the use of smaller sizes of endotracheal tubes (ETT). There was a significant reduction in the incidence of POST when smaller ETT were used (Chinachoti et al., 2017; Jaensson et al., 2012; Jaensson et al., 2010). And

also in a systemic review conducted by (El-Boghdadly et al., 2016), it was shown that the use of smaller size tubes, the use of video laryngoscopes and decreasing the endotracheal cuff pressure reduced the POST successfully, and the use of steroids intravenously (I.V), topically or inhaled, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) topically, the use of N-methyl-D-aspartate (NMDA) receptor antagonists topically or inhaled were examples of successful pharmacologic interventions to decrease the incidence and severity of POST.

The pharmacological interventions were investigated in many studies. The use of corticosteroids, then the ketamine and magnesium sulfate were the most effective drugs to be nebulized in order to prevent and reduce POST (Yu et al., 2020).

1.1 Background

1.1.1 POST pathophysiology

The cause behind POST was discussed many years ago in a study implemented on animals and human subjects, and revealed a morphological changes in the tracheal cilia as a result of injury and inadequate humidity due to the pressure produced by the endotracheal cuff on the tracheal wall at the area around the cuff even though at a very low pressures (18-25 mmHg) and in procedures less than 2 hours duration (Klainer et al., 1975). Also, in one of the latest studies, it was revealed that the cause is related to a direct tracheal mucosal trauma resulted from the increased tightness of the endotracheal tube cuff (Fenta et al., 2020).

1.1.2 POST risk factors

The associated risk factors with the incidence and severity of POST are many. One of the most common risk factors in these studies was the female gender. There was a higher rates of incidence in females than in males (Ahmed et al., 2007; Biro et al., 2005; Chinachoti et al., 2017; Christensen et al., 1994; Fenta et al., 2020; Gemechu et al., 2017), and the use of ETT was confirmed to be the highest risk factor of POST (Chinachoti et al., 2017).

The other risk factors include the use of large ETT size (Fenta et al., 2020), the air way performer who has less than 3 months of work experience is associated with higher rates (Jaensson et al., 2012), multiple intubation attempts (Fenta et al., 2020; Jaensson et al., 2012), the lower age groups are associated with higher rates (Biro et al., 2005; Chinachoti et al., 2017; Christensen et al., 1994), while it was the older age groups who have higher rates according to (Ahmed et al., 2007), also visible blood stains on the ETT after extubation, smoking and previous respiratory diseases were significantly associated with the incidence of POST (Biro et al., 2005), American Society of Anesthesiologists (ASA) physical status I to II (Chinachoti et al., 2017), the duration of anesthesia(Ahmed et al., 2007; Biro et al., 2005; Chinachoti et al., 2017), higher grade of intubation difficulty (Ahmed et al., 2007; Chinachoti et al., 2017), a heavier and taller patients and patients undergoing neck and thyroid surgeries (Piriyapatsom et al., 2013), obesity(Chinachoti et al., 2017), having an intra-cuff pressure of 17cm H_2O at emergence was significantly associated with POST (Lee et al., 2017) and the use of nasogastric tube (NGT) (Gemechu et al., 2017).

Some of these risk factors are still controversial. For example, there was no significant relationship between the duration and attempts of intubation with POST (Christensen et al., 1994). Neither airway technique, experience of airway performer, airway manipulation, intra-operative agents used, nor duration of operation was associated with the occurrence of 24-hour POST (Piriyapatsom et al., 2013), and neither the professionality nor experience of the airway performer with the incidence of POST (Biro et al., 2005; Piriyapatsom et al., 2013).

Also, the change of patients position from supine position to prone position even without moving or flexing his head and neck is proved to cause an increase in the ETT cuff pressure (Kim et al., 2015), and this change in the patient position causes a displacement in the ETT position (Minonishi et al., 2013). During emergence or even at light anesthesia, the laryngeal mucosa and the trachea may be irritated by movement of ETT, which leads to cough. Respiratory secretions can be removed by appropriate cough which decrease the aspiration risk. On the other hand, it initiates stimulation ofthe sympathetic nervous system (SNS), which causes hypertension (HTN), tachycardia, increase in the intraocular pressure, rising intracranial pressure, and possible bleeding from the surgical site (Irwin, 2006).

1.1.3 General anesthesia

General anesthesia is a loss of consciousness induced by drugs making the patients unarousable during that loss of consciousness, and even a painful stimulus won't arouse him. The ability to keep an independent ventilatory function impaired most of times, which usually makes it necessary to use assistance devices to maintain a patent airway, and because of spontaneous ventilation is depressed and the depression of neuromuscular function which induced by the drugs, a positive pressure ventilation may be required. Also the cardiovascular function may be impaired (American Society of Anesthesiologists, 2019, Octoper 23).

General anesthesia is also defined as a condition of reversible loss of consciousness that allows the patients to go through surgeries and surgical procedures safely and humanly, but even so, it's not without risks or complications. The associated morbidity of the general anesthesia (GA) ranges from minor complications like post anesthesia nausea and vomiting (PONV), POST and dental damage which causes a serious patient distress, but without long term morbidity to complications resulting in permanent disability like cardiovascular, respiratory, neurologic and renal complications (Harris & Chung, 2013).

1.1.4 Ketamine

Ketamine is an NMDA receptor antagonist with a multiple effect on the central nervous system. It acts by impeding the excitatory neurotransmitter activity in particular brain areas and the polysynaptic reflexes in the spinal cord. Also it dissociates the limbic cortex from the thalamus which is clinically known as dissociative anesthesia which causes the patient to look conscious, while he's unable to do any of the sensory input responses. It may cause hallucination as a systemic side effect, but it's very rare in clinical practice, where most patients receive at least a shot of midazolam and other related agents for amnesia and sedation. It could be given in many routes: I.V, intramuscularly (I.M), nasally, orally (P.O), rectally (P.R), subcutaneously (S.C), epidurally and topically, and it's possible to mix it with many drugs like propofol, midazolam or others, and when it is given I.M, a peak of plasma level is achieved within 10-15 min (Butterworth et al., 2013).

The brain quickly uptakes it and redistributes it subsequently. The distribution half-life is 10–15 min, and its biotransformation occurs in the liver and the anesthetic activity is retained by one of its several metabolite (norketamine). It is relatively short elimination half-life (2 h) is explained by the extensive hepatic uptake. The biotransformation end products are excreted renally, and causes some rise in the arterial blood pressure (ABP), heart rate (HR) and cardiac output particularly after I.V push injection because it stimulates the SNS centrally and inhibit the norepinephrine reuptake at nerve terminals. All of these stimulatory effects make it a good choice for patients in acute shock. It minimally affects the ventilatory drive especially when it mixed with opioids. Also the racemic ketamine is a good choice for induction in asthmatic patients because of its bronchodilator effect (Butterworth et al., 2013)**,** and also, as a NMDA receptor antagonist, it has an anti-inflammatory and anti-nociception effects when it is given topically (Carlton & Coggeshall, 1999)**.** Moreover, its level was measured in a study performed by (Chan et al., 2010) on elective gynecological surgery adult patients after giving it topically (gargling). The serum level was low which means that it has a potent topical effect and slight possible systemic effect, too.

1.1.5 Ketamine side effects (respiratory depression, hallucination and laryngospasm)

As for induction in the cesarean section, ketamine is one of the few drugs approved for that, but if the concentration exceeds 2 mg/kg or 1 mg/kg S(+)- ketamine, a respiratory depression in the newborns is anticipated. Ketamine doesn't prevent the spontaneous breathing, but respiratory depression is seen in high concentrations and the artificial ventilation become required. Its therapeutic range is wide, which means it's very difficult to get an overdose, and patients who received ten times the normal dose recovered normally and uneventfully. The observed median lethal dose (LD 50) in animals is about one hundred times the average human I.V dose and twenty times the average human I.M dose (Sinner & Graf, 2008).

Psychotomimetic reactions are possible side adverse effects. These include agitation, rhabdomyolysis, flashbacks, anxiety, chest pain, palpitations, delirium, dystonia, psychosis, dizziness, seizures, paranoia and schizophrenic-like symptoms. Other potential adverse effects of ketamine administration include muscle hypertonicity, transient clonus, hypersalivation, hyperreflexia, increased intraocular pressure, transient

rash, agitation and emesis. It is also, possible to see an effect of the sympathomimetic stimulation by ketamine like tachycardia (Sinner & Graf, 2008).

HTN, increase pulmonary pressures, arrhythmias and even pulmonary edema can be intensified when ketamine combined with halothane, catecholamine or thyroid hormones. Decreased awareness of the surrounding environment, vivid dreams, sedation, a dream-like state, increased distractibility, feelings of invulnerability and disorientation are common. Subjects are generally uncommunicative, intense hallucinations, out-of-body experiences, impaired thought processes, and changes in perception about body, time, sounds and surroundings have been reported. Similarly, delirium and hallucinations can be experienced after awakening from anesthesia (Sinner & Graf, 2008).

As for the ketamine, laryngospasm is frequently reported as an adverse effect. Children are the most susceptible, but it's very rare. A vocal cords stimulation by instrumentation or secretions is usually the cause behind it. The risk of laryngospasm that require intubation during ketamine anesthesia is 1 per 5,000 individuals (0.02%) based on pooled data, which means it's nearly 100 times lesser when compared to other anesthetic agents (Green & Krauss, 2004).

Ketamine is a suitable analgosedation drug for diagnostic and surgical procedures because of its mild deactivation of the consciousness and acceptable analgesic quality. In contrast to other anesthetics, respiratory activity is preserved in ketamine, and the blood pressure and heart rate are increased by sympathetic activation. The dissociative properties of ketamine prohibit its application as a sole analgosedative drug. By co-application of sedatives or hypnotics as benzodiazepines or propofol in subclinical concentrations, the psychotomimetic reactions can be blunted (Adams et al., 2001).

1.1.6 Laryngospasm

Laryngospasm is a condition in which vocal cords close partially or completely as a result of peri-glottic stimulus mediated via the vagus nerve. It is possible in the conscious state but usually occurs under GA. It is a problematic reflex but also a primeval reflex to protect the airway from aspiration, but it can also occur in light plans of anesthesia. It is possible to prevent it by paying attention to the anesthesia depth and the risk factors, raised respiratory efforts, inspiratory stridor which may develop to full

obstruction, tug of trachea, paradoxical respiratory effort, low oxygen saturation with or without bradycardia, or unresponsive to Guedel airway obstruction of the airway which are the common signs of laryngospasm, and when these signs occur, whether separately or collectively, laryngospasm is possible (Larson, 1998)**.**

So, the trigger must be removed as much possible as we can.The regurgitation or blood possibility in the airway must also be considered and if necessary, the plan of anesthesia must be altered. The traditional way of treating laryngospasm starts by clearing supraglottic airway obstruction and soiling, continuous positive airway pressure (CPAP) with 100% O_2, deepening of I.V anesthesia, and inducing paralysis by using succinylcholine by the I.V, I.M or intraosseous (I.O) routes as appropriate (Larson, 1998).

1.1.7 Dexamethasone

Dexamethasone is a synthetic glucocorticoid, and like other glucocorticoids it's known to have a metabolic, anti-inflammatory and immunosuppressive effect. Its anti-inflammatory effects represented in being able to decline the tissue production of transudate and decreasing cells edema in acute inflammations, prevent the circulating polymorphs and macrophages from reaching the inflamed tissue and inhibits the production of inflammatory mediators. Also it lowers macrophage function and lessen the number of circulating T-lymphocyte. The transport of lymphocyte and their ability to make the antibodies are also decreased, so the lymphocyte proliferation is reduced by the inhibition of interleukin 1 and 2. In addition to all of that, dexamethasone compared to other glucocorticoids has the greatest potency among them and has the least sodium retaining activity (Tom E. Peck & Sue Hill, 2008). Moreover, it is known to have an antiemetic effect, and its efficacy in preventing PONV can be seen when it is given before the anesthesia induction (Wang et al., 2000).

1.1.8 PONV

Nausea is a disagreeable sensation referred to a feeling that you want to vomit but it's not combined with expulsive movement of muscles. Vomiting is the powerful discharge of upper gastrointestinal contents, even of small amounts through the mouth (Islam & Jain, 2004). In general, there are multiple factors influencing PONV. Some of them are related to the patient, and some are related to the surgery and anesthesia. 5-hydroxytryptamine (5-HT) is released in a cascade of neuronal events involving both the gastrointestinal (GI) tract and the central nervous system (CNS). The 5-HT subtype 3 receptor ($5\text{-}HT_3$) participates selectively in the vomiting response. One of the general anesthesia factors that increase the risk of PONV is the use of ketamine for induction, while the use of propofol is known to decrease the risk of PONV. Dexamethasone and other corticosteroids are also effective agents to prevent PONV (Shaikh et al., 2016).

1.2 Problem statement

Many studies discussed the effect of ketamine or dexamethasone nebulization on the incidence and severity of POST as shown and described in the next chapter (literature review). However, none of them had compared the effect of these two drugs in the same clinical trial. Also, the studies about nebulized medications effect on POST have never been done before here in the West Bank. Even though POST is considered as a minor complication, an appropriate and safe prophylactic intervention is necessary to decrease the incidence and severity of POST and other associated morbidities and their consequences, to increase the patient satisfaction about the delivered anesthesia.

1.3 Aims of the study

The aim of this study was mainly to determine if preoperative nebulization of ketamine or dexamethasone has a significant influence on the incidence and severity of POST in patients undergoing elective surgeries under GA with ETT.

Secondly, it aims to determine if preoperative nebulization of ketamine or dexamethasone has a significant influence on the incidence of postoperative hoarseness and cough, the ease of endotracheal intubation, the hemodynamic response to laryngoscopy, and to see if there are any adverse effects in the various intervention groups.

1.4 Significant of the Study

By continuing and accumulating these studies, it may be possible to strengthen the results that prove the safety and efficacy of these drugs, resulting in the adoption of nebulizers that contain readymade, approved preparations of these drugs in the future. Also, the results of this study will be of great benefit to the health care system, at least in our local area. The results will help in the modification process of the preoperative interventions in order to reduce the incidence and severity of POST and other laryngeal morbidities, as well as increasing patient's satisfaction.

1.5 Null hypothesis

I hypotheses that:

- There's no significant difference at the 0.05 level in POST between groups of patients nebulized with saline, ketamine or dexamethasone.
- There's no significant difference at the 0.05 level in hoarseness between groups of patients nebulized with saline, ketamine or dexamethasone.
- There's no significant difference at the 0.05 level in cough between groups of patients nebulized with saline, ketamine or dexamethasone.
- There's no significant difference at the 0.05 level in the laryngoscopic view between groups of patients nebulized with saline, ketamine or dexamethasone.
- There's no significant difference at the 0.05 level in the hemodynamic response to the laryngoscopy and intubation between groups of patients nebulized with saline, ketamine or dexamethasone.
- There's no significant difference at the 0.05 level in the endotracheal intubation condition and easiness between groups of patients nebulized with saline, ketamine or dexamethasone.
- There's no significant difference at the 0.05 level in the side effects (nausea, vomiting, sedation, hallucination, stridor, laryngospasm, respiratory depression) between groups of patients nebulized with saline, ketamine or dexamethasone.
- There's no significant difference at the 0.05 level in anesthesia satisfaction between groups of patients nebulized with saline, ketamine or dexamethasone.

1.6 Literature Review

1.6.1 Introduction and research strategy

The searching strategy of literature review was as follow:

After accessing the PubMed at the Ncbi, Wiley online library, Science direct, American society of anesthesiologist website (asahq) and Google scholar data bases, the search was conducted by using these key words: (post-operative sore throat and its abbreviation (POST), hoarseness and cough, ketamine nebulizer, dexamethasone nebulizer, magnesium sulfate and general anesthesia).

The search was aiming to find articles about the effects of the nebulized drugs in preventing and reducing the severity of POST published in the period between the year 2000 and 2020.Several articles were demonstrated in every search in the above mentioned data bases. After choosing the option of demonstrating the most relevant articles to the key words in the advanced research, a screening of the articles topics was done. Then a screen of their abstracts was done. Then the inaccessible full text articles, the articles using other languages than the English and the articles about different prophylactic agents for reducing POST were excluded. The most relevant articles were chosen and their bibliographies were also checked to see if there are relevant good articles in the used references to be included if it was appropriate.

1.6.2 Literature review body

In a prospective randomized double blind placebo controlled clinical trial conducted by (Ahuja et al., 2015) to assess the efficacy of nebulized ketamine in reducing POST after extubation at 4^{th} hour, post-operatively, one hundred patients of ages between 20 and 60 years old were recruited for the study. The sample consisted of the patients undergoing surgeries in the supine position under GA up to 1 hour except the oral cavity, head and neck surgeries and other exclusion criteria. Patients were randomized in to two groups in the study: a group to receive saline nebulizer and a group to receive a ketamine nebulizers. Before the intervention, they did a pilot study on ten patients and it revealed that the ketamine nebulizer is tasteless. They found that the incidence of POST is significantly lower in the ketamine group, and the incidence was more than two times higher in the saline group in comparison to the ketamine group. Patient remained hemodynamically stable in both groups and there wasn’t any of the systemic ketamine

adverse effects post operatively. None of these adverse effects were noticed: nausea or vomiting or stridor or laryngospasm or cough or dry mouth or hoarseness or dissociative symptoms during the entire study period, it was concluded that the topical effect of preoperative ketamine nebulization is prophylactic to POST at least during the first few hours postoperatively.

In a randomized, double-blinded study conducted by (Rajan et al., 2017) to assess the efficacy of nebulizing ketamine and magnesium sulfate on reducing the incidence and severity of postoperative sore throat, sixty patients aged 18-80 years undergoing elective abdominal and lower limb surgeries under combined epidural and GA were enrolled into three groups: group of saline nebulizer, group of ketamine nebulizer and group of magnesium sulfate nebulizer. It was found that there's a significant decrease in POST and voice hoarseness by nebulizing 50 mg of ketamine or 500 mg of magnesium sulfate for 15 min preoperatively in comparison with the control group with a maximum efficacy on ketamine group, but the decrease in the incidence of cough for those in the intervention groups wasn't significant.

Similar results were found in another prospective, double-blind, randomized, placebo-controlled study conducted by (Thomas et al., 2018) mainly to assess the efficacy of ketamine nebulization in relieving POST in adult patients undergoing elective surgical procedures in supine position under GA up to two hours and to evaluate the incidence and severity of POST in those patients. Ninety-six patients aging 18-60 years were enrolled into two groups:ketamine group and saline group. The overall incidence of POST was 25%.It was 14.6% for the ketamine group, and 35.4% for the placebo group (saline nebulization group). It was clear that the incidence of POST was considerably less in ketamine group than in placebo group all the times postoperatively which considered statistically significant. A severe sore throat (Grade 3) wasn't seen in any patient in both groups, also none of these adverse effects (nausea, vomiting, cough, stridor, laryngospasm, dry mouth, hoarseness, hallucinations, respiratory depression, or hemodynamic instability) was noticed during the observation at any point during the study.

(Jain et al., 2017) conducted a prospective, double blind randomized clinical study to find if there is a significant difference between nebulized ketamine and nebulized mixture of ketamine with clonidine effect in alleviating POST. One hundred patients aging 20-65 years of either sex and undergoing surgeries in supine position under GA lasting up to two hours enrolled in the study were divided into two groups: group of ketamine nebulized with 1cc (50mg) of ketamine with 3cc of normal saline and group of ketamine with clonidine nebulized with 1cc (50mg) of ketamine plus 1cc (150mg) of clonidine with 2cc of normal saline. They found that the incidence of POST and its severity in ketamine clonidine mixture group was significantly lower than in ketamine group and it was concluded that nebulizing the clonidine and ketamine mixture preoperatively had a higher efficacy than nebulizing the ketamine alone in alleviating POST. Also none of the participants in both groups developed nausea, vomiting, laryngospasm or any side effects and all of them stayed hemodynamically stable.

Similar results were found by (Shekhar et al., 2019) in a randomized clinical trial aimed to evaluate the efficacy of nebulizing ketamine alone vs nebulizing a mixture of ketamine and clonidine. One hundred patients of either sex and aging 20-60 years were enrolled in two groups. The first group received a nebulizer of 50 mg ketamine in 1 ml with 3 ml of normal saline for 15 minutes and the second group received a nebulizer of 50 mg of ketamine in 1 ml with 50 mg of clonidine in 1 ml with 2 ml of normal saline for 15 minutes. The incidence of POST was significantly lower in the ketamine and clonidine group at the 4, 8, 12, and 24 hours postoperatively than in the only ketamine group, and it was more effective in alleviating POST. There was no evidence of any adverse effects after the nebulization at any time during the study like nausea, vomiting, sedation or laryngospasm, coughing or bucking after the extubation.

In another study conducted by (Mostafa et al., 2018) in Egypt to evaluate the efficacy of three nebulized drugs in pediatric patients with ages ranged from 6 to 16 years old and undergoing operations in the supine position under GA and lasting more than one hour, one hundred and eight patients (54 unilateral inguinal hernia case, 18 bilateral inguinal hernia case, 10 fracture upper limb case, 8 skin graft case, 11 hydrocele case, 7 undescended testis case) were enrolled into three equal groups. The first group received 1mg/kg of ketamine, the second group received 40mg/kg of magnesium sulfate and the third group received a fixed dose of 0.16 mg dexamethasone. It was concluded that

nebulizing with ketamine is the best in reducing POST in pediatric patients, particularly in the 4th hour. Also patients satisfaction was approximately the same in the three groups. There was more prominent sedation and some cases of vomiting in the magnesium and ketamine group, while there wasn't any effect of sedation in the dexamethasone group, and the incidence of cough was also lower in the dexamethasone group.

The same thing about the ketamine efficacy in comparison with the magnesium sulfate was founded in another prospective randomized double blind study conducted by (Segaran et al., 2018) to evaluate the efficacy of ketamine and magnesium sulfate nebulizer in decreasing the incidence of POST. The sample was of eighty patients aging 18-65 years undergoing elective surgeries under GA with endotracheal intubation who met the inclusion criteria and do not have any exclusion criteria like the surgeries involving the oral cavity, nasopharynx, larynx and neck regions, surgeries requiring prone position and surgeries lasting more than 3 hours …etc. Patients were enrolled into two groups. The first group received a nebulizer of 250 mg of magnesium sulfate in 5 ml of normal saline and the second group received a nebulizer of 50 mg of ketamine in 5 ml normal saline. The overall incidence of POST in the first group was 50% and 25% in the second group. None of the patients in both groups complained of immediate POST at 0 hour. Patients who complained of POST in the ketamine group was half the number of patients in the magnesium sulfate group at the 4th and 6th hour. It was concluded that the preoperative nebulizing of 50 mg of ketamine is more effective in decreasing POST than nebulizing 250 mg of magnesium sulfate.

