"PRE-EMPTIVE NEBULIZED KETAMINE VERSUS PRE-EMPTIVE NEBULIZED LIDOCAINE FOR PAIN CONTROL AFTER TONSILLECTOMY IN CHILDREN WITH CONCURRENT CONTROLS"

BY

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IN
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Under the guidance of
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DR. MANIKANDAN S

ABBREVIATIONS

ASA – American society of anesthesiologists

ETT – Endotracheal tube

GA – General anesthesia

NMDA – Noncompetitive N-methyl-D-aspartate

NSAIDS – Non steroidal anti-inflammatory drugs

IV – Intravenous

IM – Intramuscular

CNS – Central nervous system

ICP – Intracranial pressure

SBP – Systolic blood pressure

DBP – Diastolic blood pressure

PR – Pulse rate

SD – Standard deviation

ABSTRACT

BACKGROUND AND AIM

Tonsillectomy is associated with significant pain and post operative pain control is often unsatisfactory. There have been several methods adopted to treat post operative pain but none of the methods were effective, with patients continue to undergo severe postoperative pain. Hence our study aimed at comparing the efficacy of pre-emptive nebulized ketamine versus pre-emptive nebulized lidocaine with the control group receiving nebulized saline for pain control in children undergoing tonsillectomy surgeries.

METHODS

In this prospective randomized clinical trial, 105 patients with ASA I and II undergoing tonsillectomy surgery were enrolled and randomized into three groups which are group K, group L, and group C with 35 patients in each group. Patients in each group received nebulized ketamine, lidocaine and normal saline pre-emptively. Faces pain scale scores, sedation scale scores, and the usage of rescue analgesia were noted postoperatively for first 6 hours. Hemodynamic parameters were noted before and after nebulization. The main objective was to find the number of patients receiving rescue analgesia postoperatively.

RESULTS

On comparison of the three groups, rescue analgesia was used less in group K than groups L and C indicating the efficacy of nebulized ketamine, with only 14.3% of patients only received rescue analgesia in group K. whereas in group L and group C, 85.7% and 91.4% patients received rescue analgesia respectively which is significantly higher compared to group K.

CONCLUSION

Pre-emptive nebulized ketamine was found to be effective in reducing postoperative pain in children undergoing tonsillectomy.

KEYWORDS

Nebulized ketamine, pain control, tonsillectomy, rescue analgesia.

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INTRODUCTION

Tonsillectomy is one of the most frequently performed surgical procedures among children and pain management remains challenging. The management of postoperative pain in tonsillectomy is often inadequate. Tonsillectomy has been identified as one of the most painful surgical procedures, probably because pain remains poorly managed in clinical practice.[1]

Tonsillectomy procedures in children are associated with significant morbidity. Common complications following tonsillectomy include respiratory depression, severe pain, hypovolemia secondary to decreased oral intake, and postoperative hemorrhage. There are many reasons for undertreating pain after tonsillectomy including underestimating the degree of pain due to the fact that the surgical procedure is considered to be minimally invasive.[2]

Previously, many methods have been tried in the postoperative pain management in tonsillectomy. Those methods include usage of perioperative local anesthetics, glossopharyngeal blocks, lesser palatine nerve blocks, and the usage of honey for reducing inflammation. But all these methods were not effective in reducing early postoperative tonsillectomy pain.[3][4]

Moreover, despite numerous studies comparing and combining analgesics to find the most effective postoperative regimen, there is still no consensus on the best treatment strategy for pain management in tonsillectomy postoperatively. Factors

such as fear, anxiety, lack of social support exaggerate the physical pain in children further. Adequate postoperative pain assessment in pediatric patients may significantly improve their comfort and quality of life.[5][6]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used for pain relief following tonsillectomy in children. However, as they inhibit platelet aggregation and prolong bleeding time, they could cause increased perioperative bleeding. If bleeding is severe this may result in the child being re-admitted to hospital, having a blood transfusion or returning to theatre. It was therefore important to establish whether these drugs are safe to use in children undergoing tonsillectomy.[7]

Nebulization is primarily used for safety and ease of administration to the patient, with the benefit of the drug reaching the lower airways. During nebulization, the liquid is broken into droplets by the compressed air, and it produces large particles (10-25micrometre), which mostly deposit in mouth and throat, and smaller particles (5-10 micrometer), which deposit in a transition from mouth to airway.[8][9]