The efficacy of magnesium sulfate and ketamine nebulizers were almost the same in other double blind randomized controlled trial conducted by (Orji et al., 2020) to evaluate the prophylactic efficacy of preoperative nebulization of magnesium sulfate or ketamine on the severity and incidence of POST. Ninety-nine patients of ages between 16-65 years undergoing elective surgical procedures in supine position under GA except head and neck surgeries were enrolled into three equal groups: a group received saline nebulizer, a group received 50 mg ketamine nebulizer and a group received 250 mg of magnesium sulfate for ten minutes prior to the induction. They found that the incidence was highest at the 4th hour at all groups, especially in the placebo group, and it was the lowest in the magnesium group, but insignificant when compared with the ketamine at

all observation times. Also there was no difference on the incidence at the 4th hour between female and male genders at all groups.

In another prospective double blind randomized comparative trial conducted by (Thomas et al., 2020) to assess the efficacy of nebulizing dexmedetomidine and nebulizing ketamine preoperatively in reducing POST after undergoing thyroidectomy under GA, one hundred patients of ages between 18-60 years were enrolled into two groups, but two of them were excluded from the study because one of them in the ketamine group developed post-extubation laryngospasm and the other patient in the dexmedetomidine group had stridor in the post-operative period. Both of them were excluded from the study, while the rest of the 98 patients completedthe study. The first group received 50mg ketamine nebulizer and the second received 50mcg dexmedetomidine nebulizer. They found that the incidence was lower in both dexmedetomidine and ketamine groups with insignificant difference between them in comparison with the control group. Severity of POST was also lesser at all points during the study. Sever POST wasn't developed in any patient in both groups, and there was no adverse effects such as nausea, cough , hoarseness, or hallucination or respiratory depression at all observation points during the study, except for HR,and a rise in systolic blood pressure(SBP) and diastolic blood pressure (DBP) in the ketamine group.

(Kuriyama et al., 2020) conducted a systematic review and meta-analysis of randomized controlled trials about the effect of topical application of ketamine and safety when it is given preoperatively to reduce POST. The results showed that the application of ketamine topically is a responsible factor in reducing the incidence of moderate and severe POST when it is compared to none-analgesic methods. It was also associated with a reduction in the post-operative cough and hoarseness. In about half of the studies, there were no adverse effects related to ketamine, and in other studies it was unclear or undocumented.

Dexamethasone is one of the most usually used drugs in clinical practice and it's possible to use it in a nebulization form. Its efficacy in the nebulization form was studied many times in tens of scientific articles. One of them is a double blind placebo controlled study conducted by (Luria et al., 2001) to assess the efficacy of dexamethasone nebulization treatment versus orally treatment in children with mild to severe croup in reducing their need for an extra treatment and decreasing the symptom

duration. They found that the number of children who returned to receive a second medical treatment for their symptoms in the seven later days was higher in the nebulization and placebo group than in the orally treated group. Also a score for croup symptoms in the orally treated group was better than in the nebulization and placebo group.

In a randomized clinical trial conducted by (Salama & El-badawy, 2016) in Egypt to assess the efficacy of dexamethasone nebulization in relieving POST incidence and severity, 120 patients of either sex aging between 25-60 years were recruited for the study. The sample was of patients undergoing surgical procedures in the supine position under GA with endotracheal intubation except those who are within the exclusion criteria like undergoing head and neck surgeries. Patients were enrolled into two equal groups: a group received a nebulizer of 8 mg dexamethasone in 5 ml for 15 minutes and a group received a nebulizer of normal saline in 5 ml for 15 minutes. The results of the study revealed that the incidence and severity of POST was lesser in the dexamethasone group in comparison with the placebo group significantly at the 0, 2, 4, 8, and 12 hours after the extubation, but no significant difference was found after 24 hour. All patients remained stable hemodynamically without any adverse effects at any point in the study duration.

(Almustafa et al., 2019) conduct a randomized clinical trial to assess the efficacy of preoperative nebulized dexamethasone in reducing postoperative bouige complication which include the POST, odynophagia, voice changes , nausea and vomiting. They found that the incidence of POST is significantly lower in the dexamethasone at all times postoperatively. The change of voice was also significantly higher in the placebo group in comparison with the dexamethasone group, but no significant difference was found between the two groups in the odynophagia and PONV.

In a prospective, double-blind comparative study conducted by (Sounak Paul et al., 2019) to evaluate the efficacy of preoperative prophylactic dexamethasone nebulizer vs budesonide nebulizer in preventing POST, one hundred and twenty patient undergoing elective lumbar spine surgery in prone position under GA enrolled into two groups: Group B received 500 mcg budesonide nebulizer, and Group D received 8 mg dexamethasone nebulizer in 2 ml with 2 ml of normal saline.POST, cough and hoarseness were assessed at 5 minutes, 30 minutes, 1 hour and 24 hours after the

operation. At all the observation times, the incidence of sore throat was higher in the budesonide group in comparison with the dexamethasone group and it was statistically significant except at the 30 minutes postoperatively. The same was for the hoarseness and cough. The incidence was higher in the budesonide group at all times and it was statistically significant except at the first 30 minutes for the hoarseness and at the 24 hours for the cough. It wasn't significant at these times. It was concluded that a single prophylactic nebulizer of dexamethasone preoperatively is better than budesonide nebulizer in reducing and preventing POST.

In a prospective double blind randomized study conducted by (Ashwini et al., 2018) to assess the efficacy of dexamethasone nebulizer vs magnesium sulfate nebulizer in reducing the incidence and severity of POST, hoarseness and cough, 90 patient of ages between 20-50 years undergoing elective surgeries under GA with endotracheal intubation and lasting less than 3 hours were enrolled into two groups. The first group received dexamethasone 8 mg with 3 ml of normal saline nebulizer and the second group received magnesium sulfate [50% W/V 2ml] with 3ml normal saline nebulizer preoperatively. The incidence of POST was 27.5% in the dexamethasone group and 57.5% in the magnesium sulfate group. The number of patients who complained of POST was significantly lower in the dexamethasone group at the 0 hour, 4^{th} hour, 8^{th} hour and 12^{th} hour, but at the 24^{th} hour only one of each group complained POST which is not considered significant statistically. The incidence of odynophagia was more in the magnesium group at all times in comparison to dexamethasone group. The highest incidence of POST was in the 4^{th} hour.Also none of dexamethasone group had hoarseness at the 0 hour, 4^{th} hour and 8^{th} hour of assessment or had cough at any point, while one patient complained of cough in the magnesium group at the 4^{th} and 8^{th} hour which is not clinically significant. It was concluded that the prophylactic nebulization of dexamethasone preoperatively is more effective in reducing the incidence and severity of POST following endotracheal intubation than the magnesium sulfate nebulization.

Chapter Two

Methodology

2.1 Research design

Design: A true experimental design was used because it's one of the most accurate types of experimental research. The true experiment design criteria consists of three points (an experimental and control group, manipulation of variables and randomization), and all these points were possible in this research.

So, it was a double-blind, randomized, placebo-controlled prospective study.

2.2 Study Population

Our population was of adult patients aging between 18 to 60 years old of either sex, with ASA physical status I-II, arranged for elective limbs and lower abdominal surgeries under GA in Rafedia governmental hospital.

2.3 Setting

The research was conducted in one of the largest north West Bank surgical hospitals, Rafedia governmental hospital in Nablus city- West Bank- occupied Palestinian territories.

2.4 Sample size

Based on (Mostafa et al., 2018) study, it was shown that the number of patients with score two POST was 15 (41.67%) in ketamine group and 24 (66.67%) in dexamethasone group.

In order to determine the sample size, we used a calculator shown in Figure D.1 in appendix D (Select Statistical Services, 2021) to detect the difference between the two proportions. And with the assumption of these variables: A confidence interval of 95% and a power of 80% were chosen. We need approximately 60 patients, 30 patients in each group. As we have 3 groups, so it was 90 patients, plus 10% of the sample to cover the drop outs. So, it was 99 patients, 33 patients in each group.

2.5 Randomization

99 patients corresponding to our inclusion criteria were randomly enrolled into three equal groups with a 33 participant in every one by using the opaque and well-sealed envelopes. Random Allocation software 1.0 was used to generate the sequence on a computer.

Group (C) (n = 33), [a nebulizer of normal saline 5 ml for the control group].

Group (K) (n = 33), [a nebulizer of ketamine 50 mg/1 ml plus 4 ml of normal saline for the ketamine group].

Group (D) (n = 33), [a nebulizer of dexamethasone 8 mg/2 ml plus 3 ml of normal saline for the dexamethasone group].

The numbers were printed on wrappers, and the group type was printed on a card along with the sequential number, and when the patients arrived, they were given wrappers to find out which group they would be allocated to, as shown in Figure D.2 in appendix D.

Three groups as follows:

1-33 : Saline group

34-66 : Ketamine group

67-99 : Dexamethasone group

2.6 Blindness

Patients, researchers, anesthesiologists and the other health caregivers in the operation rooms weren't aware in which group the patients are nor the intervention type they received.

2.7 Drug preparation

The drug was prepared by a separate nurse who wasn't involved in data collection and the care for the patients in the operation rooms or in the postoperative period. The drugs were preserved in an identical syringes of 5 ml volume.

2.8 Study period

The preparation of the proposal of this thesis started in April 2021 and was approved by An-Najah National University on 6/October/2021. The institutional review board (IRB) was received on 17/November/2021 and the MOH's approval to conduct the research was received on 6/December/2021 and the data collection period lasted from 8/December/2021 to 24/February/2022.

2.9 Inclusion and exclusion criteria

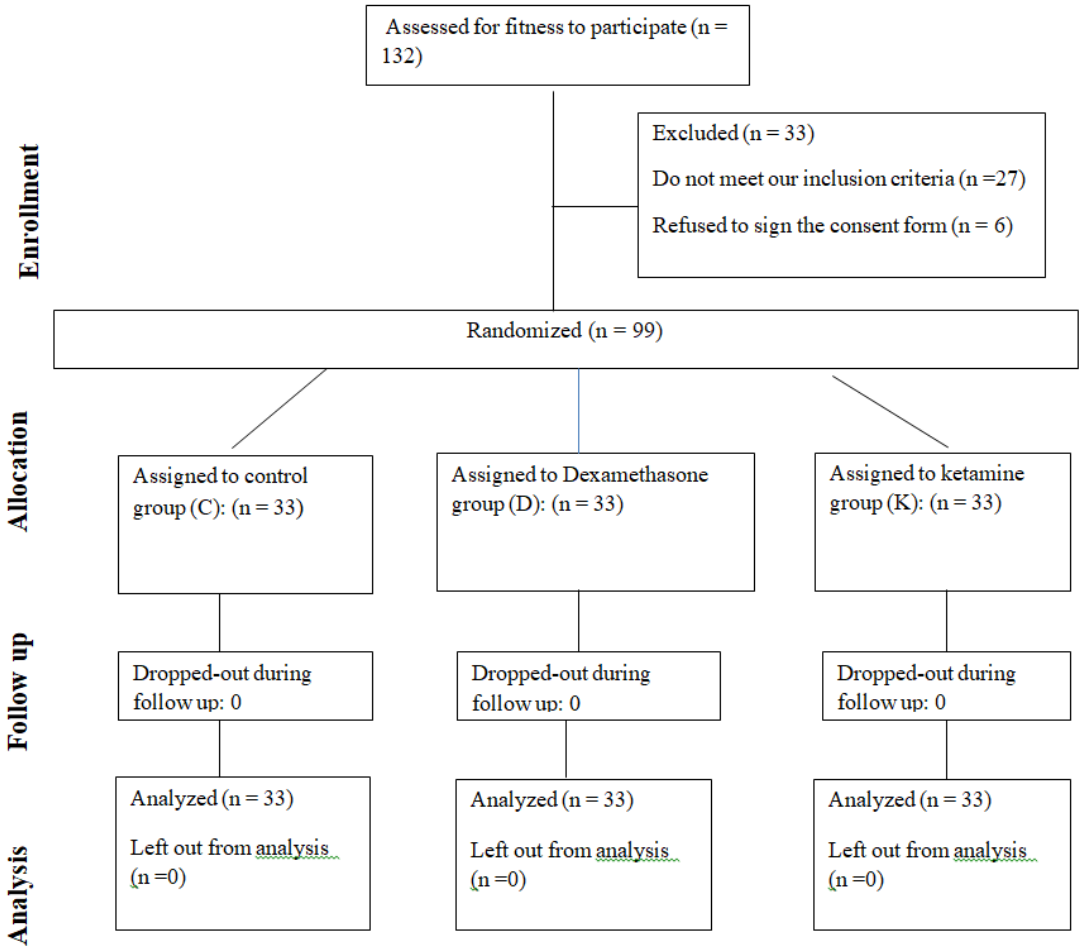
The inclusion criteria for the study was as follow:

1. 18 to 60 years old patients.
2. Elective surgeries under GA, in supine position andremained up to two hours.
3. ASA Physical Status I or II.
4. Both genders.

The exclusion criteria was as follow:

1. Patients who have sore throat before the operation.
2. History of infections in the upper respiratory tract(RTI).
3. Chronic obstructive pulmonary disease (COPD).
4. HTN patients.
5. Patients who have allergy to the used drug in the study.
6. Pregnant women.
7. A mallampati Grade more than 2.
8. Patients allocated for oral, ENT, head-and-neck surgeries.
9. Patients intubated by more the one intubation attempt.
10. Patientswho do not want to sign the consent form.
11. Patients using steroids or NSAIDS.

CONSORT FLOW DIAGRAM



2.10 Study variables:

- Dependent variables: POST, cough, hoarseness, PONV, laryngoscopic view, hemodynamic status and endotracheal intubation condition.

- Independent variables: Normal saline, ketamine and dexamethasone.

2.11 The intervention protocol

After we got the agreement of IRB from An-Najah National University and the permission from the Palestinian Ministry of Health to conduct our study in Rafedia governmental hospital, every participant was given a written consent form to sign it on after explaining the objectives of the study.

The intervention protocol was as follows:

- Every participant in the study was examined separately in the pre-op visit by anesthesia resident doctor who is not involved in the intra-operative or PACU care for those participants. The admission file number, age, height, weight, sex, brief history medically and surgically, ASA physical status as shown in appendix E (American Society of Anesthesiologists, 2020, december 13), smoking history was recorded for all participants, Noninvasive Blood pressure (NIBP), HR, respiratory rate (RR), ECG rhythm, and SpO_2 were recorded for all participants before and during nebulization, all participant patients were kept fasting for 8 hours preoperatively.

- Before entering the operation theaters, every participant patient was evaluated for the NIBP, HR, RR and SpO_2. I.V access (green cannula gauge 18) was applied for the patients and a drip of normal saline 500 cc was infused for every participant 30 minute before the induction.

- Then a staff nurse who is not involved in the intraoperative and postoperative period care administered a nebulizer lasting 15 minutes via a wall-mounted O_2 source at 8 L/min of normal saline 5 ml for the control group (C group), ketamine in 50 mg /1 ml plus 4 ml of normal saline for the ketamine group (K group) and dexamethasone 8 mg /2 ml plus 3 ml of normal saline for the (D group), just 15 minutes before the anesthesia induction.

2.12 Anesthesia and analgesia protocol

The used anesthesia methods and analgesics for GA were standardized for all participants and performed in cooperation with a professional anesthesiologists.

On arrival to the operating room, just 15 minutes after completing nebulization, patients were monitored by electrocardiogram, NIBP,mean arterial pressure (MAP), HR, SpO2 and capnography before anesthesia induction, after the induction, every 5 minutes during the surgical procedure and when the patient arrivedto the PACU. A does of 2 mcg/kg of I.V fentanyl was used to induce GA,2-3 mg of I.V midazolam and 2 mg/kg of I.V propofol. A 0.5 mg/kg of I.V atracurium were administered over 60 seconds to decrease every possible trauma, then a gentle endotracheal intubation lasting less than

15 seconds was done by a qualified anesthesiologist. Macintosh laryngoscope blades size 3 or 4 were used after approximately 3-5 minutes of mask ventilation 6 L/min 100% O2 and losing all the ulnar nerve four twitches by train-of-four stimulation. Atracurium 0.08-0.1 mg/kg dose was repeated every 20-45 minutes after the first dose to keep neuromuscular block. A sterile single-lumen cuffed polyvinyl chloride ETTs sizes 7–7.5 mm for women and 8–8.5 mm for men were used for intubation. ETT cuffs were inflated with a 2-4 ml of air until no air leakage was noticeable, pressure was assessed at the intubation, every 15 minutes and at the emergence phase and kept between 20-25 cm H_2O by using the available pressure manometer.

GA was maintained by using isoflurane 1-2.5% and 50% oxygen in air. Paracetamol 1 g IV was used for additional analgesia intraoperatively and Q 6 hours postoperatively. When the surgery finished, the isoflurane was terminated and 100% disposed, gentle suction to the oropharyngeal space was done, and 50 mcg/kg of I.V neostigmine and 0.4-0.6 mg of atropine were used to reverse the neuromuscular blockade. The mechanical ventilation continued until spontaneous respiration or swallowing started, then was transformed to assisted manual ventilation. When all these criteria (spontaneous breathing, able to follow spoken instructions, eyes opening or hand grasp, and able to specify appropriate movements) were met, the ETT was removed and the participant regained complete consciousness under the anesthesiologist responsibility. Then, the patient received a 6 L oxygen via simple face mask and transferred to PACU. And when he became stable,he was transferred to the surgical wards with the company of nurses.

2.13 Data collection

The data sheet information in the preoperative phase was filled in the PACU with the help of another staff nurse. In the operative phase, it was filled with anesthesia technician’s help and in the ward phase with the help of nurses on-duty.

Routine monitoring in the operation room include (BP, HR, RR, SpO2, EtCO2 and ECG rhythm) were documented every 5 minutes during operation and every 3 minutes in emergence phase, plus the tidal volume and cough.

BP, HR, RR and Spo2 were documented in the PACU one to two times as possible. POST and other complaints (cough, hoarseness and PONV) were assessed by an independent nursein the PACU who doesn't know which group the participants were in, and in the wards at 0, 2, 4, 6, 8, 12, and 24 h postoperatively by the nurses on-duty.

Laryngoscopy view and endotracheal intubation condition was assessed by the airway performer before intubation and laryngospasm occurrences were observed before induction, after extubation and in the PACU.

Hallucination and any other psychotomimetic effects were observed and noted if they happened or not after nebulization, during the emergence phase, after extubation and in the PACU.

Sedation was assessed after 1 hour after extubation, and patient satisfaction about the anesthetic care was assessed in the ward after full recovery by the nurses on-duty.

Every drug given during the operation, in PACU and in post-operative period was documented, the intra-cuff pressure, the duration of anesthesia and operation was also documented.

2.14 Assessment tools

POST was measured by a scale of four points (0–3), used by (Canbay et al., 2008).

0 means no POST.

1. 1 means a mild sore throat (grumbles of POST only on asking).

2. 2 means moderate sore throat (grumbles of POST on his/her own).

3. 3 means severe sore throat (hoarseness or voice changes, with pain in throat).

Cough and hoarseness were measured by using a similar assessment scale of four points (0 – 3).

Cough:

0 meansno cough at any time postoperatively.

1 means mild cough or scratches in the throat.

2 means moderate cough.

3 means severe cough.

Hoarseness:

0 means no grumble of hoarseness postoperatively at any time.

1 means minimal quality of voice change. Patient confirms only when asked about it.

2 means moderate quality of voice change. Patient nags on his own.

3 means sever quality of voice change. Observed by the staffs.

The laryngoscopic view was evaluated by using the Modified Cormack-Lehane grade (Yentis & Lee, 1998). It's shown in figure D.3 in appendix D

1 means full glottis view.

2a means partial glottis view.

2b means only posterior extremity of glottis seen or only arytenoid cartilages.

3 means only epiglottis seen, none of glottis seen.

4 means neither glottis nor epiglottis seen.

The endotracheal intubation condition was assessed by using the 1994 Copenhagen Consensus Conference recommended score (Viby-Mogensen et al., 1996) which depend on using six variables:

1-jaw relaxation, 2- the resistance apparent to the laryngoscope blade (laryngoscopevariable), 3- location of the vocal cords, 4- the remaining movement of the vocal cords (vocal cord variable), 5-coughingreflex to intubation and 6- limb movement responding to intubation (reflection to intubation variable).

These factors were rated as excellent, good or poor, each one separately. Intubating conditions were excellent if all factors were excellent. They were good if all factors were good or excellent and they were poor if any factor was poor. It is shown in figure D.4 in appendix D.

The Ramsay sedation score was used to assess the sedation 1 hour after extubation (Ramsay et al., 1974).

1 means awake; agitated or restless or both.

2 means awake; complaisant, oriented, and calm.

3 means awake but replies only to commands.

4 means asleep; brisk reaction to light glabellar hit or powerful auditory stimulus.

5 means asleep; sluggish reaction to light glabellar hit or powerful auditory stimulus.

6 means asleep; no reaction to glabellar hit or powerful auditory stimulus.

Patient satisfaction to the anesthetic care at the postoperative 24 hours was recorded by numeric rating scale (NRS) from 0 to 10.

0 as no satisfaction.

10 as the greatest satisfaction.

Nausea was measured by Morrow Assessment of Nausea and Emesis (MANE) six point scale (0-6) where 0 means no nausea, 1 means very slight, 2 means mild, 3 means moderate, 4 means severe, 5 means very severe and Grade 6 means intolerable.

Rescue antiemetic was metoclopramide (Pramine) 10 mg I.V, when Likert scale is ≥3 on (0-6 scale) or/and frequency of vomiting two times and above (Morrow, 1984) and vomiting was measured by frequency.

2.15 Data analysis plan

IBM SPSS Statistics Version 26 was used to analyze the data. The specific analysis methods were as follows:

1. Personal and demographic variables were described by using the Percentages and Frequencies.

2. The differences between the three study groups among the Qualitative or Categorical variableswere tested by using chi Square test and there chi square tests used for Pairwise Post Hoc tests.

3. One Way ANOVA test with means and Standard Deviations were used to analyze the differences between the three study groups among the Scale or Quantitative variable, with LCD Post Hoc Pairwise test.