Ketamine is a noncompetitive N-methyl-D-aspartate (NMDA)-receptor complex antagonist that decreases pain by diminishing central sensitization, hyperalgesia, and wind-up phenomenon at the level of the spinal cord (dorsal ganglion) and central nervous system. In recent years, studies have shown that ketamine plays a protective role against lung injury, via its anti-inflammatory properties. Ketamine, an NMDA receptor antagonist, has been used for decreasing post operative pain and sore throat

because of its anti-nociceptive and anti-inflammatory action, as gargle as well as in nebulized form. However nebulized ketamine is better tolerated in patients due to many reasons such as it saves the patient from bitter taste of lidocaine, also much lesser volume is needed as against larger volumes required for gargle.[8]

Lidocaine is one of the most frequently used local anesthetics and is available in multiple dosage forms. Lidocaine has been evaluated in numerous trials as a spray or gel to suppress acute cough associated with bronchoscopy, lung biopsy and laryngoscopy. Lidocaine nebulizer attenuates airway circulatory reflexes during induction and emergence, tube tolerance, nasal pack tolerance and reduced total dose of opioid analgesia postoperatively. It was found that lidocaine nebulization suppresses the excitatory sensory C fibres in airways and thus reduces the release of neuropeptide. After nebulization at normal doses, lidocaine levels in the blood were safe and well tolerated.[9][10]

Hence, we have compared the efficacy of nebulized ketamine with nebulized lidocaine given pre-emptively in controlling pain postoperatively. We have analyzed the need for rescue analgesia which indicates the good postoperative pain management.

AIMS AND OBJECTIVES OF THE STUDY

AIM:

This study aims to investigate the postoperative analgesic efficacy of pre-emptive nebulized ketamine in comparison with pre-emptive nebulized lidocaine administered before general anesthesia in children undergoing tonsillectomy.

OBJECTIVE:

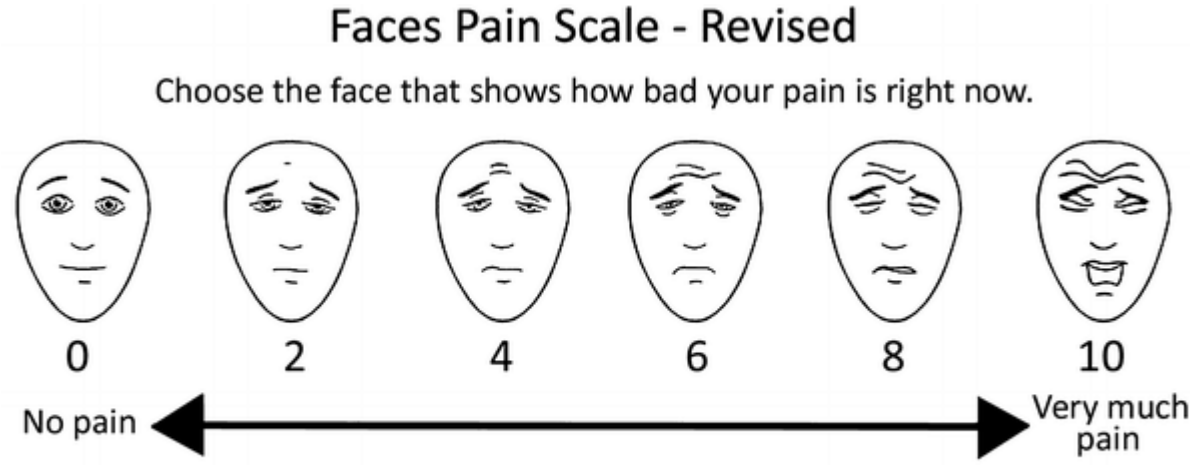
PRIMARY OBJECTIVE:

- To compare nebulized ketamine and nebulized lidocaine for post operative analgesia effect.
- To evaluate the usage and frequency of rescue analgesia.

SECONDARY OBJECTIVE:

- Assessment of spo2, respiratory rate, heart rate, and blood pressure pre-nebulization and post-nebulization.
- Observation of the side effects such as vomiting, increased secretions, and hallucinations.

OBSERVATIONAL INDICATORS



From Hicks CL. von Baeyer CL, Spafford P, van Korlaar I, Goodenough B.
Faces Pain Scale-Revised: Toward a Common Metric in Pediatric Pain Maeasurement. PAIN 2001; 93:173-183. This Figure has been reproduced with permission of the International Association for the Study of Pain* (ISAP*). The figure may not be reproduced for any other purpose without permission.