2.16 Ethical concerns

This study was conducted in conformance with the Helsinki Declaration and wasn't started before taking the IRB from An-Najah National University and the approval of the Palestinian MOH. The study didn't cause any emotional or physical harm for any one of the participants and their rights (self-determination, autonomy and confidentiality, privacy, fair treatment and protection from discomfort and hurt) were protected.

A consent form with a discussed details was given to the participants and every participant had the right to drop-out from the study whenever he wants to and without mentioning the reason.

2.17 Budget

This research was a self-financed study.

Chapter Three

Results

1. Patients demographic data

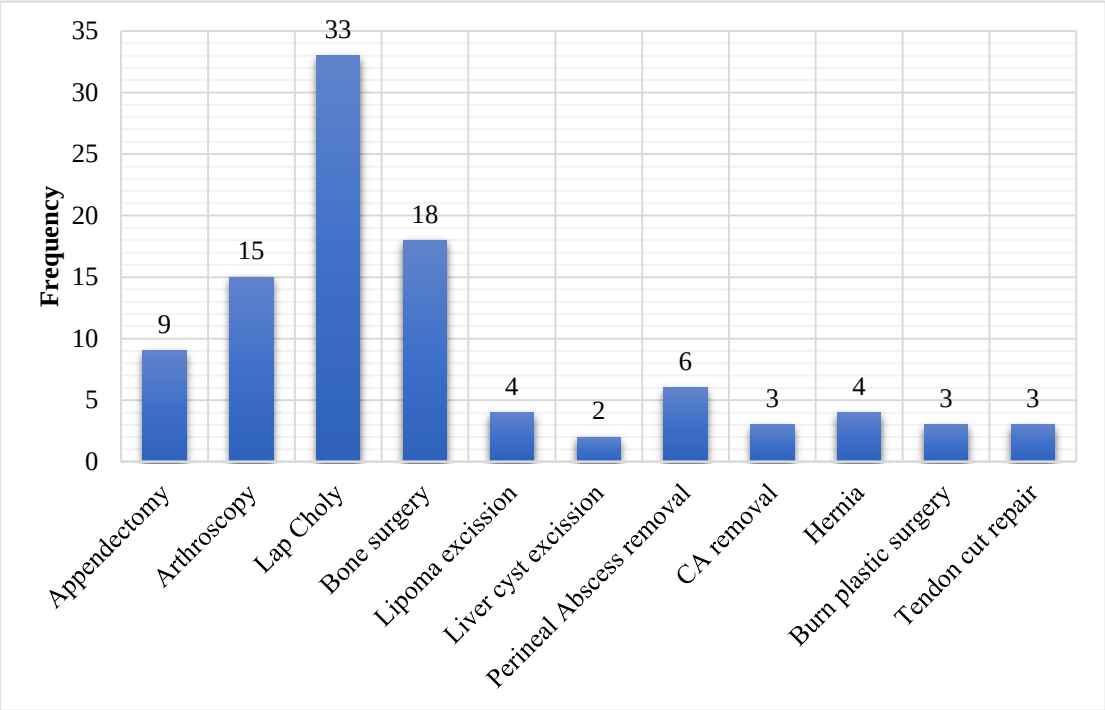
(Tables from C.1 to C.37 are listed in appendix C).

The distribution of the frequencies and percentages of the demographic data and history information regarding patients included in the sample is shown in table C.1 in appendix C. The patients in the sample were allocated equally into three groups: saline, dexamethasone and ketamine, with 33 patients in each group, resulting in a total of 99 patients included in the study. The mean age of the patients was 38.06 years old (SD = 12.87 years), ranging from 18 to 60 years old, with mostly are older than 45 years old (34.3%). The allocation of patients was similar between male (51.5%) and female (48.5%) genders, with approximately half of the patients having normal weight (45.5%). Also, 6.1% of patients had a past medical history, mainly diabetes mellitus, while 36.4% had a past surgical history, including tonsillectomy, obstetric operations, and 3% reported using in-home medications. About one fourth of the patients (27.3%) are smokers, with around 1 packet of cigarettes daily, and among them, 18.2% stopped smoking before the surgery. Finally, only 6.1% of the patients had a type of drug allergy, with absent food or other allergies among all of the patients included in the study.

The following figure 3.1 illustrates the distribution of surgery types that were performed for the study patients.

Figure 3.1

Distribution of surgery types



2. Before entering the operation room phase

Descriptive statistics of the preoperative data among patients

Table C.2 in appendix C shows the distribution of patients' preoperative information and shows that all of the patients had a normal sinus rhythm (NSR) preoperatively, while more than half of them (51.5%) had been anesthetized before. Regarding scores, majority of the patients were in the first ASA classification, while more than two thirds of them (69.7%) had a Mallampati score of ' I '.

Pre-and post-nebulizer hemodynamics

Table C.3 in appendix C shows the hemodynamic readings before and after giving the nebulizers to the patients preoperatively and it shows that there was a significant increase in SBP, DBP, HR and SpO_2 between the pre and post-nebulizer stages (p-value < 0.05), while there was no significant difference in respiratory rate. Figures 3.2 to 3.4 shows the differences in the hemodynamic mean readings between pre- and post-nebulizers phases preoperatively among the three study groups.

Table C.4 in appendix C shows the comparison between pre-nebulizer and post-nebulizer hemodynamics, and concludes that there was a significant increase in all of hemodynamics after giving the nebulizers compared to hemodynamics before nebulizers (p-value < 0.05), except for the respiratory rate (p-value = 0.058), while tables from C.5 to C.13 in appendix C shows the differences in the post-nebulizer hemodynamics between the study groups, according to one-way ANOVA test and post hoc.

Results revealed that there was a significantly higher mean of post-nebulizer SBP among ketamine group (mean = 127.182 mmHg) than both dexamethasone (mean = 120.727 mmHg) and saline (mean = 115.364 mmHg) groups (p-value < 0.001) as table C.5 shows in appendix C, while table C.6 in appendix C shows, using Post Hoc test, that the mean difference between some groups individually is also significant, where the ketamine group has a mean difference of 11.818 mmHg more than saline group (p-value < 0.001), and a mean difference of 6.455 mmHg more than dexamethasone group (p-value = 0.008), while dexamethasone group has a mean difference of 5.364 mmHg higher than saline group (p-value = 0.026), which means that the ketamine nebulizer is more effective in elevating the SBP than both dexamethasone and saline and the saline nebulizer is less effective.

There was no significant difference in the mean of post-nebulizer DBP among saline group (mean = 71.909 mmHg) which is lower than both dexamethasone (mean = 74.545 mmHg) and ketamine (mean = 77.00 mmHg) groups (p-value = 0.060) as table C.7 shows in appendix C, and therefore Post Hoc test is not required.

Table C.8 in appendix C shows that there was a significantly higher mean of post-nebulizer HR among ketamine group (mean = 81.636 bpm) than both dexamethasone (mean = 79.091 bpm) and saline (mean = 74.182 bpm) groups (p-value = 0.020), while table C.9 in the appendix C shows, using Post Hoc test, that the mean difference between some groups individually is also significant, where the ketamine group has a mean difference of 7.455 higher than saline group (p-value = 0.006), with no significant difference between dexamethasone and both of saline and ketamine groups (p-value > 0.05), which means that the ketamine nebulizer is significantly more effective in elevating the HR in comparison with saline nebulizer but not with the dexamethasone

nebulizer, and the dexamethasone has insignificant effect in elevating the HR in comparison with both ketamine and saline nebulizers.

Table C.10 in appendix C shows that there was a significantly higher mean post-nebulizer RR among ketamine group (mean = 15.182 breath/min) than both dexamethasone (mean = 15.091 breath/min) and saline (mean = 14.364 breath/min) groups (p-value = 0.001), while table C.11 in appendix C shows, using Post Hoc test, that the mean difference between some groups individually is also significant, where the ketamine group has a mean difference of 0.818 breath/min more than saline group (p-value < 0.001), while dexamethasone group has a mean difference of 0.727 breath/min more than saline group (p-value = 0.002), with no significant difference between dexamethasone and ketamine groups (p-value = 0.689),which means that the saline nebulizer is less effective than both of ketamine and dexamethasone nebulizers in elevating the RR with no significant difference between ketamine and dexamethasone in elevating the RR.

Table C.12 in appendix C shows that there was a significantly higher mean post-nebulizer SpO2 among ketamine group (mean = 99.364%) than both dexamethasone (mean = 98.909%) and saline (mean = 97.363%) groups (p-value < 0.001), while Table C.13 in the appendix C shows, using Post Hoc test, that the mean difference between some groups individually is also significant, where the ketamine group has a mean difference of 1.727% more than saline group (p-value < 0.001), while dexamethasone group has a mean difference of 01.273% more than saline group (p-value < 0.001), with no significant difference between dexamethasone and ketamine groups (p-value = 0.093), which means that the saline nebulizer is less effective than both ketamine and dexamethasone nebulizer in rising the SpO2 with no significant difference between the ketamine and dexamethasone in rising the SpO2.

Figure 3.2

Difference in pre-nebulizer and post-nebulizer mean SBP between study groups

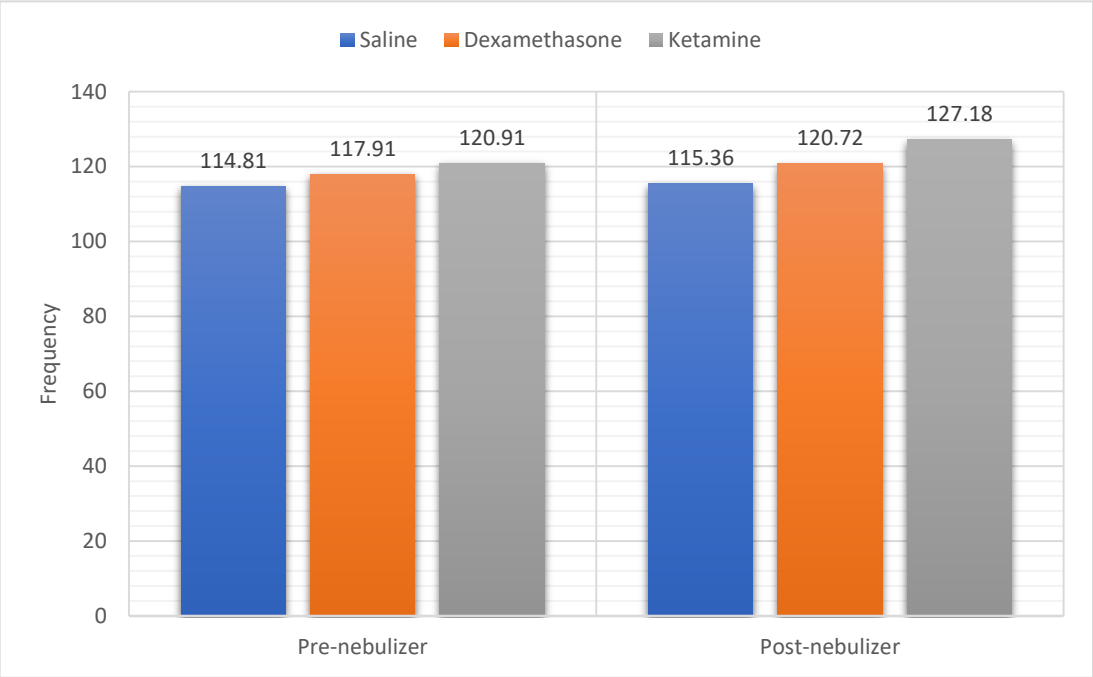


Figure 3.3

Difference in pre-nebulizer and post-nebulizer mean DBP between study groups

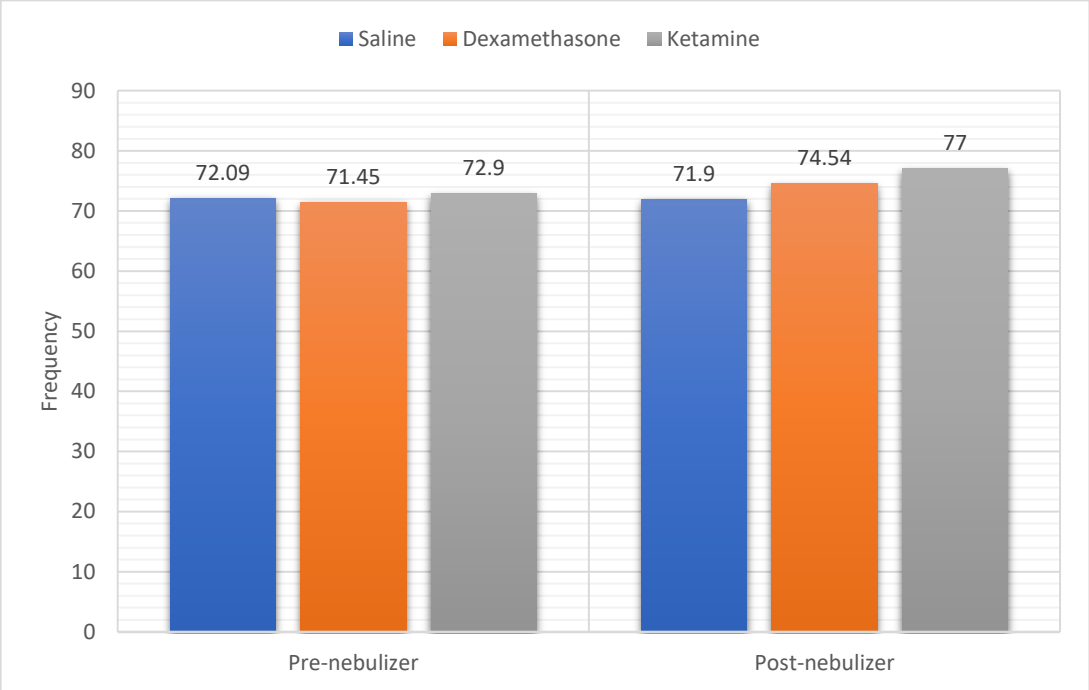
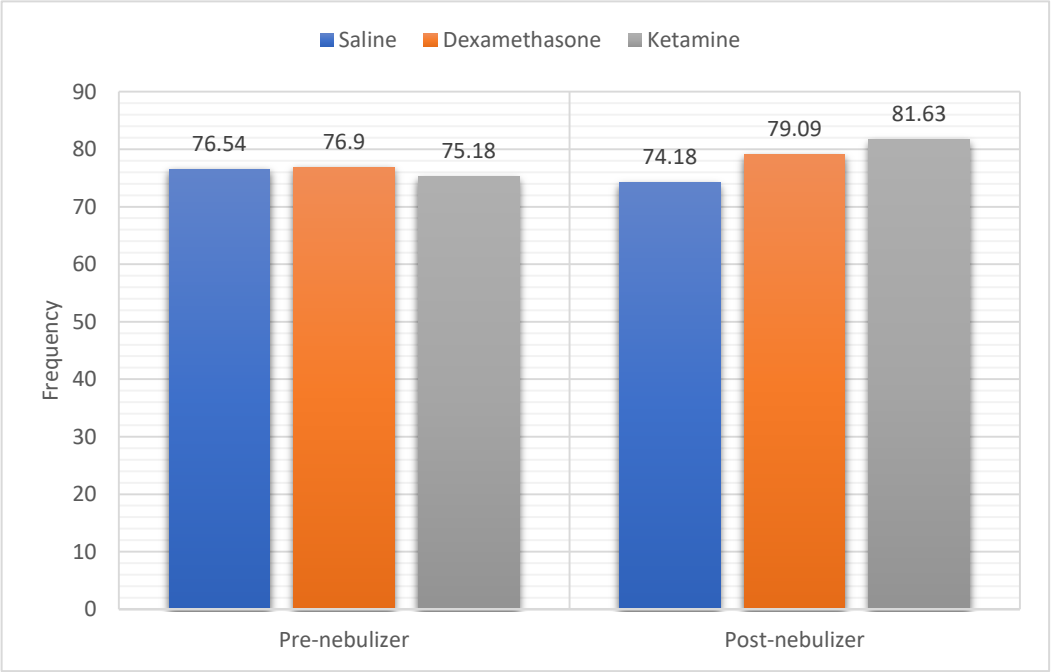


Figure 3.4

Difference in pre-nebulizer and post-nebulizer mean heart rate between study groups



3. Intraoperative phase

Descriptive statistics of intraoperative information

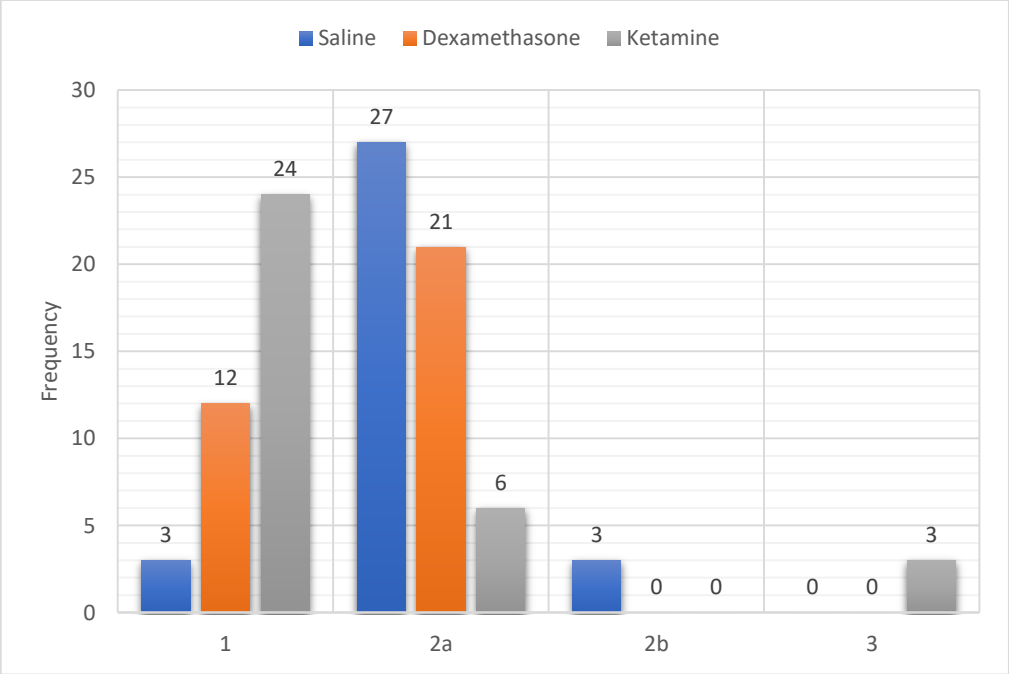
Table C.14 in appendix C shows results related to patients' intraoperative status and management. It shows that all of the patients were intubated using a laryngoscope blade of size three, with around third of patients were intubated with 7.0 mm (36.4%), 7.5 mm (30.3%) or 8.0 mm (30.3%) endotracheal tube size. The intubation process was mostly performed by an experienced performer of 2 – 5 years (63.6%), and from the first attempt (100%).More commonly, patients had a laryngoscope view of 2a (54.5%), with excellent endotracheal intubation conditions.

None of the patients had laryngospasm before induction or after extubation. Also, the intra-cuff pressure remained in normal range in all patients, with a mean pressure between 22 mmHg and 25 mmHg from zero to 60-minute duration. The difference between the initial volume inserted in the cuff and the final volume withdrawn from the cuff was absent in 84.8% of the patients, while the volume decreased in 15.2% of them. The mean anesthesia duration was 56.66 minutes, with a mean of surgical duration of 48.48 minutes. Also, there was no visible blood stain in the endotracheal tube or the

nasogastric tube in all patients. The mean of duration between the first spontaneous breath up to the extubation was 6.90 minutes (SD = 1.85 minutes), ranging from 4 to 11 minutes. Finally, no patient experienced post-extubation vomiting, while around fourth of the patients experienced post-extubation cough, ranging from 1 to 5 times, with a mean of 1.77 times. Figure 3.5 shows the difference in laryngoscope view and Figure D.5 in appendix D shows the mean anesthesia surgical durations between the three study groups.

Figure 3.5

Difference in laryngoscope view between study groups



Differences in intraoperative information related to study groups

Table C.15 in appendix C shows the difference in laryngoscope view between study groups, and tables from (C.16 to C.21) in appendix C show the differences of endotracheal intubation condition between study groups according to Chi-Square test.

Table C.15 in appendix C shows that there was a significant difference in laryngoscope view among the three study groups (p-value < 0.001), where the patients in ketamine group had the clearest view (72.7% in class 1), followed by dexamethasone group (36.4% in class 1 and 63.6% in class 2a), and then saline group (9.1% in class 1 and 81.8% in class 2a), which means that the ketamine nebulizer is more effective than both

saline and dexamethasone nebulizers and the saline group is the less effective one in clearing the laryngoscopic view.

Table C.16 in the appendix C shows that there was a significant difference in intubation condition between study groups (p-value < 0.001), where ketamine group had more excellent intubation conditions 72.7%, compared to 63.6% and 81.8% of good conditions in saline and dexamethasone groups, respectively.

Intraoperative hemodynamics

Table C.17 in appendix C shows the descriptive statistics of the hemodynamics before and 30 minutes after the induction of anesthesia. The EtCO2 was absent before the induction because it is measured using capnogram which is not present before induction and insertion of endotracheal tube. Tables (C.18 to C.29)in appendix C show the results related to the differences in post-anesthesia induction (which is an indicator for the response of the patients to laryngoscopy and intubation) among the study groups.

Table C.18 in appendix C shows that there was no significant difference in the mean of SBP post-intubation among saline group (mean = 111.545 mmHg) which is insignificantly higher than dexamethasone (mean = 111.364 mmHg) and insignificantly lower than ketamine (mean = 112.364 mmHg) (p-value = 0.918). This means that there's no effect of the nebulizer on the SBP among the groups and therefore Post Hoc test is not required.

Table C.19 in appendix C shows that there was a significantly higher mean of post-intubation DBP among ketamine group (mean = 71.182 mmHg) than both dexamethasone (mean = 63.00 mmHg) and saline (mean = 71.00 mmHg) groups (p-value = 0.001), while table C.20 in appendix C shows, using Post Hoc test, that the mean difference among some groups individually is also significant, where the saline group has a mean difference of 8.00 mmHg more than dexamethasone group (p-value = 0.001), and dexamethasone group has a mean difference of 8.182 mmHg less than ketamine group (p-value = 0.001). This means that dexamethasone nebulizer has a reducing effect on DBP while there's no significant difference between ketamine and saline nebulizer on DBP which means that ketamine is more effective than dexamethasone nebulizer in keeping the DBP on its baseline.