RAMSAY SEDATION SCALE

Sedation level	score
Patient is anxious and agitated or restless, or both	1
Patient is co- operative, oriented, and tranquil	2
Patient responds to commands only	3
Patient exhibits brisk response to light glabellar tap or loud auditory stimulus	4
Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus	5
Patient exhibits no response	6

REVIEW OF LITERATURE

Hye et al (2014)[11] conducted a meta-analysis study based on three databases Med line, Scopus, and Cochrane. Studies that compared preoperative ketamine administration in any form with no treatment where the outcomes of interest were postoperative pain intensity, rescue analgesic consumption, or adverse effects 0-24 hours after leaving operating room. They concluded that preoperative administration of ketamine systemically or locally could provide pain relief in children undergoing tonsillectomy.

Dreher et al (2016) [12] conducted a study on the nebulized lidocaine versus local application of lidocaine during flexible bronchoscopy by a randomized controlled trial patients requiring bronchoscopy were randomly assigned with local lidocaine or nebulized lidocaine. Thirty patients were included, with 15 in each group. Patients in the nebulizer group required lower endobronchial lidocaine and intravenous fentanyl doses. Endobronchial administration of lidocaine during bronchoscopy via nebulizer was found to well tolerated and safe.

David L Walner et al (2017) [13] conducted a study on pain control following tonsillectomy. This was a prospective study to assess pain management utilization and satisfaction. 111 pediatric patients included in this study underwent tonsillectomy with or without adenoidectomy. Postoperatively patients were given alternatively with acetaminophen and ibuprofen. Some patients were given acetaminophen with hydrocodone. A survey was administered during the 2 week patient follow up regarding pain level, worst post-op pain day, pain medications during recovery. Patient satisfaction over acetaminophen or ibuprofen were also recorded.

Derlin Thomas et al (2018) [8] undertook a study on efficacy of preoperative nebulization of ketamine in attenuating the incidence and severity of postoperative sore throat. After written informed consent, a total of 96 patients undergoing GA with tracheal intubation were enrolled in this study. Patients were divided into two groups each group receiving ketamine and saline nebulization preoperatively. On reaching post anesthesia care unit, post operative sore throat was monitored and graded on a four point scale.

Javad Mozafari et al (2019) [9] conducted a study on efficacy of nebulized fentanyl and low dose ketamine for pain control of patients with long bone fractures. In this double blinded randomized study total of 127 patients were included. They were divided into two groups with one group receiving fentanyl nebulization and other receiving ketamine nebulization. Pain was assessed using a visual analog scale just before treatment and post treatment. Multiple comparison analysis showed that pain scores were significantly higher in the patients of group receiving fentanyl

nebulization. Moreover patients who received fentanyl nebulization required additional treatment for pain control.

Hala S. Abdel Ghaffar et al (2019) [7] Conducted a study on nebulized ketamine for pain control after Tonsillectomy in children. Total of 100 children aged 7-12 years were taken up for analysis. They were randomly selected and divided into four groups. The study concluded that nebulized ketamine administered before Tonsillectomy prolonged the time to first request for postoperative rescue analgesia in the first 24-hour postoperative period without significant adverse effects.

Shereen E. Abd Ella et al. (2020) [14] Conducted a study on 60 adult patients scheduled for endoscopic nasal surgeries to evaluate the efficacy of nebulized ketamine versus nebulized lidocaine. Patients were allocated into three groups and randomly nebulized. The outcome measures included hemodynamics, sedation, time of the first request for rescue analgesia, and adverse effects. It was concluded that nebulization with ketamine or lidocaine before induction of general anesthesia is efficacious and enhances postoperative analgesia.

Jefferson Drapkin et al. (2020) [15] Conducted a study on the administration of nebulized ketamine for managing acute pain in the emergency department. ketamine administration in sub dissociative doses in the emergency department results in effective pain relief in patients with acute traumatic pain. This case series describes five adult patients in the emergency department. Three patients received nebulized

ketamine at different doses. The inhalational route of ketamine delivery via breath actuated nebulizer may have utility for managing pain in the emergency department.

Shital A. Dharamkhele et al. (2021) [16] Conducted a study on comparative study of nebulized ketamine and its combination with dexmedetomidine as pre-medication for pediatric patients undergoing surgeries under general anesthesia. Patients received either nebulized ketamine or dexmedetomidine 30 minutes before shifting inside the operation theatre. The sedation level, hemodynamic response, and ill effects were recorded for 30 minutes. They found that nebulization is a satisfactory method for pain control in children. A combination of nebulized ketamine with dexmedetomidine can produce an adequate level of sedation more effectively than sedation induced by nebulized ketamine alone.