Table C.21 in appendix C shows that there was a significantly higher mean of post-intubation HR among dexamethasone group (mean = 82.273 bpm) than both saline (mean = 77.909 bpm) and ketamine (mean = 77.182 bpm) groups (p-value = 0.047), while table C.22 in appendix C shows, using Post Hoc test, that the mean difference among some groups individually is also significant, where the saline group has a mean difference of 4.364 bpm less than dexamethasone group (p-value = 0.049), while dexamethasone group has a mean difference of 5.091 bpm more than ketamine group (p-value = 0.022), with no significant difference between saline and ketamine groups (p-value = 0.741). This means that dexamethasone is more effective than both ketamine and saline nebulizers in elevating the HR during the operation.

Table C.23 in appendix C shows that there was a significantly higher mean post-intubation EtCO2 among saline group (mean = 35.091 mmHg) than both dexamethasone (mean = 32.545 mmHg) and ketamine (mean = 34.273 mmHg) groups (p-value = 0.015), while table C.24 in appendix C shows, using Post Hoc test, that the mean difference between some groups individually is also significant, where the saline group has a mean difference of 2.545 mmHg more than dexamethasone group (p-value = 0.005), with no significant difference between saline and ketamine groups (p-value = 0.354), or between dexamethasone and ketamine groups (p-value = 0.052), which means that dexamethasone nebulizer has a more effective reducing effect on EtCO2 than both ketamine and saline nebulizers.

Table C.25 in appendix C shows that there was no significant difference in the mean of post-intubation RR among saline group (mean = 12.636 breath/min) than both dexamethasone (mean = 12.727 breath/min) and ketamine (mean = 12.727 breath/min) groups (p-value = 0.973), and therefore no Post Hoc test is required.

Table C.26 in appendix C shows that there was a significantly higher mean of post-intubation temperature among saline group (mean = 36.409 °C) than both dexamethasone (mean = 36.309 °C) and ketamine (mean = 36.400 °C) groups (p-value = 0.009), while table C.27 in appendix C shows, using Post Hoc test, that the mean difference between some groups individually is also significant, where the saline group has a mean difference of 0.1 °C more than dexamethasone group (p-value = 0.006), and dexamethasone groups has a mean difference of 0.091 °C less than ketamine group (p-value = 0.012), with no significant difference between saline and ketamine groups (p-

value = 0.797). This means that dexamethasone nebulizer is less effective than both ketamine and saline nebulizer in keeping the temperature at its baseline during the operation.

Table C.28 in the appendix C shows that there was a significantly higher mean of post-intubation SpO2 among dexamethasone group (mean = 99.818%) than both saline (mean = 99.455%) and ketamine (mean = 99.545%) groups (p-value = 0.037), while table C.29 in the appendix C shows, using Post Hoc test, that the mean difference between some groups individually is also significant, where the saline group has a mean difference of 0.364% less than dexamethasone group (p-value = 0.014), with no significant difference between saline and ketamine groups (p-value = 0.532), or between dexamethasone and ketamine groups (p-value = 0.063). This means that dexamethasone nebulizer is more effective than saline nebulizer in rising the SpO2 during the operation.

4. PACU phase

Table C.30 in appendix C describes the hemodynamics among patients when being in the PACU, taking in consideration that the statistics are the mean of two readings. The mean of duration of staying in PACU was 9.81 minutes (SD = 0.67 minute), ranging from 7 to 11 minutes, mostly 10 minutes (84.8%). Also, no patient experienced occurrence of laryngospasm inside the PACU. Table C.31 in appendix C also shows the incidences of PACU phase POST, hoarseness and PONV, with most of the patients having mild symptoms and only 3% experienced vomiting. Figure D.6 in appendix D shows the differences in the mean of hemodynamic readings between the three study groups in the PACU phase, while figures (3.6 to 3.10) shows the differences in POST, cough, hoarseness and PONV in the PACU after full consciousness between the three study groups.

Figure 3.6

Difference in POST in PACU between study groups

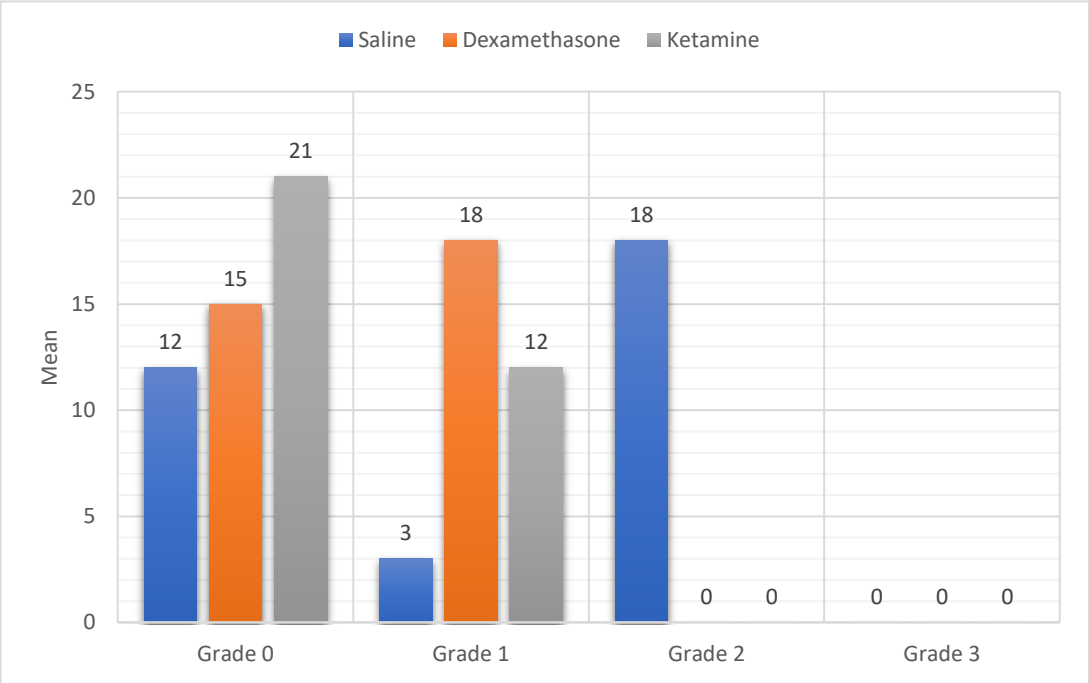


Figure 3.7

Difference in cough in PACU between study groups

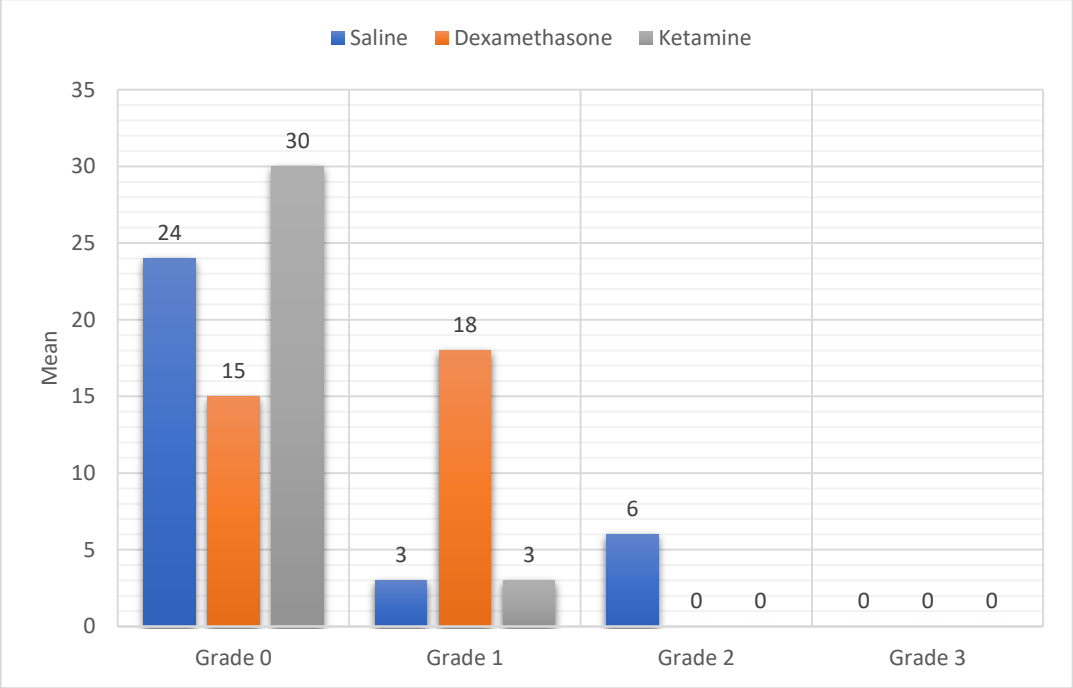


Figure 3.8

Difference in hoarseness in PACU between study groups

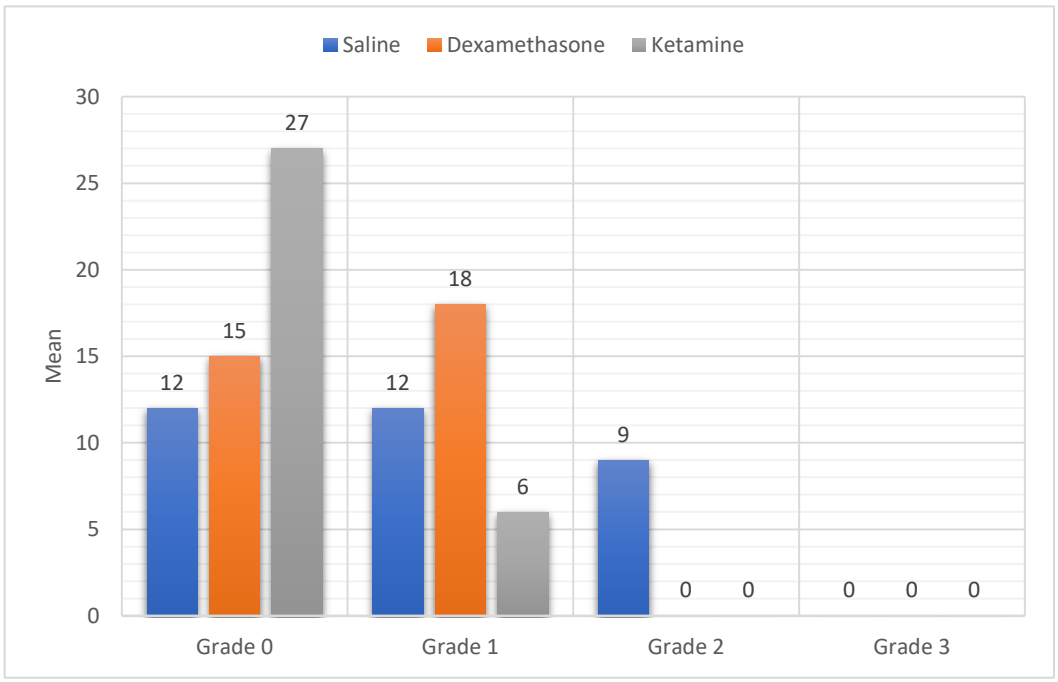


Figure 3.9

Difference in nausea in PACU between study groups

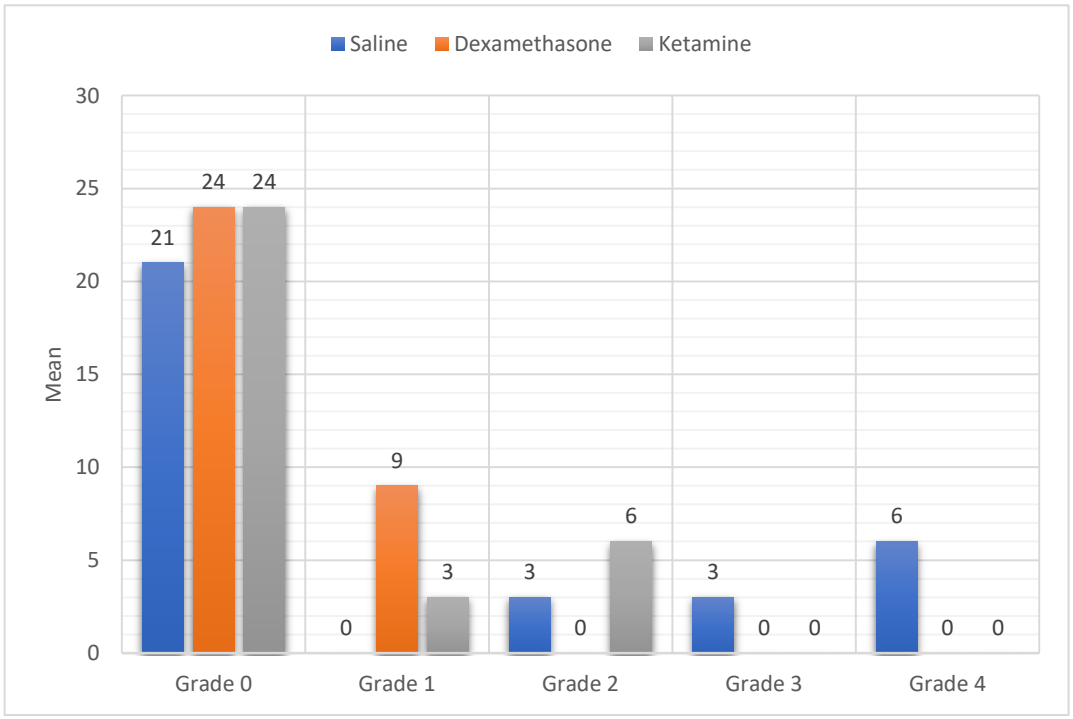
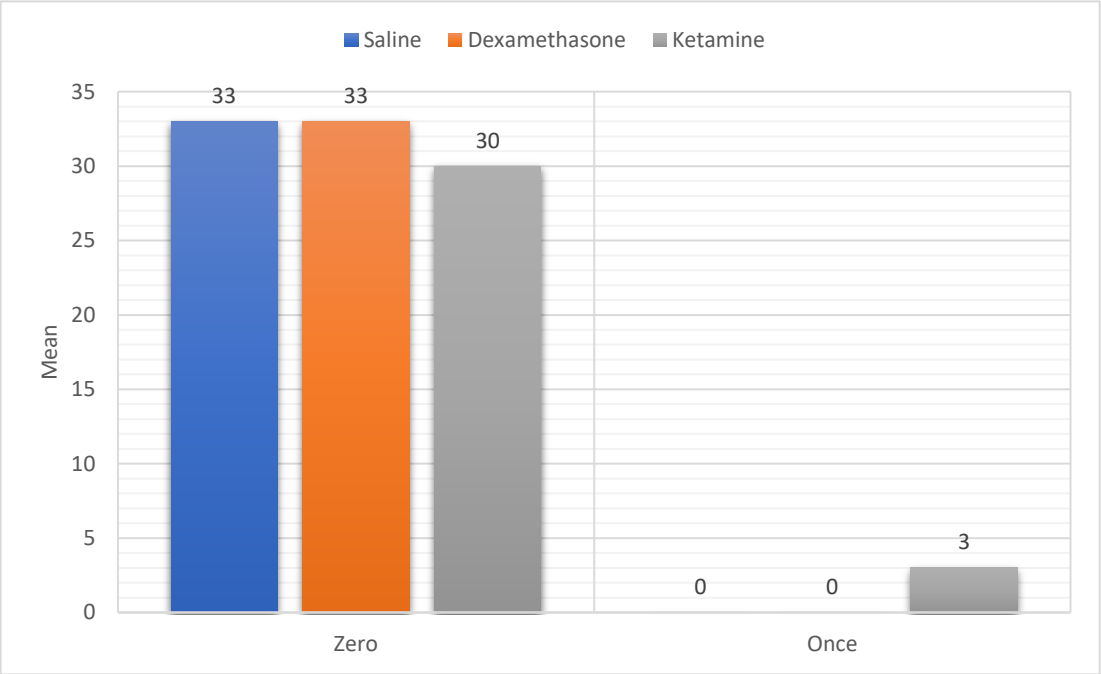


Figure 3.10

Difference in vomiting frequency in PACU between study groups



5. Ward phase

Ward hemodynamics, 1-hour sedation scale and satisfaction level

Table C.32 in appendix C describes the hemodynamics among patients when being in the ward, taking into consideration that the statistics are the mean of two readings (1-hour and 8-hour), and figure D.7 in appendix D shows that the hemodynamics are very similar for the patients in the three groups. The mean of sedation scale among patients 1-hour after the extubation was 1.75/6.00 (SD = 0.43), while the mean satisfaction level was 7.09/10.00 (SD = 1.03), as shown in table C.33 in appendix C. Table 3.1 shows that there was no significant difference in 1-hour sedation scale in the ward between study groups according to Chi-Square test which means that ketamine and dexamethasone have no effect in increasing the sedation period in patients after the operation, while Table 3.2 shows the difference in patient's satisfaction between study groups, where the patients in ketamine group were the most satisfied (mean = 7.90/10.0), compared to dexamethasone (mean = 7.27/10.0) and saline (mean = 6.09/10.0) groups (p-value < 0.001), while table 3.3 shows, according to Post Hoc test, that the patients in ketamine group have a mean difference of 1.818 out of 10 more than patients in saline group (p-value < 0.001), and a mean of 0.636 out of 10 more than patients in dexamethasone

group (p-value < 0.001), with patients in dexamethasone group having a mean difference of 1.182 out of 10 more than saline group (p-value < 0.001). Which means that ketamine nebulizer is more effective than both dexamethasone and saline nebulizers in increasing patients satisfaction and saline nebulizer is less effective than both ketamine and dexamethasone nebulizers.

Table 3.1

Difference in 1-hour sedation scale between study groups

Group	1-hour sedation scale		Total	Chi-Square	p-value
	Agitated	Cooperative			
Saline	6 (18.2%)	27 (81.8%)	33 (100%)	3.960	0.138
Dexamethasone	6 (18.2%)	27 (81.8%)	33 (100%)		
Ketamine	12 (36.4%)	21 (63.6%)	33 (100%)		
Total	24 (24.2%)	75 (75.8%)	99 (100%)		

Table 3.2

Difference in patient satisfaction of anesthesia between study groups

Dependent variable	Group	Satisfaction mean (out of 10)	St. Dev.	p-value
Patient satisfaction of sedation	Saline	6.090	1.011	
	Dexamethasone	7.272	0.452	< 0.001
	Ketamine	7.909	0.522	
	Total	7.090	1.031	

Table 3.3

Post Hoc test for the difference in patient satisfaction about anesthetic care between study groups

Dependent variable	Group (I)	Group (J)	Mean difference	p-value
Patient satisfaction of sedation	Saline	Dexamethasone	-1.182	< 0.001
		Ketamine	-1.818	< 0.001
	Dexamethasone	Saline	1.182	< 0.001
		Ketamine	-0.636	< 0.001
	Ketamine	Saline	1.818	< 0.001
		Dexamethasone	0.636	< 0.001

Differences in ward events between study groups

Table C.34 in appendix C shows that all of ward events are decreasing with time from the zero hour to 24th hour. The following tables describes the differences in ward events in overall time frames between study groups.

Table C.35 in appendix C shows that there was a significantly higher mean of POST, hoarseness and nausea reporting among patients in the first 24 hours in the ward among saline-nebulized patients than in patients who received dexamethasone and ketamine nebulizers (p-value < 0.05), while dexamethasone group had significantly higher cough incidence in the first 24 hours in the ward than both saline and ketamine groups (p-value < 0.001). Tables 3.4 to 3.7 show the differences in ward events among study groups according to Post Hoc test.

Table 3.4 shows, using Post Hoc test, that the mean difference of overall POST between all groups individually is also significant, where the saline group has a mean difference of 4.091 more than dexamethasone group (p-value < 0.001), and 5.363 more than ketamine group (p-value < 0.001), while dexamethasone group has a mean difference of 1.272 more than ketamine group (p-value = 0.002), which means that ketamine nebulizer is more effective than both dexamethasone and saline nebulizers in preventing the POST incidence, and dexamethasone is more effective than saline nebulizer in that.

Table 3.4

Post Hoc test of the differences in overall POST in ward between study groups

Dependent variable	Group (I)	Group (J)	Mean difference	p-value
Overall POST in ward	Saline	Dexamethasone	4.091	< 0.001
		Ketamine	5.363	< 0.001
	Dexamethasone	Saline	-4.091	< 0.001
		Ketamine	1.272	0.002
	Ketamine	Saline	-5.363	< 0.001
		Dexamethasone	-1.272	0.002

Table 3.5 shows, using Post Hoc test, that the mean difference of overall cough between some groups individually is also significant, where the saline group has a mean difference of 1.182 more than ketamine group (p-value < 0.001), but not with the dexamethasone group (p-value = 0.562), while dexamethasone group has a mean difference of 1.364 more than ketamine group (p-value < 0.001). This means that ketamine nebulizer is more effective than both dexamethasone and saline nebulizer in preventing the cough after the operation in the ward and the dexamethasone is less effective than both ketamine and saline nebulizers in that.

Table 3.5

Post Hoc test of the differences in overall cough in ward between study groups

Dependent variable	Group (I)	Group (J)	Mean difference	p-value
Overall cough in ward	Saline	Dexamethasone	-0.182	0.562
		Ketamine	1.182	< 0.001
	Dexamethasone	Saline	0.182	0.562
		Ketamine	1.364	< 0.001
	Ketamine	Saline	-1.182	< 0.001
		Dexamethasone	-1.364	< 0.001

Table 3.6 shows, using Post Hoc test, that the mean difference of overall hoarseness between all groups individually is also significant, where the saline group has a mean difference of 1.182 more than dexamethasone group (p-value = 0.027), and 2.273 more than ketamine group (p-value < 0.001), while dexamethasone group has a mean difference of 1.091 more than ketamine group (p-value = 0.041). That means ketamine nebulizer is more effective than both saline and dexamethasone nebulizers in preventing hoarseness and dexamethasone is more effective than saline nebulizer.

Table 3.6

Post Hoc test of the differences in overall hoarseness in ward between study groups

Dependent variable	Group (I)	Group (J)	Mean difference	p-value
Overall hoarseness in ward	Saline	Dexamethasone	1.182	0.027
		Ketamine	2.273	< 0.001
	Dexamethasone	Saline	-1.182	0.027
		Ketamine	1.091	0.041
	Ketamine	Saline	-2.273	< 0.001
		Dexamethasone	-1.091	0.041

Table 3.7 shows, using Post Hoc test, that the mean difference of overall PONV between some groups individually is also significant, where the saline group has a mean difference of 2.454 more than ketamine group (p-value = 0.003), but not with the dexamethasone group (p-value = 0.060), and dexamethasone group has no significant mean difference compared to ketamine group (p-value 0.265), and this means the ketamine nebulizer is more effective than saline nebulizer in preventing PONV, but it is not significantly more effective than dexamethasone nebulizer and also the dexamethasone nebulizer is not significantly more effective than saline nebulizer in that respect.