Catsim Fassassi et al (2021) [17] conducted a case series study on nebulized ketamine used for management of orthopedic trauma. Ketamine has been found to provide effective pain relief when administered via IV, intranasal, and subcutaneously. However in situations when IV access is not available ketamine can be administered via inhalational route. This provides smaller particles and greater dose with good efficacy in reducing pain.

Irem Ates et al (2021) [18] undertook a study on perioperative intravenous low dose ketamine infusion to minimize pain for septorhinoplasty. This randomized, prospective, double blind study was conducted with 48 patients, divided into two groups, who underwent septorhinoplasty. In ketamine group, intravenous ketamine bolus was administered at anesthesia induction and ketamine infusion was continued

during the surgery. To other group saline was used instead of ketamine. Pain scores were significantly lower in group which received ketamine at all postoperative periods. There was no significant difference between two groups in terms of intraoperative sevoflurane and remifentanil consumptions.
They concluded that the administration of low dose ketamine infusion reduces the requirement of rescue opioid analgesia and postoperative pain scores.

Geeta singariya et al. (2022) [19]Conducted a study on seventy patients to compare nebulized dexmedetomidine and ketamine for pre-medication in children undergoing hernia repair surgery aged between 2 to 8 years .patients were divided into two groups and randomly nebulized. The study findings are satisfactory parent child separation and better mask acceptance in children pre-medicated with nebulized dexmedetomidine compared to nebulized ketamine. The sedation effects and adverse reactions of nebulized dexmedetomidine and nebulized ketamine are discussed in this study.

Yu et al (2022) [20]in a systemic review and meta analysis of approximately 32 randomized clinical trials, compared the efficacy of different available nebulized agents for the management of postoperative pharyngeal pain. A systemic bibliographic search of the updated medical literature using databases such as pub med and google scholar was carried out. Descriptions such as postoperative pharyngeal pain, ketamine, lidocaine were used. They have concluded in the study that ketamine due to its antinociceptive, anti inflammatory, broncho dilatory effects, has been the choice of drug for the management of postoperative pharyngeal pain.

Priyanka Dwivedi et al (2022) [21] compared the efficacy and safety of intranasal ketamine with intranasal dexmedetomidine as a premedication in pediatric patients undergoing general anesthesia for elective surgery. They conducted a systemic literature search in Pub med, Scopus, Cochrane databases for randomized control trials on nebulized ketamine and dexmedetomidine. They found intra nasal ketamine treated patients showed a higher incidence of postoperative nausea and vomiting. Patients who received intra nasal dexmedetomidine showed increased incidence or bradycardia.

Zainab Abd Alkhader et al (2023) [22] conducted a study on pre emptive nebulization of dexmedetomidine versus ketamine for postoperative analgesia in nasal surgeries. In this study 105 patients were divided into three groups each group nebulization of dexmedetomidine, ketamine and normal saline respectively. Hemodynamics, intraoperative opioids, the first time of rescue analgesia requested, the total amount of rescue analgesia administered and side effects were all included in the outcome measures. They have concluded that preemptive nebulization of dexmedetomidine produces extremely good analgesia in nasal surgeries, when compared with other groups it can effectively reduce the intra and postoperative opioid consumption.

Safoora Omidvar et al (2023) [23] compared the effect of ketamine and lidocaine on agitation and pain in rhinoplasty. Totally 72 patients scheduled to undergo elective rhinoplasty were enrolled in this study. Patients were randomly divided into three groups each group having 24 patients. Twenty minutes before completion of surgery each group received IV saline, lidocaine and ketamine respectively. The emergence agitation level was evaluated using Richmond agitation scale in the PACU. There was significant difference between pain level in ketamine and lidocaine group. Ketamine was found to be effective in pain control postoperatively. There was no significant difference found in level of agitation and sedation in lidocaine and ketamine groups.

Xiangjun Zhou et al (2023) [24] conducted a study on lidocaine aerosol sprayed on oral and nasal mucosa for the rescue of acute trigeminal neuralgia exacerbations. A total of 152 patients were included in this study analyzing the efficacy of lidocaine aerosol for the treatment of acute trigeminal neuralgia exacerbations. A positive response was considered a decrease in the VAS score of at least 50% at 30min of treatment. Out of all patient, 109 patients responded well with treatment with significant decrease in VAS scores. Multivariate logistic analyses showed the treatment may provide better clinical outcomes in trigeminal neuralgia.