Table 3.7

Post Hoc test of the differences in overall PONV in ward between study groups

Dependent variable	Group (I)	Group (J)	Mean difference	p-value
Overall Nausea in ward	Saline	Dexamethasone	1.545	0.060
		Ketamine	2.454	0.003
	Dexamethasone	Saline	-1.545	0.060
		Ketamine	0.909	0.265
	Ketamine	Saline	-2.454	0.003
		Dexamethasone	-0.909	0.265

Differences in ward events according to other factors

Table 3.8 shows that there was a significantly higher incidence of cough in ward among females (mean = 1.688 times) than males (mean = 0.588 times), and higher incidence of PONV in ward among females (mean = 3.313 times) than males (mean = 1.353 times), with higher mean hoarseness in females (mean = 2.813 times) compared to males (mean = 1.471 times), while there was no significant difference in POST according to gender.

Table 3.8

Differences in ward events according to patients' gender

Ward event	Gender	Mean events	St. Dev	p-value
POST	Male	3.176	3.005	0.897
	Female	3.250	2.613	
Cough	Male	0.588	0.853	< 0.001
	Female	1.688	1.626	
Hoarseness	Male	1.471	2.501	0.003
	Female	2.813	1.898	
PONV	Male	1.353	2.423	0.004
	Female	3.313	4.006	

Table C.36 in appendix C shows that there was a moderate negative correlation (-0.291) between patient's age and the incidence of PONV, which means that older patients have a significantly less incidence of PONV (p-value = 0.004) compared to younger patients. On the other hand, there was no significant correlation between patient's age and the incidence of POST, cough or hoarseness at ward (p-value > 0.05).

Table C.37 in appendix C shows that there was no significant difference in all ward events between smoker and non-smoker patients (p-value > 0.05).

Chapter Four

Discussions and Conclusions

This study was the first to compare the effect of ketamine nebulizer to the effect of dexamethasone nebulizer in reducing the severity of POST and other laryngeal morbidities.Most of the risk factors that contribute in POST incidence were avoided by using a precise inclusion and exclusion criteria in choosing the participants.According to our findings, the overall incidence was 75.7% of patients who suffered mild and moderate POST at zero hour and 57.5% at the 4^{th} hour, with no one suffered of severe POST throughout all hours, while in the previous studies it was ranging from 14.4% to 59.6% (Christensen et al., 1994; Gemechu et al., 2017) respectively. This high incidence rate in our study may be due to the fact that anesthesiologist did not wait long enough for full patient relaxation before intubation due to the large number of patients on operation waiting list.

The aim of this study was to assess the efficacy of nebulizing ketamine vs dexamethasone preoperatively on the POST and other laryngeal morbidities, in addition to other secondary aims and results.

4.1 Pre-and post-nebulizer hemodynamics

In this study there was a significant increase in SBP,DBP, HR and SpO2 between the pre and post-nebulizer stages, while there was no significant difference in RR after finishing the nebulizers.

There was a significant higher mean post-nebulizer SBP among ketamine group than both dexamethasone and saline groups but it wasn't significant for the DBP, and that means ketamine nebulizer is more effective in elevating the SBP than both dexamethasone and saline nebulizers but not in elevating the DBP. Also, there was a significantly higher mean post-nebulizer HR among ketamine group in comparison with saline group, but it wasn't significant in comparison with the dexamethasone nebulizer.These results are considered compatible with what(Adams et al., 2001; Butterworth et al., 2013) mentioned about the ketamine particularly after I.V push which causes some rise in the arterial BP, HR and cardiac output because it stimulates the SNS centrally and inhibit the norepinephrine reuptake at nerve terminals.

Also there was a significantly higher mean of post-nebulizer RR among ketamine group (mean = 15.182 breath/min) than both dexamethasone (mean = 15.091 breath/min) and saline (mean = 14.364 breath/min) groups (p-value = 0.001), and there was a significantly higher mean of post-nebulizer SpO_2 among ketamine group (mean = 99.364%) than both dexamethasone (mean = 98.909%) and saline (mean = 97.363%) groups (p-value < 0.001), which means that ketamine and dexamethasone nebulizers are more effective than saline nebulizer in elevating the RR and the SpO2 with no significant difference between them (p-value = 0.689) for the rise of RR and (p-value = 0.093) SpO_2, but even though it is statistically significant for the RR and SpO2, clinically it is considered the same base line as pre-op.

4.2 Sample characteristics and the associated risk factors

The majority of patients in this study were ASA physical status I and more than two thirds of them (69.7%) had a Mallampati score of ‘ I ’. All of them had a normal sinus rhythm (NSR) preoperatively and during the operation, the duration mean of anesthesia was 56.66 minutes, with a mean surgical duration of 48.48 minutes. The intra-cuff pressure kept in normal range for all patients by using the manometer, with a pressure mean between 22 mmHg and 25 mmHg from zero to 60-minute duration.

The mean of age of the patients was 38.06 years old, ranging from 18 to 60 years old, with mostly are older than 45 years old (34.3%). The allocation of patients was similar between male (51.5%) and female (48.5%), with approximately half of the patients having normal weight (45.5%). ETT of size 8-8.5 were used for men and size7-7.5 for women. All of the patients were intubated using a laryngoscope blade of size three, with around third of patients were intubated with 7.0 mm (36.4%), 7.5 mm (30.3%) or 8.0 mm (30.3%). This means that our groups were comparable in distribution of age, gender, body weight, ASA PS, Mallampati score, intra-cuff pressure and duration of surgery.

Many risk factors are associated with POST.(Biro et al., 2005; Chinachoti et al., 2017; Christensen et al., 1994) mentioned that it was the lower age groups who have a higher incidence rate, and according to (Ahmed et al., 2007), it was the older age group who have a higher rates, while in our study there was no significant correlation between patient’s age and the incidence of POST, cough or hoarseness at ward, but there was a

moderate negative correlation between patient's age and the incidence of PONV in our study, which means that older patients have a significantly less incidence of PONV compared to younger patients. The air way performer who has less than 3 month work experience is a risk factor and associated with higher rates (Jaensson et al., 2012), so we ensured that the intubation was performed by an experienced performer, and it was of 2–5 years' experience in (63.6%), and from the first attempt (100%). Visible blood stains on the ETT after extubation, smoking and previous respiratory disease were significantly associated with the incidence of POST (Biro et al., 2005), but in contrast with him, our study showed that there's no significant difference in all ward events (POST and other morbidities) between smoker and non-smoker patients and visible blood stains on the ETT after extubation and previous respiratory diseases were from the exclusion criteria and there was no visible blood stain in the ETT or the NGT in all patients.

The laryngoscopic view was measured for all patients and it was 39.4% in class 1, 54.5% in class 2a, 3% in class 2b and 3% in class 3 based on the Modified Cormack &Lehane score. Also, 42.4% of them had an excellent intubation condition, 57.6% of patients had a good intubation condition and no one had poor intubation condition according to the 1994 Copenhagen Consensus Conference recommended score, where ketamine group had more excellent intubation conditions (72.7%), compared to 63.6% and 81.8% of good conditions in saline and dexamethasone groups respectively. It is important to note that we can't support if these differences between the study groups related to the nebulizers, especially because there was no previous studies about the effect of nebulizers on intubation condition, but in this study we can see that the patients who had the lowest quality of intubation conditions were in the saline group. On the other hand, they had the highest rate of POST incidence, which is compatible with what (Ahmed et al., 2007; Chinachoti et al., 2017) mentioned about POST, that a higher grade of intubation difficulty is an associated risk factor.

Moreover, there was a significantly higher incidence of cough, hoarseness and PONV in ward among females than males, but there was no significant difference in POST according to gender in our study, which is compatible with what was mentioned by (Orji et al., 2020) about POST at the 4^{th} hour, there was nodifference on the incidence at the 4^{th} hour between female and male genders at all groups. While according to (Ahmed

et al., 2007; Biro et al., 2005; Chinachoti et al., 2017; Christensen et al., 1994; Fenta et al., 2020; Gemechu et al., 2017) there was a higher rates of POST incidence in females than in males and they didn't mentioned the difference between the two genders regarding other morbidities in their studies.

None of our patients had laryngospasm after nebulization, before induction or after extubation and that's compatible with what (Green & Krauss, 2004) mentioned about laryngospasm. It is very rare, even though it is frequently mentioned as an adverse effect of ketamine. And the risk of laryngospasm that require intubation during ketamine anesthesia is 1 per 5,000 individuals (0.02%) based on pooled data, which means it is nearly 100 times lesser when compared to other anesthetic agents.

4.3 Intra-op hemodynamics

In this study there was no significant difference in the mean of SBP post-intubation among study groups, but there was a significantly lower mean post-intubation DBP among dexamethasone group than both saline and ketamine groups.Also there was a significantly higher mean of post-intubation HR among dexamethasone group than both saline and ketamine groups, which seems to be a compensatory mechanism in response to the decreased DBP among the dexamethasone group. These findings support that there's no effect of the given nebulizers on the SBP, and dexamethasone nebulizer has a little reducing effect on DBP. On the other hand, it cause some elevation on the HR during the operation as a compensatory mechanism.

These absence of significant differences in patients' hemodynamics in response to the intubation and during the operation particularly between the ketamine and the saline groups support that there's no systemic side-effects of ketamine nebulizer on patients hemodynamics which suggests that ketamine nebulizer has a potent topical effect without serious systemic side-effects and that's compatible with what was mentioned by (Chan et al., 2010) when he conducted a study to measure the blood serum ketamine level after administering it topically (gargling) to adult patients who underwent elective gynecological surgeries, and found they had a low serum level which means it has a potent topical effect and a slight possible systemic effect.

It is also worth noting that in this study we observed the patients during and after the nebulization, post-op after the extubation and in the PACU and we didn't notice any of

these ketamine systemic side effects: hallucination, respiratory depression, agitation, flashbacks, anxiety, chest pain, palpitation, delirium, dystonia, psychosis, dizziness, seizures, paranoia, schizophrenic-like symptoms, muscle hypertonicity, transient clonus, hypersalivation, hyperreflexia, transient rash, nausea, tachycardia, HTN, pulmonary edema, decreased awareness, distractibility, feelings of invulnerability, disorientation, impaired thought processes, laryngospasm, sedation and stridor.

There was no significant difference in the mean of post-intubation RR among study groups, because all of them were mechanically ventilated approximately by the same RR and the other parameters.

There was a statistically significant higher mean of post-intubation EtCO2 among saline group (mean = 35.091 mmHg) than both dexamethasone (mean = 32.545 mmHg) and ketamine (mean = 34.273 mmHg) groups (p-value = 0.015). There was also a statistically significant higher mean of post-intubation temperature among saline group (mean = 36.409 °C) than both dexamethasone (mean = 36.309 °C) and ketamine (mean = 36.400 °C) groups (p-value = 0.009), and there was a significantly higher mean of post-intubation SpO_2 among dexamethasone group (mean = 99.818%) than both saline (mean = 99.455%) and ketamine (mean = 99.545%) groups (p-value = 0.037). Even though these finding statistically means that dexamethasone nebulizer is effective in reducing $EtCO_2$ in comparison to both ketamine and saline nebulizers, but less effective than both of them in keeping the temperature on its baseline during the operation and more effective than saline nebulizer in rising the SpO2 during the operation.Clinically, it is not a big difference and it is not considered an intrinsic change on patients hemodynamics.

4.4 Ward events

Many studies discussed that ketamine nebulization has a promising prophylactic effect to prevent and to decrease the incidence of POST (Ahuja et al., 2015; Jain et al., 2017; Kuriyama et al., 2020; Orji et al., 2020; Rajan et al., 2017; Segaran et al., 2018; Shekhar et al., 2019; Thomas et al., 2018; Thomas et al., 2020), and the same was discussed about dexamethasone (Ashwini et al., 2018; Salama & El-badawy, 2016; Sounak Paul et al., 2019).

In our study,the higher the mean was the higher the incidence was, and the mean difference of overall POST during the 24 hour post-op in ketamine group was significantly less than saline nebulizer mean, and insignificantly less than dexamethasone nebulizer mean.This means that ketamine nebulizer was more effective than saline nebulizer and comparable with dexamethasone nebulizer in alleviating the POST. Also, it was noticed POST and other laryngeal morbidities were decreasing with time from the zero hour to 24th hour, while in (Ashwini et al., 2018; Mostafa et al., 2018; Orji et al., 2020) studies it was mentioned that the highest incidence was on the 4th hour.

In (Ahuja et al., 2015) study, the incidence of POST at least during the first few hours postoperatively was significantly decreased due to ketamine potent topical effect, and the incidence was more than two times higher in the saline group in comparison to the ketamine group, while in (Thomas et al., 2018) study, the results were in line with our results to a large extent.The incidence of POST was significantly lesser in ketamine group than in placebo group all the times postoperatively up to 24 hours and a severe sore throat (Grade 3) wasn't seen in any patient in both groups.Also in Thomas study, none of these adverse effects (nausea, vomiting, cough, stridor, laryngospasm, dry mouth, hoarseness, hallucinations, respiratory depression, or hemodynamic instability) were noticed during the observation in any point during the study.

In (Rajan et al., 2017) study, patients underwent surgeries under combined epidural and general anesthesia to decrease the operation pain and to increase the patients concern on POST postoperatively.The study showed that there was a significant decrease not only in the POST by nebulizing ketamine or magnesium sulfate preoperatively, but also in the voice hoarseness with a maximum efficacy on ketamine group, and that's in line with the results of our study which showed that there's a significant effect of ketamine nebulizer over both saline and dexamethasone nebulizers in preventing the hoarseness.However, in Rajan study the decrease in the incidence of cough for those in the intervention groups wasn't significant, while in our study there was a significant effect of ketamine nebulizer over both dexamethasone and saline nebulizers in preventing the cough postoperatively with no significant difference between dexamethasone and saline nebulizers. Also, (Kuriyama et al., 2020) meta-analysis support our results about POST, hoarseness and cough, it showed that the application of

ketamine topically is aneffective factor in reducing the incidence and severity of moderate and sever POST when compared to none-analgesic methods.Also it was associated with a reduction in the post-operative cough and hoarseness. And in about half of the studies, there were no adverse effects related to ketamine, but in other studies, it was unclear or undocumented.

In (Jain et al., 2017; Shekhar et al., 2019) studies, they nebulized a mixture of ketamine and clonidine and they found that the incidence of sore throat and its severity in ketamine clonidine mixture group was significantly lower than in only ketamine group. In our study, we couldn't nebulize a mixture of ketamine with dexamethasone because there are no previous studies about this mixture.

(Mostafa et al., 2018) study showed that nebulizing ketamine is better than magnesium sulfate and affixed dose of I.V dexamethasone in reducing the POST in pediatric patient, particularly in the 4^{th} hour.Also patients satisfaction was approximately the same in his study groups. There was more prominent sedation and some cases of vomiting in the magnesium and ketamine group while there wasn't in the dexamethasone group.The incidence of cough was also lower in the dexamethasone group, while in our study the ketamine nebulized patients were more satisfied than both dexamethasone and saline nebulized patients. There was no significant difference in 1-hour sedation scale in the ward between study groups.Ketamine and dexamethasone nebulizers were significantly more effective than saline nebulizer in preventing PONV with no significant difference between them, and in contrast to Mostafa's study results, in our study the ketamine nebulizer was more effective than both dexamethasone and saline nebulizer in preventing the cough, but we can't count on these results because our patients were adults while Mostafa's patients were pediatrics.

(Segaran et al., 2018) study showed that none of the ketamine and magnesium sulfate nebulized patients complained of immediate POST postoperatively at 0 hour, and the number of patients who complained of POST in the ketamine group was half the number of patients in the magnesium sulfate group at the 4^{th} and 6^{th} hour, while in (Orji et al., 2020) study,it was found that the incidence was the lowest in the magnesium group but insignificantly when compared with the ketamine at all observation times.The incidence was the highest at the 4^{th} hour at all groups, especially in the placebo group, but there was no significant difference of the incidence at the 4^{th} hour between female

and male genders at all groups. In our study the difference between the ketamine nebulized and the dexamethasone nebulized patients in POST incidence wasn't significant, which confirms that dexamethasone nebulizer is more efficient than magnesium sulfate or at least has the same efficacy in preventing POST.

(Thomas et al., 2020)found that the incidence was lower in both dexmedetomidine and ketamine nebulized groups with insignificant difference between them in comparison with the control group after undergoing thyroidectomy under GA.Severity of POST was also lesser at all points during the study. Severe POST wasn't developed in any patient in both groups, and there was no adverse effects such as nausea, cough , hoarseness, or hallucination or respiratory depression at all observation points during the study, except HR, SBP and DBP where there was a rise in pre induction period in ketamine group, which is almost the same thing in our study which may be due to ketamine mild systemic absorption. In Thomas' study, there were two excluded patients, one in the ketamine group who developed laryngospasm post-extubation and one in the dexmedetomidine group developed stridor in the post-operative period, while in our study there were not anyone who developed laryngospasm after nebulization, before induction or after extubation, and that's might be because our criteria excluded the neck and ENT surgeries, while Thomas' study was about patients undergoing thyroidectomy.

In another studies about dexamethasone,(Luria et al., 2001) compared the effect of nebulizing and oral routes in treating pediatrics croup, it wasfound that the number of children who returned to receive a second medical treatment for their symptoms in the seven later days was higher in the dexamethasone nebulized and placebo groups than in the dexamethasone orally treated group.Also a score for croup symptoms in the orally treated group was better than in the nebulization and placebo group, which means that dexamethasone wasn't significantly effective in treating the children croup, but it is effect was significant in treating POST in (Salama & El-badawy, 2016) study , which revealed that the incidence and severity of POST was lesser in the dexamethasone group in comparison with the placebo group significantly at the 0, 2, 4, 8, and 12 hours after the extubation, but no significant difference was found after 24 hour.All patients remained stable hemodynamically without any adverse effects at any point in the study duration, which was almost the same in our study results for the dexamethasone nebulized patients POST during the 24 hours post-op, but the different thing in our

study was no one of our patients in the dexamethasone or ketamine group complained of POST at the24 hour, and there was just a mild decrease in DBP and mild elevation in the HR during the intra-op period.

(Almustafa et al., 2019) found that the incidence of POST is significantly lower in the dexamethasone at all times postoperatively.There was also a change of voice which was significantly higher in the placebo group in comparison with the dexamethasone group but no significant difference was found between the two groups in the odynophagia and PONV.The same was found in our study about PONV.The dexamethasone nebulizer wasn't significantly more effective than saline nebulizer in decreasing the PONV, it is possible that dexamethasone's antiemetic effect is activated by systemic absorption, something we think it didn't happenin our study or at least was very little after the nebulizer.

In (Sounak Paul et al., 2019) study, the dexamethasone nebulizer was compared with budesonide in preventing post-operative sore throat, hoarseness of voice and cough, in patients undergoing lumbar spine surgery in the prone position.In all the observation times, the incidence of sore throat was higher in the budesonide group in comparison with the dexamethasone group and it was statistically significant except at the 30 minutes postoperatively, and the same was for the hoarseness and cough.The incidence was higher in the budesonide group at all times and it was statistically significant except at the first 30 minutes for the hoarseness and at the 24 hour for the cough.It was not significant at these times.These findingscould be due to half-lives of dexamethasone (t1/2-36 hours) and budesonide (t1/2-3 hours). In our study,a similar results were found about the hoarseness and POST, but not for the cough.The incidence rate of cough was significantly higher in the dexamethasone nebulized patients in comparison with ketamine group and insignificantly higher than saline group, which means it has no effect in preventing the post-op cough or it has a little insignificant inducing effect of cough.

4.5 Limitations

1. We couldn't nebulize a mixture of ketamine and dexamethasone because there are no previous studies about this mixture.

2. We didn't measure the ketamine and dexamethasone serum level post-op to determine if there's a systemic absorption or just a topical effect.

3. We didn't combine spinal or epidural anesthesia with the GA for our patient so they could focus only on POST in the ward without another disturbing pain.

4. Our study was not multicenter because of the lengthy and complicated approval process for the MoH.

4.6 Recommendations

1. To conduct a similar study with a larger sample, longer duration and with a more flexible inclusion criteria.

2. To conduct the study with four groups, and to give the fourth group the two nebulizers, but sequentially without mixing them.to compare the efficacy different doses of the used drugs.

3. To conduct a similar study with different doses of the used drugs to compare the efficacy of these different doses.

4. To measure the blood serum ketamine levels post-op, to make sure that there is no or just a little systemic absorption of ketamine.

5. To conduct another researches to see if there is any relation between the nebulizers and the endotracheal intubation condition and easiness.

4.7 Nursing implications

POST and other laryngeal morbidities are the most anxious complain post-op, a nebulizer is very simple acceptable rout for delivering a prophylactic agent to decrease the incidence and severity of these morbidities, and it could be given in the ward before entering the operation room.

4.8 Conclusion

We conclude that nebulizing 50 mg of ketamine or 8 mg of dexamethasone is an effective way to prevent and decreasing the incidence of POST and other laryngeal morbidities with no serious side effects and with a maximum efficacy in the ketamine nebulizer.

List of Abbreviations

Abbreviation	Meaning
ASA	American society of anesthesiologist
CPAP	Continues positive air way pressure
COPD	Chronic obstructive pulmonary disease
DBP	Diastolic blood pressure
ETT	Endo tracheal tube
GA	General Anesthesia
GI	Gastrointestinal
HR	Heart rate
HTN	Hypertention
I.M	Intramuscular
I.O	Intraosseous
I.V	Intravenous
IRB	Institutional review board
MAP	Mean arterial blood pressure
Ncbi	National Center for Biotechnology Information
NIBP	Noninvasive blood pressure
NMDA	N-Methyl-D-Aspartate
NSAID	Non-steroidal anti-inflammatory drug
PACU	Post anesthesia care unit
PONV	Post-operative nausea and vomiting
POST	Post-operative sore throat
RR	Respiratory rate
SBP	Systolic blood pressure
SNS	Sympathetic nervous system
SPO_2	Oxygen saturation in blood

References

[1] Adams, H., Brausch, M., Schmitz, C., Meyer, M., & Hecker, H. (2001). Analgosedation with (S)-ketamine/propofol vs.(S)-ketamine/midazolam: Control and qualitiy of sedation, stress response and haemodynamic reactions. *ANASTHESIOLOGIE INTENSIVMEDIZIN NOTFALLMEDIZIN SCHMERZTHERAPIE*, *36*(7), 417-424.

[2] Ahmed, A., Abbasi, S., Ghafoor, H. B., & Ishaq, M. (2007). Postoperative sore throat after elective surgical procedures. *Journal of Ayub Medical College*, *19*(2), 12.

[3] Ahuja, V., Mitra, S., & Sarna, R. (2015). Nebulized ketamine decreases incidence and severity of post-operative sore throat. *Indian J Anaesth*, *59*(1), 37-42. https://doi.org/10.4103/0019-5049.149448

[4] Almustafa, M., Obeidat, F., Mismar, A., Rashdan, M., Jabaiti, K., Alryalat, S. A., . . . Suleiman, A. (2019). Role of Preoperative Dexamethasone Nebulization in Reducing Bougie Complications Encountered After Sleeve Gastrectomy: a Prospective Double-Blind Control Interventional Study. *Obes Surg*, *30*(2), 501-506. https://doi.org/10.1007/s11695-019-04202-x

[5] American Society of Anesthesiologists. (2019, Octoper 23). *Continuum of Depth of Sedation: Definition of General Anesthesia and Levels of Sedation/Analgesia*. https://www.asahq.org/standards-and-guidelines/continuum-of-depth-of-sedation-definition-of-general-anesthesia-and-levels-of-sedationanalgesia

[6] American Society of Anesthesiologists. (2020, december 13). *ASA Physical Status Classification System*. https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system

[7] Ashwini, H., Seema Kumari, K., & Lavanya, R. (2018). Comparative study of dexamethasone nebulisation with magnesium sulphate nebulisation in preventing post operative sore throat following endotracheal intubation. *Indian Journal of Clinical Anaesthesia*, *5*(3), 341-347.

[8] Biro, P., Seifert, B., & Pasch, T. (2005). Complaints of sore throat after tracheal intubation: a prospective evaluation. *European journal of anaesthesiology*, *22*(4), 307-311.

[9] Butterworth, J. F., Mackey, D. C., Wasnick, J. D., Morgan, G. E., Mikhail, M. S., & Morgan, G. E. (2013). *Morgan and Mikhail's clinical anesthesiology* (5th edition / ed.). McGraw-Hill. https://proxy.mul.missouri.edu/login?url=http://www.accessmedicine.com/resourceTOC.aspx?resourceID=806

[10] Canbay, O., Celebi, N., Sahin, A., Celiker, V., Ozgen, S., & Aypar, U. (2008). Ketamine gargle for attenuating postoperative sore throat. *Br J Anaesth*, *100*(4), 490-493.

[11] Carlton, S., & Coggeshall, R. (1999). Inflammation-induced changes in peripheral glutamate receptor populations. *Brain research*, *820*(1-2), 63-70.

[12] Chan, L., Lee, M., & Lo, Y. (2010). Postoperative sore throat and ketamine gargle. *Br J Anaesth*, *105*(1), 97.

[13] Chinachoti, T., Pojai, S., Sooksri, N., & Rungjindamai, C. (2017). Risk factors of post-operative sore throat and hoarseness. *J Med Assoc Thai*, *100*(4), 463-468.

[14] Christensen, A. M., Willemoes-Larsen, H., Lundby, L., & Jakobsen, K. B. (1994). Postoperative throat complaints after tracheal intubation. *Br J Anaesth*, *73*(6), 786-787. https://doi.org/10.1093/bja/73.6.786

[15] El-Boghdadly, K., Bailey, C. R., & Wiles, M. D. (2016). Postoperative sore throat: a systematic review. *Anaesthesia*, *71*(6), 706-717. https://doi.org/10.1111/anae.13438

[16] Fenta, E., Teshome, D., Melaku, D., & Tesfaw, A. (2020). Incidence and factors associated with postoperative sore throat for patients undergoing surgery under general anesthesia with endotracheal intubation at Debre Tabor General Hospital, North central Ethiopia: A cross-sectional study. *International Journal of Surgery Open*, *25*, 1-5. https://doi.org/10.1016/j.ijso.2020.06.003

[17] Gemechu, B. M., Gebremedhn, E. G., & Melkie, T. B. (2017). Risk factors for postoperative throat pain after general anaesthesia with endotracheal intubation at the University of Gondar Teaching Hospital, Northwest Ethiopia, 2014. *Pan Afr Med J*, *27*, 127. https://doi.org/10.11604/pamj.2017.27.127.10566

[18] Green, S. M., & Krauss, B. (2004). Ketamine is a safe, effective, and appropriate technique for emergency department paediatric procedural sedation. *Emerg Med J*, *21*(3), 271-272. https://doi.org/10.1136/emj.2004.015370

[19] Harris, M., & Chung, F. (2013). Complications of general anesthesia. *Clin Plast Surg*, *40*(4), 503-513. https://doi.org/10.1016/j.cps.2013.07.001

[20] Irwin, R. S. (2006). Complications of cough: ACCP evidence-based clinical practice guidelines. *Chest*, *129*(1), 54S-58S.

[21] Islam, S., & Jain, P. (2004). Post-operative nausea and vomiting (PONV): A review article. *Indian Journal of Anaesthesia*, *48*(4), 253-258.

[22] Jaensson, M., Gupta, A., & Nilsson, U. G. (2012). Gender differences in risk factors for airway symptoms following tracheal intubation. *Acta Anaesthesiol Scand*, *56*(10), 1306-1313. https://doi.org/10.1111/j.1399-6576.2012.02771.x

[23] Jaensson, M., Olowsson, L. L., & Nilsson, U. (2010). Endotracheal tube size and sore throat following surgery: a randomized-controlled study. *Acta Anaesthesiol Scand*, *54*(2), 147-153. https://doi.org/10.1111/j.1399-6576.2009.02166.x

[24] Jain, S., Bendwal, H. P., Gohiya, S., Alwani, N., Pancholi, S., & Romday, R. (2017). Comparison of nebulized ketamine and ketamine with clonidine in postoperative sore throat. *International Surgery Journal*, *4*(5), 1579. https://doi.org/10.18203/2349-2902.isj20171515

[25] Kim, D., Jeon, B., Son, J. S., Lee, J. R., Ko, S., & Lim, H. (2015). The changes of endotracheal tube cuff pressure by the position changes from supine to prone and the flexion and extension of head. *Korean J Anesthesiol*, *68*(1), 27-31. https://doi.org/10.4097/kjae.2015.68.1.27

[26] Klainer, A. S., Turndorf, H., Wu, W.-H., Maewal, H., & Allender, P. (1975). Surface alterations due to endotracheal intubation. *The American journal of medicine*, *58*(5), 674-683.

[27] Kuriyama, A., Nakanishi, M., Kamei, J., Sun, R., Ninomiya, K., & Hino, M. (2020). Topical application of ketamine to prevent postoperative sore throat in adults: A systematic review and meta-analysis. *Acta Anaesthesiol Scand*, *64*(5), 579-591. https://doi.org/10.1111/aas.13553

[28] Larson, P. C. (1998). Laryngospasm-the best treatment. *The Journal of the American Society of Anesthesiologists, 89*(5), 1293-1294.

[29] Lee, J. Y., Sim, W. S., Kim, E. S., Lee, S. M., Kim, D. K., Na, Y. R., . . . Park, H. J. (2017). Incidence and risk factors of postoperative sore throat after endotracheal intubation in Korean patients. *J Int Med Res*, *45*(2), 744-752. https://doi.org/10.1177/0300060516687227

[30] Liu, J., Zhang, X., Gong, W., Li, S., Wang, F., Fu, S., . . . Hang, Y. (2010). Correlations between controlled endotracheal tube cuff pressure and postprocedural complications: a multicenter study. *Anesth Analg*, *111*(5), 1133-1137. https://doi.org/10.1213/ANE.0b013e3181f2ecc7

[31] Luria, J. W., Gonzalez-del-Rey, J. A., DiGiulio, G. A., McAneney, C. M., Olson, J. J., & Ruddy, R. M. (2001). Effectiveness of oral or nebulized dexamethasone for children with mild croup. *Archives of pediatrics & adolescent medicine*, *155*(12), 1340-1345.

[32] Macario, A., Weinger, M., Truong, P., & Lee, M. (1999). Which clinical anesthesia outcomes are both common and important to avoid? The perspective of a panel of expert anesthesiologists. *Anesthesia & Analgesia*, *88*(5), 1085-1091.

[33] Mazzone, S. B. (2005). An overview of the sensory receptors regulating cough. *Cough, 1*, 2. https://doi.org/10.1186/1745-9974-1-2

[34] Minonishi, T., Kinoshita, H., Hirayama, M., Kawahito, S., Azma, T., Hatakeyama, N., & Fujiwara, Y. (2013). The supine-to-prone position change induces modification of endotracheal tube cuff pressure accompanied by tube displacement. *J Clin Anesth*, *25*(1), 28-31. https://doi.org/10.1016/j.jclinane.2012.05.007

[35] Monroe, M. C., Gravenstein, N., & Saga-Rumley, S. (1990). Postoperative sore throat: effect of oropharyngeal airway in orotracheally intubated patients. *Anesth Analg*, *70*(5), 512-516.

[36] Morrow, G. R. (1984). The assessment of nausea and vomiting: past problems, current issues, and suggestions for future research. *Cancer*, *53*, 2267-2278.

[37] Mostafa, R. H., Saleh, A. N., & Hussein, M. M. (2018). A Comparative Study of Three Nebulized Medications for the Prevention of Postoperative Sore Throat in the Pediatric Population. *The Open Anesthesia Journal*, *12*(1), 85-93. https://doi.org/10.2174/2589645801812010085

[38] Orji, M., Osinaike, B., Amanor-Boadu, S., & Ugheoke, A. (2020). Nebulized magnesium versus ketamine for prevention of postoperative sore throat in patients for general anaesthesia. *Annals of Ibadan Postgraduate Medicine*, *18*(1), 3-8.

[39] Piriyapatsom, A., Dej-Arkom, S., Chinachoti, T., Rakkarnngan, J., & Srishewachart, P. (2013). Postoperative sore throat: incidence, risk factors, and outcome. *J Med Assoc Thai*, *96*(8), 936-942.

[40] Rajan, S., Malayil, G. J., Varghese, R., & Kumar, L. (2017). Comparison of Usefulness of Ketamine and Magnesium Sulfate Nebulizations for Attenuating Postoperative Sore Throat, Hoarseness of Voice, and Cough. *Anesthesia, essays and researches*, *11*(2), 287-293. https://doi.org/10.4103/0259-1162.181427

[41] Ramsay, M., Savege, T., Simpson, B., & Goodwin, R. (1974). Controlled sedation with alphaxalone-alphadolone. *Br med J*, *2*(5920), 656-659.

[42] Salama, A., & El-badawy, A. (2016). Does nebulized dexamethasone decrease the incidence of postextubation sore throat?: a randomized controlled study. *Ain-Shams Journal of Anaesthesiology*, *9*(1), 104. https://doi.org/10.4103/1687-7934.178888

[43] Segaran, S., Bacthavasalame, A. T., Venkatesh, R. R., Zachariah, M., George, S. K., & Kandasamy, R. (2018). Comparison of Nebulized Ketamine with Nebulized Magnesium Sulfate on the Incidence of Postoperative Sore Throat. *Anesthesia, essays and researches*, *12*(4), 885-890. https://doi.org/10.4103/aer.AER_148_18

[44] Select Statistical Services. (2021). *Comparing Two Proportions – Sample Size*. https://select-statistics.co.uk/calculators/sample-size-calculator-two-proportions/

[45] Shaikh, S. I., Nagarekha, D., Hegade, G., & Marutheesh, M. (2016). Postoperative nausea and vomiting: A simple yet complex problem. *Anesthesia, essays and researches*, *10*(3), 388-396. https://doi.org/10.4103/0259-1162.179310

[46] Shekhar, S., Gupta, A., Gunjan, Gupta, S., & Singh, K. (2019). Comparison of Nebulized Ketamine and Ketamine with Clonidine in Postoperative Sore Throat. *Anesthesia, essays and researches*, *13*(2), 313-316. https://doi.org/10.4103/aer.AER_19_19

[47] Sinner, B., & Graf, B. (2008). Ketamine. *Modern anesthetics*, 313-333.

[48] Sounak Paul, Richa Gangwar, & Pratap, K. M. (2019). Comparative Evaluation of Efficacy of Nebulised Budesonide with Nebulised Dexamethasone in Reducing Post-operative Sore Throat in Patients undergoing Elective Lumbar Spine Surgery in Prone Position. *Journal of Clinical Anesthesiology: Open Access*, *3*, 111.

[49] Thomas, D., Bejoy, R., Zabrin, N., & Beevi, S. (2018). Preoperative ketamine nebulization attenuates the incidence and severity of postoperative sore throat: A randomized controlled clinical trial. *Saudi J Anaesth*, *12*(3), 440-445. https://doi.org/10.4103/sja.SJA_47_18

[50] Thomas, D., Chacko, L., & Raphael, P. O. (2020). Dexmedetomidine nebulisation attenuates post-operative sore throat in patients undergoing thyroidectomy: A randomised, double-blind, comparative study with nebulised ketamine. *Indian J Anaesth*, *64*(10), 863-868. https://doi.org/10.4103/ija.IJA_406_20

[51] Tom E. Peck, & Sue Hill. (2008). <*pharmacology-for-anaesthesia-and-intensive-care-3rd-ed.pdf*> (3rd ed.). Cambridge University Press.

[52] Viby-Mogensen, J., Engbaek, J., Eriksson, L., Gramstad, L., Jensen, E., Jensen, F., . . . Østergaard, D. (1996). Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents. *Acta Anaesthesiol Scand*, *40*(1), 59-74.

[53] Wang, J.-J., Ho, S.-T., Tzeng, J.-I., & Tang, C.-S. (2000). The effect of timing of dexamethasone administration on its efficacy as a prophylactic antiemetic for postoperative nausea and vomiting. *Anesthesia & Analgesia*, *91*(1), 136-139.

[54] Yentis, S. M., & Lee, D. J. (1998). Evaluation of an improved scoring system for the grading of direct laryngoscopy. *Anaesthesia*, *53*(11), 1041-1044. https://doi.org/10.1046/j.1365-2044.1998.00605.x

[55] Yu, J., Ren, L., Min, S., Yang, Y., & Lv, F. (2020). Nebulized pharmacological agents for preventing postoperative sore throat: A systematic review and network meta-analysis. *PLoS One*, *15*(8), e0237174. https://doi.org/10.1371/journal.pone.0237174

Appendices

Appendix A

Consent form

موافقة على الاشتراك في البحث العلمي

اسم الباحث: محمد مفيد يوسف محمود– طالب ماجستير تمريض التخدير.

مشرف على البحث د. نور المصري– أخصائي طب تخدير

جامعة النجاح الوطنية

عنوان البحث:التأثير الوقائيلتبخيرة الكيتامين مقابل تبخيرة الديكساميثازون قبل العملية على التهاب الحلق ما بعد الجراحة لدى المرضى الذين يخضعوا لجراحة مبرمجة تحت تأثير التخدير العام. تجربة عشوائية مزدوجة التعمية خاضعة للتحكم الوهمي.

أنت مدعو/ة للمشاركة في بحث علمي سريري, خذ الوقت الكافي لقراءة المعلومات التالية بتأنّي قبل اتخاذ قرار المشاركة.

بإمكانك/ي طلب أي إيضاحات أو معلومات اضافية عن أي شيء مذكور في هذه الاستمارة أو عن هذه الدراسة ككل من الباحث.

عند التخدير العام يتم إدخال أنبوب إلى القصبة الهوائية للمحافظة على عملية التنفس وهذا الأنبوب له تأثيرات جانبية بالعادة.

الهدف من البحث/ تقليل التأثيرات الجانبية لهذا الأنبوب بعد العملية.

في حال وافقت على المشاركة في هذه الدراسة سيبقى اسمك في طي الكتمان ولن يكون لأي شخص –ما لم ينص القانون على ذلك– حق الاطلاع على ملفك الطبي باستثناء الباحث والطبيب المشرف على الدراسة ومشرف الدراسة من جامعة النجاح الوطنية.

موافقة الباحث

لقد شرحت بالتفصيل للمشترك في البحث الطبي السيد/ة:----------
-------- طبيعة البحث ومجرياته وآثاره السلبية. ولقد أجبت على كل أسئلته بوضوح تام.

الباحث:الطبيب:

موافقة المشترك

لقد قرأت استمارة القبول هذه وفهمت مضمونها وتمت الإجابة على أسئلتي جميعها, و بناءً عليه فأنني حراً ومختاراً أجيز إجراء هذا البحث وأوافق على الاشتراك فيه, وإني أعلم أن الباحث والطبيب سيكونان مستعدين للإجابة عن أسئلتي, وانه باستطاعتي الاتصال بهم على الرقم 0592077979, كما أنني اعرف تمام المعرفة بأن لي الحق في الانسحاب من الدراسة في أي وقت بعد توقيع الموافقة ودون الاضطرار لتقديم أي سبب او عذر, ولن يؤثر هذا على الخدمة الطبية المقدمة لي, واعلم أيضا أنني سوف احصل على نسخة طبق الأصل من هذه الموافقة.

اسم المشترك في البحث:----------

التوقيع:----------

التاريخ:----------

Appendix B

Data sheet

Demographic data

Date: _____ Participant number: _____ Hospital file number: _____

Type of surgery: _____

Age: _____ Gender: _____ Weight[kg]: _____

Height[cm]: _____ BMI: _____

-The participant randomized scheduled group according to his number:

Saline: ( ) Dexamethasone group: ( ) Ketamine: ( )

(History)

-PMHx: _____

-PSHx: _____

-Medications Hx: _____

-Smoking: Yes ( ) No ( ).

If yes, How many cigarette in a day: _____

How many year you have been smoking: _____

Did you stopped the smoking before the surgery: _____

-Allergy for:- Drugs: _____ Foods: _____

Others: _____

(Before entering the operation room phase)

-ECG rhythm: _____

-Have you ever been anesthetized before: Yes ( ) No ( ).

-If yes, what type was it: _____

-Have you faced any problems: _____

-ASA class: I ( ) II ( ).

-Mallampati score: 1 ( ) 2 ( ).

-Hemodynamic status and VS:

Time	NIBP mmHg	HR Beat/min	RR Breath/min	SpO2%
Before nebulization				
During nebulization at 5 min				
During nebulization at 10 min				
During nebulization at 15 min				

-Hallucination and psychotomimetic reaction effect notation after nebulization:

Side effect	Exist	Doesn't exist	Note
Hallucination			Its type:
Respiratory depression			
Agitation			
Flashbacks			
Anxiety			
Chest pain			
Palpitation			
Delirium			
Dystonia			
Psychosis			
Dizziness			
Seizures			
Paranoia			
Schizophrenic-like symptoms			

Muscle hypertonicity			
Transient clonus			
Hypersalivation			
Hyperreflexia			
Transient rash			
Nausea			Its grade:
Tachycardia			
HTN			
Pulmonary edema			
Decreased awareness			
Distractibility			
Feelings of invulnerability			
Disorientation			
Impaired thought processes			
Laryngospasm			
Sedation			
Stridor			

(Intra operation room phase)

-Laryngoscope blade size: _____

-ETT size: _____

-The air way performer work experience: _____

-Intubation attempts number: _____

-**The used medications during the operation:**

Time in minutes	Medication/Dose	Inhalation agent/MAC	Note
0-15			
15-30			
30-45			
45-60			
60-75			
75-90			
90-105			
105-120			

-**Laryngoscopy view , (showed in fig.1):**

( ) 1 = Full view of glottis.

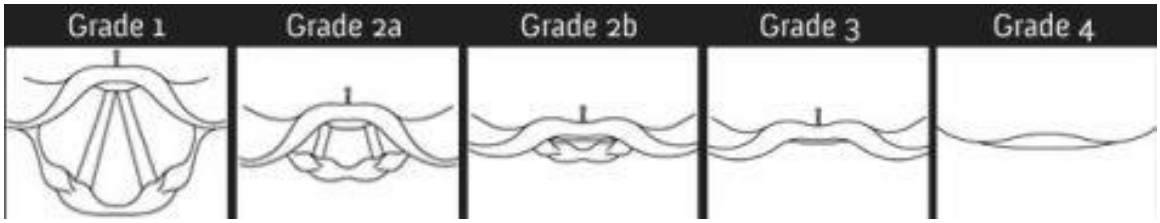
( )2a = Partial view of glottis.

( ) 2b = Only posterior extremity of glottis seen or only arytenoid cartilages.

( ) 3 = Only epiglottis seen, none of glottis seen.

( ) 4 = Neither glottis nor epiglottis seen.

Fig.1



-Endotracheal intubation condition, (showed in fig.2):

1-jaw relaxation. Excellent: ( ) Good: ( ) Poor: ( ).

2-perceived resistance to the laryngoscopy blade.Excellent:( ) Good:( ) Poor:( ).

3-position of the vocal cords. Excellent: ( ) Good: ( ) Poor: ( ).

4-residual movement of the vocal cords. Excellent: ( ) Good: ( ) Poor: ( ).

5-coughing in response to intubation. Excellent: ( ) Good: ( ) Poor: ( ).

6-limb movement in reaction to intubation. Excellent: ( ) Good: ( ) Poor: ( ).

Each of these variables will be rated as excellent, good or poor. Intubating conditions were excellent if all variables were excellent, they were good if all variables were good or excellent and they were poor if any variable was poor, it showed in Fig.2 in the appendixes.

Fig.2

	Excellent	Good	Poor
Jaw relaxation	relaxed	relaxed	poor relaxation
Resistance to laryngoscope	none	slight resistance	active resistance
Vocal cord position	abducted	intermediate	closed
Vocal cord movement	none	moving	closing
Limb movement	none	slight	vigorous
Diaphragmatic reaction	none	diaphragm	sustained coughing

-Occurrence of laryngospasm:

Before induction: Yes ( ) No ( ).

After extubation: Yes ( ) No ( ).

-Intracuffpressure every 15 min:

Time	Pressure [cmH2O]
0	
15 min	
30 min	
45 min	
60 min	
75 min	
90 min	
105 min	
120 min	

-Initial volume inserted in cuff: _____

-Final volume withdrawal from cuff: _____

-Anesthesia duration [from induction until first spontaneous breathing]:

_____min

-Surgical duration [from first incision until final suture]: _____min

-Visible blood stains in the tube: Yes ( ) No ( )

-Use of NG tube: Yes ( ) No ( )

-Changing in patient position from supine position to prone position even without moving or flexing his head and neck: Yes ( ) No ( )

-**Hemodynamic status and VS during operation:**

TIME	ECG monitor	NIBP	HR	ETCO2	RR	Temp	SpO2	MAP
Before anesthesia induction								
After in induction at 0 min								
At 15 min								
At 30 min								
At 45 min								
At 60 min								
At 75 min								

At 90 min								
At 105 min								
At 120 min								

(Emergence Phase)

-Hemodynamic status and VS every 3 min from first spontaneous breathing until transfer to PACU:

TIME	NIBP	HR	Sat	RR	EtCO2	TV	MAP
0 min							
3 min							
6 min							
9 min							
12 min							
15 min							
18 min							

-Time from first spontaneous breathing until Extubation: _____min

-Hallucination and psychotomimetic reaction effect notation during the emergence phase and after extubation:

Side effect	Exist	Doesn't exist	Note
Hallucination			Its type:
Respiratory depression			
Agitation			
Flashbacks			
Anxiety			
Chest pain			
Palpitation			
Delirium			
Dystonia			
Psychosis			
Dizziness			
Seizures			
Paranoia			
Schizophrenic-like symptoms			
Muscle hypertonicity			
Transient clonus			
Hypersalivation			
Hyperreflexia			
Transient rash			
Nausea			Its grade:
Tachycardia			
HTN			
Pulmonary edema			
Decreased awareness			
Distractibility			

Feelings of invulnerability			
Disorientation			
Impaired thought processes			
Laryngospasm			
Sedation			
Stridor			

-Vomiting after extubation:

Yes ( ) No ( ).

If yes how many time: _____

-Cough after extubation:

Yes ( ) No ( ).

If yes how many time: _____

-Head tilt support after extubation duration: _____sec

(PACU phase)

-Hemodynamic status and VS two times in PACU:

Time	NIBP	HR	RR	SpO2	Temp	MAP
1						
2						

-Occurrence of laryngospasm in the PACU:

Yes ( ) No ( ).

-Duration of PACU: _____

-Medication given in PACU: _____

-POST, cough, Hoarseness and PONV in PACU:

Time	POST grade (0-3)	Cough grade (0-3)	Hoarseness grade (0-3)	Nausea grade (0-6)	Vomiting frequency
After full consciousness in the PACU					

Sore throat: (0) No sore throat, (1) Mild sore throat (complains of sore throat only on asking), (2) Moderate sore throat (complains of sore throat on his/her own), (3) Severe sore throat (change of voice or hoarseness, associated with throat pain).

Cough: (0) = No cough at any time since the operation, (1) = Minimal cough or scratchy throat, (2) = Moderate cough (like what is seen in common cold), (3) = Severe cough (more than what is seen in common cold).

Hoarseness: (0) = No complaint of hoarseness at any time since the operation, (1) = Minimal (minimal change in quality of speech, patient answers in the affirmative only when enquired about), (2) = moderate (moderate change in quality of speech of which the patient complains on his own), (3) = Sever (gross change in the quality of voice perceived by the observer).

Nausea: (0) = No nausea, (1) = Very mild, (2) = Mild, (3) = Moderate, (4) = Severe, (5) = Very severe, (6) = Intolerable.

(Ward phase)

-Hemodynamic status and VS:

Time	NIBP	HR	RR	Sat	Temp	MAP
1 hr						
8 hr						

-Sedation 1 hour after extubation:

( ) 1 = Awake; agitated or restless or both.

( ) 2 = Awake; Cooperative, oriented, and tranquil.

( ) 3 = Awake but respond to commands only.

( ) 4 = Asleep; brisk response to light glabellar tap or loud auditory stimulus.

( ) 5 = Asleep; sluggish response to light glabellar tap or loud auditory stimulus.

( ) 6 = Asleep; no response to glabellar tap or loud auditory stimulus.

-Patient satisfaction from 0 to 10:

0 as no satisfaction and 10 as the greatest satisfaction: _____

-POST, cough, Hoarseness and PONV in the ward:

Time	POST grade (0-3)	Cough grade (0-3)	Hoarseness grade (0-3)	PONV grade (0-6)	Vomiting frequency
0 hr					
2 hr					
4 hr					
6 hr					
8 hr					
12 hr					
24 hr					

Sore throat: (0) No sore throat, (1) Mild sore throat (complains of sore throat only on asking), (2) Moderate sore throat (complains of sore throat on his/her own), (3) Severe sore throat (change of voice or hoarseness, associated with throat pain).

Cough: (0) = No cough at any time since the operation, (1) = Minimal cough or scratchy throat, (2) = Moderate cough (like what is seen in common cold), (3) = Severe cough (more than what is seen in common cold).

Hoarseness: (0) = No complaint of hoarseness at any time since the operation, (1) = Minimal (minimal change in quality of speech, patient answers in the affirmative only when enquired about), (2) = moderate (moderate change in quality of speech of which

the patient complains on his own), (3) = Sever (gross change in the quality of voice perceived by the observer).

Nausea: (0) = No nausea, (1) = Very mild, (2) = Mild, (3) = Moderate, (4) = Severe, (5) = Very severe, (6) = Intolerable.

Appendix C

Tables of Study

Table C.1

Distribution of patients' demographic data and history

Variable	Values	Frequency	Percentage
Age	Up to 25 years old	23	23.2%
	26 – 35 years old	24	24.2%
	36 – 45 years old	18	18.2%
	Older than 45 years old	34	34.3%
Gender	Male	51	51.5%
	Female	48	48.5%
Body Mass Index	Underweight (< 18.5)	8	8.1%
	Normal weight (18.5 – 24.9)	45	45.5%
	Overweight (25 – 29.9)	33	33.3%
	Obese (30 and more)	13	13.1%
Past medical history	Present	6	6.1%
	Absent	93	93.9%
Past surgical history	Present	36	36.4%
	Absent	63	63.6%
Medication history	Present	3	3.0%
	Absent	96	97.0%
Smoking	Yes	27	27.3%
	No	72	72.7%
Stopped smoking before operation	Yes	18	18.2%
	No	9	9.1%
Having allergies	Drug	6	6.1%
	Food	0	0.0%
	Others	0	0.0%

Table C.2

Distribution of preoperative information of the patients

Variable	Values	Frequency	Percentage
ECG rhythm	Normal sinus rhythm	99	100%
Been anesthetized before	Yes	51	51.5%
	No	48	48.5%
ASA classification	One	93	93.9%
	Two	6	6.1%
Mallampati score	One	69	69.7%
	Two	30	30.3%

Table C.3

Descriptive statistics of the pre- and post-nebulizer hemodynamics among the patients preoperatively

Hemodynamics	Mean		St. Dev.		Minimum		Maximum	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
SBP	117.88	121.09	12.26	10.76	80	104	150	154
DBP	72.15	74.48	9.50	8.84	54	51	92	92
HR	76.21	78.30	8.32	11.25	60	57	101	105
RR	14.73	14.88	1.32	1.28	11	13	17	17
SpO2	98.42	98.64	1.29	1.18	95	96	100	100

Table C.4

Differences in pre- and post-nebulizers hemodynamic among all patients

Hemodynamic reading	Mean difference (pre – post)	St. Dev.	p-value
SBP	-3.212	6.905	< 0.001
DBP	-2.333	4.764	< 0.001
HR	-2.091	7.325	0.005
RR	-0.152	0.787	0.058
SpO2	-0.212	1.043	0.046

Table C.5

Differences in mean post-nebulizer SBP between study groups

Group	Number	Mean post-nebulizer SBP	St. Dev.	p-value
Saline	33	115.364	8.139	< 0.001
Dexamethasone	33	120.727	8.928	
Ketamine	33	127.182	11.593	
Total	99	121.091	10.730	

Table C.6

Post Hoc multiple comparison for the differences post-nebulizer SBP

Dependent variable	Group (I)	Group (J)	Mean difference	p-value
post-nebulizer SBP	Saline	Dexamethasone	-5.364	0.026
		Ketamine	-11.818	< 0.001
	Dexamethasone	Saline	5.364	0.026
		Ketamine	-6.455	0.008
	Ketamine	Saline	11.818	< 0.001
		Dexamethasone	6.455	0.008

Table C.7

Differences in mean post-nebulizer DBP between study groups

Group	Number	Mean post-nebulizer DBP	St. Dev.	p-value
Saline	33	71.909	5.784	0.060
Dexamethasone	33	74.545	8.367	
Ketamine	33	77.000	10.843	
Total	99	74.485	8.749	

Table C.8

Differences in mean post-nebulizer HR between study groups

Group	Number	Mean post-nebulizer HR	St. Dev.	p-value
Saline	33	74.182	9.050	0.020
Dexamethasone	33	79.091	11.153	
Ketamine	33	81.636	11.979	
Total	99	78.303	11.130	

Table C.9

Post Hoc multiple comparison for the differences post-nebulizer HR

Dependent variable	Group (I)	Group (J)	Mean difference	p-value
post-nebulizer HR	Saline	Dexamethasone	-4.909	0.068
		Ketamine	-7.455	0.006
	Dexamethasone	Saline	4.909	0.068
		Ketamine	-2.545	0.341
	Ketamine	Saline	7.455	0.006
		Dexamethasone	2.545	0.341

Table C.10

Differences in mean post-nebulizer RR between study groups

Group	Number	Mean post-nebulizer RR	St. Dev.	p-value
Saline	33	14.364	0.783	0.001
Dexamethasone	33	15.091	1.011	
Ketamine	33	15.182	0.950	
Total	99	14.879	0.982	

Table C.11

Post Hoc multiple comparison for the differences post-nebulizer RR

Dependent variable	Group (I)	Group (J)	Mean difference	p-value
post-nebulizer RR	Saline	Dexamethasone	-0.727	0.002
		Ketamine	-0.818	< 0.001
	Dexamethasone	Saline	0.727	0.002
		Ketamine	-0.091	0.689
	Ketamine	Saline	0.818	< 0.001
		Dexamethasone	0.091	0.689

Table C.12

Differences in mean post-nebulizer SpO2 between study groups

Group	Number	Mean post-nebulizer SpO2	St. Dev.	p-value
Saline	33	97.636	1.245	< 0.001
Dexamethasone	33	98.909	1.011	
Ketamine	33	99.364	0.994	
Total	99	98.636	1.305	

Table C. 13

Post Hoc multiple comparison for the differences post-nebulizer SpO2

Dependent variable	Group (I)	Group (J)	Mean difference	p-value
post-nebulizer SpO2	Saline	Dexamethasone	-1.273	< 0.001
		Ketamine	-1.727	< 0.001
	Dexamethasone	Saline	1.273	< 0.001
		Ketamine	-0.455	0.093
	Ketamine	Saline	1.727	< 0.001
		Dexamethasone	0.455	0.093

Table C.14

Information related to intraoperative phase

Variable	Values		Frequency		Percentage	
Laryngoscope blade size	Three		99		100%	
Endotracheal tube size (internal diameter)	7.0 mm		36		36.4%	
	7.5 mm		30		30.3%	
	8.0 mm		30		30.3%	
	8.5 mm		3		3.0%	
Intubation performer experience	One year or less		21		21.2%	
	2 – 5 years		63		63.6%	
	More than 5 years		15		15.1%	
Intubation attempts number	One attempt		99		100.0%	
Laryngoscope view	1		39		39.4%	
	2a		54		54.5%	
	2b		3		3.0%	
	3		3		3.0%	
Endotracheal intubation condition	Excellent		Good		Poor	
	F	%	F	%	F	%
Jaw relaxation	78	78.8%	21	21.2%	0	0.0%
Perceived resistance to blade	48	48.5%	51	51.5%	0	0.0%
Position of the vocal cord	90	90.9%	9	9.1%	0	0.0%
Vocal cord residual movement	93	93.9%	6	6.1%	0	0.0%
Coughing in response to intubation	93	93.9%	6	6.1%	0	0.0%
Limb movement in response to intubation	93	93.9%	6	6.1%	0	0.0%
Occurrence of laryngospasm	Yes		No			
	F	%	F	%		
Before induction	0	0.0%	99	100%		
After extubation	0	0.0%	99	100%		
Intracuff pressure every 15 minutes	22 mmHg	23 mmHg	24 mmHg	25 mmHg		
Zero-minute	0	48	45	6		
15 minutes	6	45	45	3		
30 minutes	9	60	27	3		
45 minutes	24	57	15	3		
60 minutes	24	55	17	3		
Change in intracuff volume	Change	Frequency	Percentage			
	Kept the same	84	84.8%			
	Decreased	15	15.2%			
Operative durations	Mean	St. Dev.	Minimum	Maximum		
Anesthesia duration (minutes)	56.66	12.27	20	95		
Surgical duration (minutes)	48.48	15.66	20	120		
Other incidences	Options	Frequency	Percentage			
Visible blood stain in tube	Yes	0	0.0%			
	No	99	100%			
Use of NG tube	Yes	9	9.1%			
	No	90	90.9%			
Changing of position from supine to prone without head or neck flexion	Yes	0	0%			
	No	99	99%			
Post-extubation events	Vomiting	0	0.0%			
	Cough	27	27.3%			

Table C. 15

Difference in laryngoscope view between study groups

Group	Laryngoscope view				Total	Chi-Square	p-value
	1	2a	2b	3			
Saline	3 (9.1%)	27 (81.8%)	3 (9.1%)	0 (0.0%)	33 (100%)	42.077	< 0.001
Dexamethasone	12 (36.4%)	21 (63.6%)	0 (0.0%)	0 (0.0%)	33 (100%)		
Ketamine	24 (72.7%)	6 (18.2%)	0 (0.0%)	3 (9.1%)	33 (100%)		
Total	39 (39.4%)	54 (54.5%)	3 (3.0%)	3 (3.0%)	99 (100%)		

Table C.16

Difference in intubation condition between study groups

Group	Intubation condition			Total	Chi-Square	p-value
	Excellent	Good	Poor			
Saline	12 (36.4%)	21 (63.6%)	0 (0.0%)	33 (100%)	20.842	< 0.001
Dexamethasone	6 (18.2%)	27 (81.8%)	0 (0.0%)	33 (100%)		
Ketamine	24 (72.7%)	9 (27.3%)	0 (0.0%)	33 (100%)		
Total	42 (42.4%)	57 (57.6%)	0 (0.0%)	99 (100%)		

Table C.17

Descriptive statistics of the pre- and post-anesthesia induction hemodynamics among the patients intraoperatively.

Hemodynamics	Mean		St. Dev.		Minimum		Maximum	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
SBP (mmHg)	119.21	111.75	8.09	10.52	101	88	141	132
DBP (mmHg)	71.00	68.39	8.18	10.26	52	49	89	88
HR (bpm)	80.24	79.12	9.05	9.24	60	59	97	98
EtCO2 (mmHg)	-	33.96	-	3.78	-	22	-	41
RR (breath/min)	14.42	12.68	1.55	1.96	11	10	18	21
Temp	36.49	36.37	0.15	0.15	36	36	37	37
SpO2	98.96	99.60	0.92	0.60	97	98	100	100

Table C.18

Differences in mean post-intubation SBP between study groups

Group	Number	Mean post-intubation SBP	St. Dev.	p-value
Saline	33	111.545	9.579	0.918
Dexamethasone	33	111.364	13.179	
Ketamine	33	112.364	8.034	
Total	99	111.758	10.389	

Table C.19

Differences in mean post-intubation DBP between study groups

Group	Number	Mean post-intubation DBP	St. Dev.	p-value
Saline	33	71.000	8.800	0.001
Dexamethasone	33	63.000	9.731	
Ketamine	33	71.182	10.144	
Total	99	68.394	10.223	

Table C.20

Post Hoc multiple comparison for the differences post-intubation DBP

Dependent variable	Group (I)	Group (J)	Mean difference	p-value
post-intubation DBP	Saline	Dexamethasone	8.000	0.001
		Ketamine	-0.182	0.939
	Dexamethasone	Saline	-8.000	0.001
		Ketamine	-8.182	0.001
	Ketamine	Saline	0.182	0.939
		Dexamethasone	8.182	0.001

Table C. 21

Differences in mean post-intubation HR between study groups

Group	Number	Mean post-intubation HR	St. Dev.	p-value
Saline	33	77.909	7.800	0.047
Dexamethasone	33	82.273	8.991	
Ketamine	33	77.182	9.796	
Total	99	79.121	9.094	

Table C.22

Post Hoc multiple comparison for the differences post-intubation HR

Dependent variable	Group (I)	Group (J)	Mean difference	p-value
post-intubation HR	Saline	Dexamethasone	-4.364	0.049
		Ketamine	0.727	0.741
	Dexamethasone	Saline	4.364	0.049
		Ketamine	5.091	0.022
	Ketamine	Saline	-0.727	0.741
		Dexamethasone	-5.091	0.022

Table C. 23

Differences in mean post-intubation EtCO2 between study groups

Group	Number	Mean post-intubation EtCO2	St. Dev.	p-value
Saline	33	35.091	4.095	0.015
Dexamethasone	33	32.545	3.833	
Ketamine	33	34.273	2.601	
Total	99	33.970	3.691	

Table C.24

Post Hoc multiple comparison for the differences post-intubation EtCO2

Dependent variable	Group (I)	Group (J)	Mean difference	p-value
post-intubation EtCO2	Saline	Dexamethasone	2.545	0.005
		Ketamine	0.818	0.354
	Dexamethasone	Saline	-2.545	0.005
		Ketamine	-1.727	0.052
	Ketamine	Saline	-0.818	0.354
		Dexamethasone	1.727	0.052

Table C.25

Differences in mean post-intubation RR between study groups

Group	Number	Mean post-intubation RR	St. Dev.	p-value
Saline	33	12.636	0.895	0.973
Dexamethasone	33	12.727	2.335	
Ketamine	33	12.727	1.941	
Total	99	12.697	1.810	

Table C.26

Differences in mean post-intubation temperature between study groups

Group	Number	Mean post-intubation temperature	St. Dev.	p-value
Saline	33	36.409	0.080	0.009
Dexamethasone	33	36.309	0.196	
Ketamine	33	36.400	0.130	
Total	99	36.373	0.149	

Table C.27

Post Hoc multiple comparison for the differences post-intubation temperature

Dependent variable	Group (I)	Group (J)	Mean difference	p-value
post-intubation temperature	Saline	Dexamethasone	0.100	0.006
		Ketamine	0.009	0.797
	Dexamethasone	Saline	-0.100	0.006
		Ketamine	-0.091	0.012
	Ketamine	Saline	-0.009	0.797
		Dexamethasone	0.091	0.012

Table C.28

Differences in mean post-intubation SpO2 between study groups

Group	Number	Mean post-intubation SpO2	St. Dev.	p-value
Saline	33	99.455	0.794	0.037
Dexamethasone	33	99.818	0.392	
Ketamine	33	99.545	0.506	
Total	99	99.606	0.603	

Table C.29

Post Hoc multiple comparison for the differences post-intubation SpO2

Dependent variable	Group (I)	Group (J)	Mean difference	p-value
post-intubation SpO2	Saline	Dexamethasone	-0.364	0.014
		Ketamine	-0.091	0.532
	Dexamethasone	Saline	0.364	0.014
		Ketamine	0.273	0.063
	Ketamine	Saline	0.091	0.532
		Dexamethasone	-0.273	0.063

Table C.30

Descriptive statistics of the hemodynamics among the patients in the PACU phase

Hemodynamics	Mean	St. Dev.	Minimum	Maximum
SBP (mmHg)	119.51	9.01	103	146
DBP (mmHg)	73.93	8.45	59	92
HR (bpm)	78.18	7.37	65	101
RR (breath/min)	14.54	0.90	14	16
SpO2	98.63	1.10	96	100
Temp	36.29	0.21	36.0	36.6

Table C.31

Distribution of POST, cough, hoarseness and PONV in the PACU after full consciousness

Event	Grade: Freq. (%)				
	0	1	2	3	4
POST grade	48 (48.5%)	33 (33.3%)	18 (18.2%)	0 (0.0%)	-
Cough grade	66 (66.7%)	21 (21.2%)	12 (12.1%)	0 (0.0%)	-
Hoarseness grade	54 (54.5%)	30 (30.3%)	15 (15.2%)	0 (0.0%)	-
Nausea grade	69 (69.7%)	12 (12.1%)	9 (9.1%)	3 (3.0%)	6 (6.1%)
Vomiting (frequency)	96 (7.0%)	3 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table C.32

Descriptive statistics of the hemodynamics among the patients in the ward phase

Hemodynamics	Mean	St. Dev.	Minimum	Maximum
SBP (mmHg)	119.12	8.62	106	136
DBP (mmHg)	72.93	6.84	61	86
HR (bpm)	75.34	5.37	64	89
RR (breath/min)	14.71	1.27	13	17
SpO2	98.53	0.96	95	100
Temp	36.49	0.16	36.1	36.8

Table C.33

Distribution of 1-hour after extubation sedation scale and 10-point patient satisfaction

Variable	Values	Frequency	Percentage
Sedation 1-hour after extubation (out of 6)	1 (agitated)	24	24.2%
	2 (cooperative)	75	75.8%
Patient satisfaction (out of 10)	5	12	12.1%
	6	9	9.2%
	7	39	39.4%
	8	36	36.4%
	9	3	3.0%

Table C.34

Frequency of POST, cough, hoarseness and PONV of the patients in the ward phase in the first 24 hours.

Event	Grades	Time frame						
		0-hour	2-hour	4-hour	6-hour	8-hour	12-hour	24-hour
POST	0	24	33	42	63	87	87	99
	1	45	48	45	36	12	12	0
	2	30	18	12	0	0	0	0
Cough	0	45	69	90	99	99	99	99
	1	42	24	9	0	0	0	0
	2	12	6	0	0	0	0	0
Hoarseness	0	33	51	63	81	96	96	96
	1	45	39	33	18	3	3	3
	2	21	9	3	0	0	0	0
Nausea	0	51	60	81	81	90	99	99
	1	18	18	6	18	9	0	0
	2	18	12	12	0	0	0	0
	3	6	3	0	0	0	0	0
	4	6	6	0	0	0	0	0
Vomit freq.	0	90	93	99	99	99	99	99
	1	9	6	0	0	0	0	0

Table C.35

Differences in overall ward events between study groups according to ANOVA test (higher mean indicates higher incidence of the event during the first 24 hours)

Event	Group						p-value
	Saline		Dexamethasone		Ketamine		
	Mean	SD	Mean	SD	Mean	SD	
POST	6.363	1.997	2.272	1.625	1.000	1.145	< 0.001
Cough	1.454	1.855	1.636	0.783	0.272	0.875	< 0.001
Hoarseness	3.272	2.565	2.091	1.809	1.000	1.984	< 0.001
Nausea	3.636	4.182	2.091	3.075	1.182	2.364	0.011

Table C.36

Correlation between patient's age and ward events

Dependent variable	Correlation with age	
	Pearson correlation value	p-value
POST	0.182	0.072
Cough	-0.024	0.814
Hoarseness	0.005	0.814
PONV	-0.291	0.004

Table C.37

Differences in ward events according to smoking status

Ward event	Smoking	Mean events	St. Dev	p-value
POST	Yes	2.444	2.407	0.096
	No	3.500	2.907	
Cough	Yes	0.778	0.934	0.134
	No	1.250	1.518	
Hoarseness	Yes	2.444	3.401	0.398
	No	2.000	1.768	
PONV	Yes	2.000	3.076	0.591
	No	2.417	3.547	

Appendix D

Figures of Study

Figure D.1

The used a calculator to detect the difference between the two proportions.

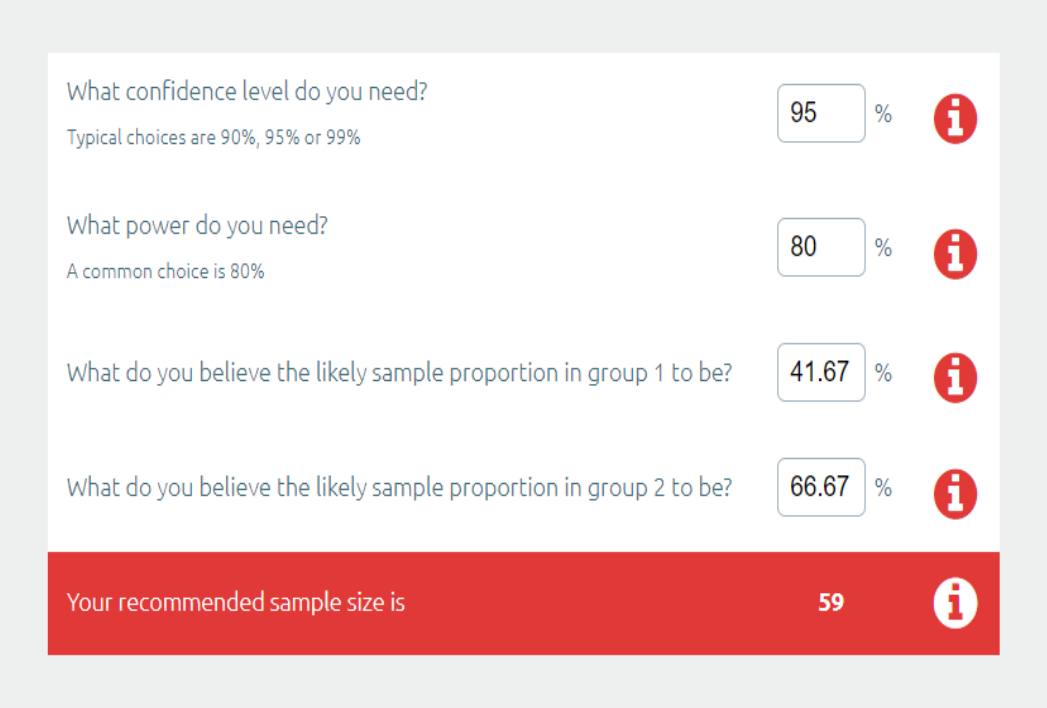


Figure D.2

The printed numbers on wrappers by using Random Allocation software 1.0.

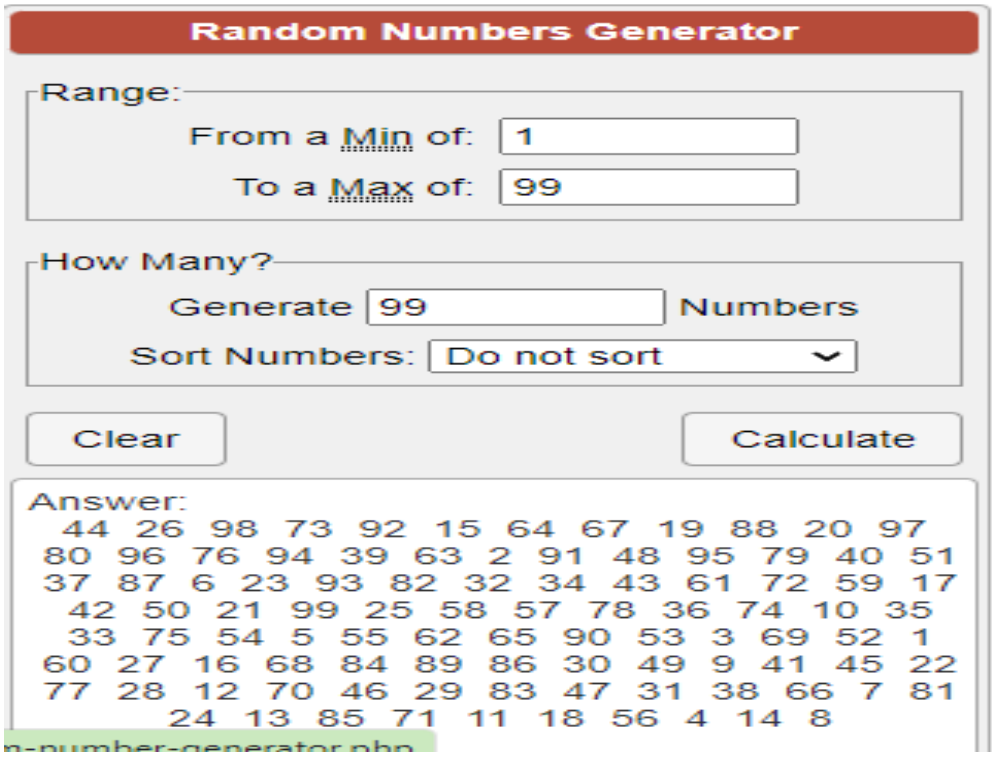


Figure D.3

The Modified Cormack-Lehane grade.

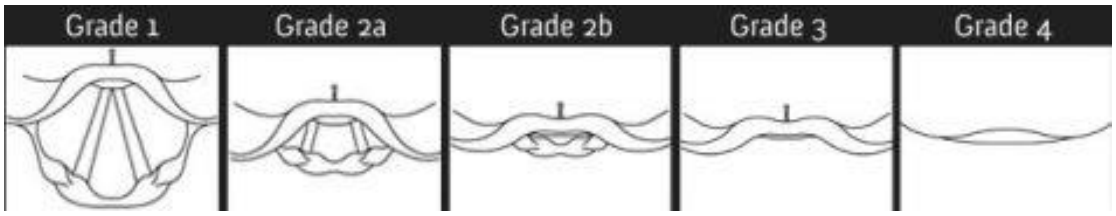


Figure D.4

The 1994 Copenhagen Consensus Conference recommended score.

	Excellent	Good	Poor
Jaw relaxation	relaxed	relaxed	poor relaxation
Resistance to laryngoscope	none	slight resistance	active resistance
Vocal cord position	abducted	intermediate	closed
Vocal cord movement	none	moving	closing
Limb movement	none	slight	vigorous
Diaphragmatic reaction	none	diaphragm	sustained coughing

Figure D.5

The mean anesthesia surgical durations between the three study groups.

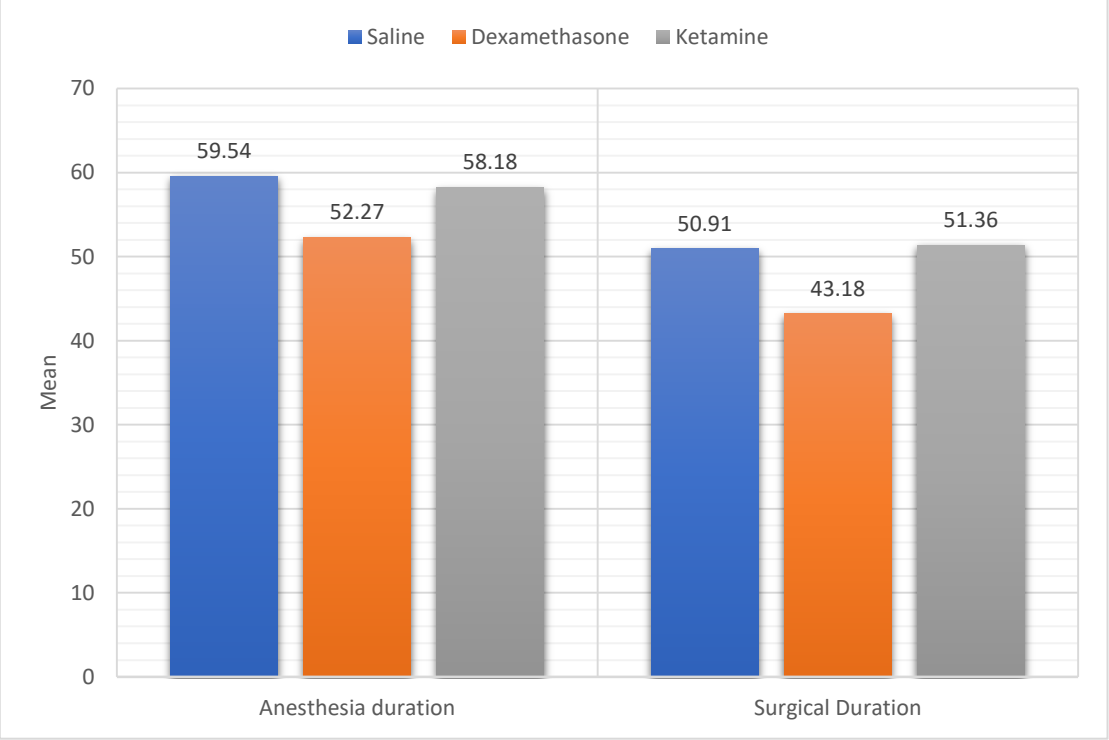


Figure D.6

The differences in the mean of hemodynamic readings between the three study groups in the PACU phase.

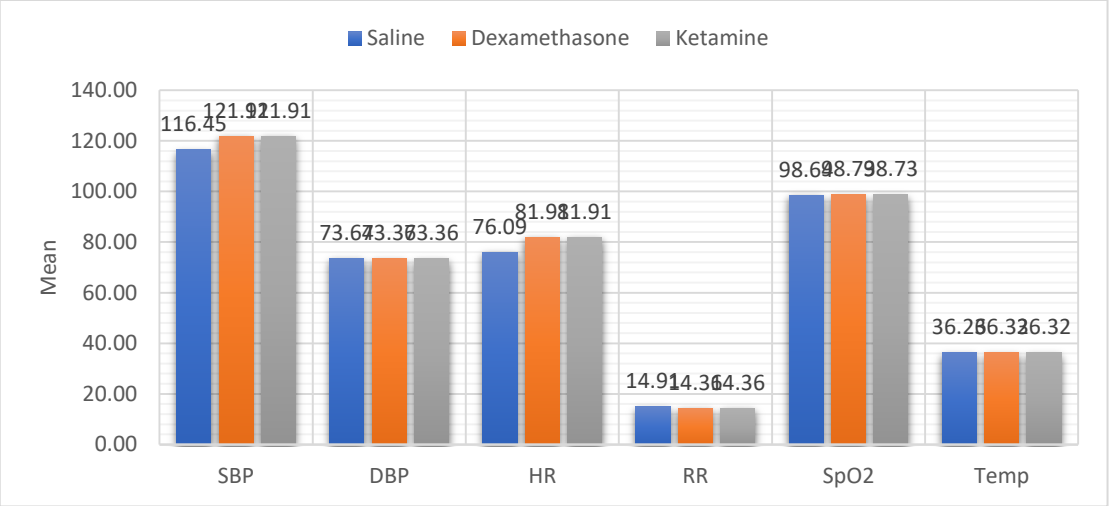
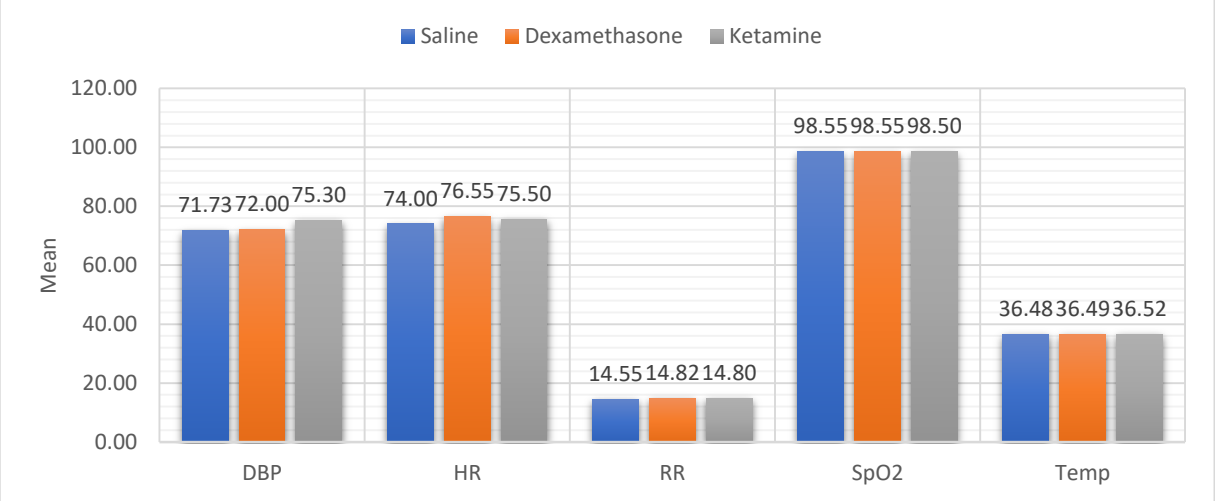


Figure D.7

The mean of two readings of the ward hemodynamics for the patients in the three groups



Appendix E

ASA Classification

American Society of Anesthesiologists Classification System:

Class	ASA physical classification system
I	A normal healthy patient
II	A patient with mild systemic disease
III	A patient with severe systemic disease
IV	A patient with severe systemic disease that is a constant threat to life
V	A moribund patient who is not expected to survive without the operation
VI	A declared brain-dead patient whose organs are being removed for donor purposes

Appendix F

IRB Approval Letter

An-Najah National University
Faculty of Medicine & Health Sciences
Institutional Review Board

جامعة النجاح الوطنية
كلية الطب وعلوم الصحة
لجنة اخلاقيات البحث العلمي

Ref : Mas. Nov. *2021/29*

IRB Approval Letter

Title of Research:

The effect of prophylactic preoperative nebulized ketamine vs. nebulized dexamethasone on postoperative sore throat in patients undergoing surgery under general anesthesia. A randomized, placebo-controlled, double-blind trial.

Submitted by:
Mohammad Moufeed Mahmoud

Supervisor:
Aidah Al-Kaisi , Noor Al-Deen Al-Masri

Approved:
17 th Nov. 2021

Your Study Title **"The effect of prophylactic preoperative nebulized ketamine vs. nebulized dexamethasone on postoperative sore throat in patients undergoing surgery under general anesthesia. A randomized, placebo-controlled, double-blind trial."** reviewed by An-Najah National University IRB committee and was approved on 17th Nov.2021.

Hasan Fitian, MD

IRB

IRB Committee Chairman

Nablus - P.O Box :7 or 707 | Tel (970) (09) 2342902/4/7/8/14 | Faximile (970) (09) 2342910| E-mail : hgs@najah.edu

State of Palestine
Ministry of Health
General Directorate of Education in
Health and Scientific Research

دولة فلسطين
وزارة الصحة
الإدارة العامة للتعليم الصحي
والبحث العلمي

Ref.: .....
Date:.....

الرقم: ٢٠٢١/٢٠٨٤/٢٦٢
التاريخ: ٢٠٢١/٦/٢٦

الأخ مدير عام الادارة العامة للمستشفيات المحترم،،،

تحية واحترام،،

الموضـــوع: تسهيل مهمة بحث

يرجى التكرم بتسهيل مهمة الطالب: **محمد مفيد يوسف محمود، تخصص ماجستير تمريض العناية المكثفة- جامعة النجاح**، لعمل بحث بعنوان:

"التأثير الوقائي لتبخيرة الكيتامين مقابل تبخيرة الديكساميثازون قبل العملية على التهاب الحلق ما بعد الجراحة لدى المرضى الذين يخضعوا لجراحة مبرمجة تحت تأثير التخدير العام. تجربة عشوائية مزدوجة التعمية خاضعة للتحكم الوهمي "

مع العلم أن مشرف الدراسة: د. عائدة القيسي ود. نور الدين المصري، حيث سيقوم الطالب بجمع معلومات الدراسة، **بشرط الحصول على موافقة رئيس قسم التخدير في المشفى**، وذلك في:

- **مستشفى رفيديا**

على ان يتم الالتزام بجميع تعليمات واجراءات الوقاية والسلامة الصادرة عن وزارة الصحة بخصوص جائحة كورونا، وتحت طائلة المسؤولية.
على ان يكون الطالب حاصل على تطعيم فيروس كورونا.
على ان يتم تزويد الوزارة بنسخة PDF من نتائج البحث، التعهد بعدم النشر.

مع الاحترام،،

د. عبدالله القواسمي
مدير التعليم الصحي والبحث العلمي

نسخة: منسقة برنامج ماجستير تمريض التخدير المحترمة/ جامعة النجاح

P.O .Box: 14
Telfax.:09-2333901
scientificresearch.dep@gmail.com
ص.ب. 14
تلفاكس: 09-2333901

جـامعـــة النجاح الوطنية

كليـــة الدراســـات العليـــا

التأثير الوقائي لتبخيرة الكيتامين مقابل تبخيرة الديكساميثازون قبل العملية على التهاب الحلق ما بعد الجراحة لدى المرضى الذين يخضعوا لجراحة مبرمجة تحت تأثير التخدير العام. تجربة عشوائية مزدوجة التعمية خاضعة للتحكم الوهمي

إعداد

محمد مفيد محمود

إشراف

د. عائدة أبو السعود القيسي

د. نور الدين المصري

قدمت هذه الرسالة استكمالا لمتطلبات الحصول علي درجه الماجستير في تمريض التخدير، من كلية الدراسات العليا، في جامعة النجاح الوطنية، نابلس– فلسطين.

2022

التأثير الوقائي لتبخيرة الكيتامين مقابل تبخيرة الديكساميثازون قبل العملية على التهاب الحلق ما بعد الجراحة لدى المرضى الذين يخضعوا لجراحة مبرمجة تحت تأثير التخدير العام. تجربة عشوائية مزدوجة التعمية خاضعة للتحكم الوهمي

إعداد

محمد مفيد محمود

إشراف

د. عائدة أبو السعود القيسي

د. نور الدين المصري

الملخص

المقدمة: التهاب الحلق بعد الجراحة هو مضاعفة بسيطة غير مرغوبة بعد التخدير العام مع التنبيب الرغامي, بالإضافة لكونه سببا لعدم الراحة وتقليل الرضا عن رعاية التخدير المقدمة. تهتك مباشر للأغشية المخاطية وقلة الرطوبة بسبب ضغط كفة الأنبوب الرغامي هو سبب التهاب الحلق بعد الجراحة، ما يعني انه امر لا يمكن تفاديه تقريباً، لذلك لابد من تدخل دوائي وقائي لتقليل نسبة حدوثه وحدته. العديد من الدراسات اثبتت نتائج واعدة لكل من تبخيرة الكيتامينو الديكساميثازون لمنع وتقليل نسبة حدوث وحدة التهاب الحلق والمضاعفات الحنجرية الاخرى مثل الكحة وبحة الصوت بعد الجراحة.

الأهداف: لتحديد ما اذا كانت تبخيرة الكيتامين او الديكساميثازون قبل العملية لها تأثير مهم على نسبة حدوث وحدة التهاب الحلق بعد الجراحة والمضاعفات الحنجرية الاخرى لدى المرضى الذين يخضعوا لجراحة مبرمجة تحت تأثير التخدير العام مع أنبوب التنفس الرغامي، ولتحديد ما اذا كان لها تأثير مهم على حالة التنبيب الرغامي واستجابة الدورة الدموية لعملية تنظير الحنجرة.

منهجية الدراسة: تسع وتسعون مريض مسجلين لعمليات مبرمجة تحت تأثير التخدير العام التحقوا بهذه الدراسة المستقبلية العشوائية مزدوجة التعمية الخاضعة للتحكم الوهمي، كل مشارك تلقى تبخيرة لمدة 15 دقيقة قبل بدء التخدير ب 15 دقيقة تماما كالتالي: 33 مشارك تلقوا تبخيرة 5 ملم من المحلول الملحي العادي، 33 مشارك تلقوا تبخيرة 8 ملغرام من الديكساميثازون بحجم 5 ملم، 33 تلقوا تبخيرة 50 ملغرام من الكيتامين بحجم 5 ملم.

النتائج: تبخيرتا الكيتامينو الديكساميثازون كانتا فعالتين في منع التهاب الحلق بعد الجراحة (p-value < 0.001) وبحة الصوت بعد الجراحة وبفعالية اكبر في مجموعة الكيتامين، بالاضافة الى ان تبخيرة الكيتامين كانت فعالة في منع الكحة والغثيان بعد الجراحة بينما تبخيرة الديكساميثازون لم تكن كذلك. ايضا، المرضى في مجموعة الكيتامين كانوا اكثر رضا بالمقارنة مع مجموعة الديكساميثازون ومجموعة المحلول الملحي العادي (p-value < 0.001). كان هنالك ارتفاع مهم في الضغط الانقباضي ومعدل نبضات القلب في مجموعة الكيتامين بعد التبخيرة بلا أية اعراضجهازية جانبية جادة.

الخلاصة: تبخيرة 50 ملغم من الكيتامين او 8 ملغم من الديكساميثازون فعالة في منع وتقليل نسبة حدوث التهاب الحلق بعد الجراحة والمضاعفات الحنجرية الاخرى، وبفعالية أكبر للكيتامين.

الكلمات المفتاحية: الكيتامين، الديكساميثازون، تبخيرة، التهاب الحلق.