CLINICAL ANATOMY [25][26][27]

The tonsils represent a circular band of mucosa associated with lymphoid tissues, Waldeyer's ring, which is located at the entrance of the upper aerodigestive tract, with a significant role in the immune defense system. Waldeyer's ring is composed of the pharyngeal, tubal, palatine, and lingual tonsils acting as secondary lymphoid tissues. Particularly, the palatine tonsils are the largest of the tonsils with deep branching crypts and contain B and T lymphocytes and M cell which plays a role in the uptake and transport of antigens.

The tonsils are located posterior to the nasal and oral portions of the pharynx to form a circumferential ring, known as the Waldeyer's ring, which was first described by German anatomist Wilhem Gottfried Waldeyer Hartz. The unpaired nasopharyngeal and lingual tonsils and the paired palatine and tubal tonsils are responsible for both innate and adaptive immunological responses which have a role in defense mechanism of the pharynx.

Tonsils are derivatives of 2^{nd} pharyngeal pouch. They typically appear around 4^{th} or 5^{th} month of gestation and continue to develop with the growth of the child. Present at birth, tonsils tend to reach the full size between 6^{th} and 8^{th} years of life. Tonsils and adenoid tissue are found to be most immunologically active between 4^{th} and 12^{th} years of life and begin to involute or atrophy after first decade of life.

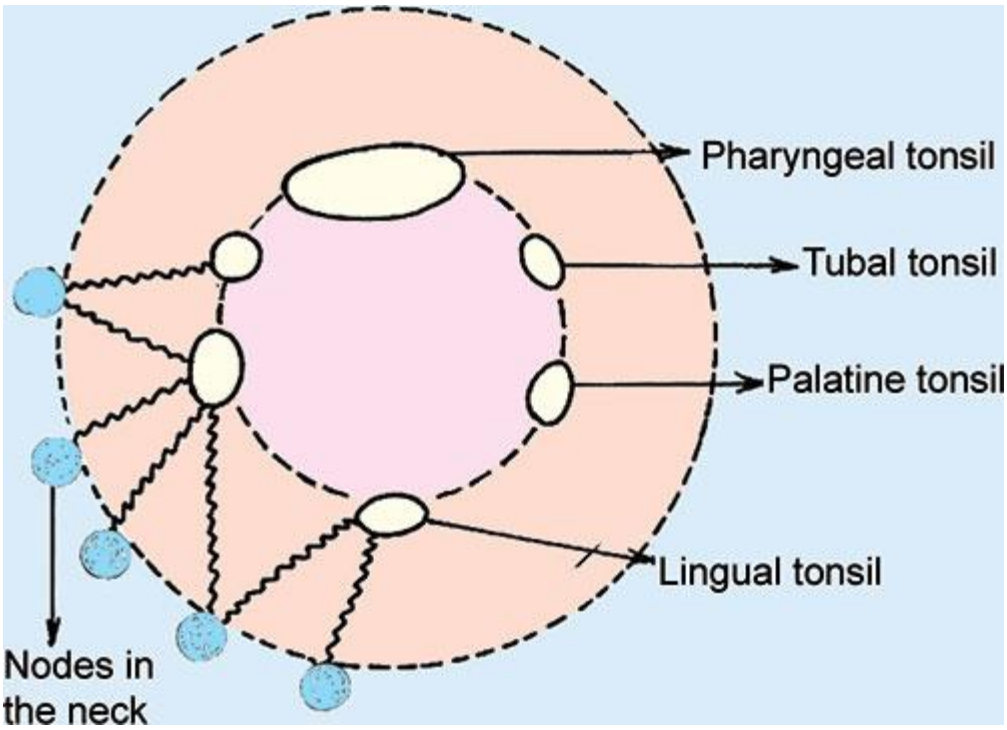


Figure 1: waldeyer's ring

PHARYNGEAL TONSIL

Pharyngeal tonsil is the superior most of the Waldeyer's ring and located above the soft palate in the posterosuperior roof of the nasopharynx as a single median unencapsulated mass with 12-15 shallow, crypt like invaginations. The pharyngeal bursa, a blind mucosal sac, may be seen in the posteromedian wall of the nasopharynx. A median longitudinal groove extends from this sac inferiorly.

Antero superiorly, the pharyngeal tonsil is usually lined by pseudostratified ciliated columnar epithelium (respiratory epithelium), whereas posteroinferiorly the areas adjacent to the oropharynx is covered by stratified epithelium. These mucosal folds containing numerous lymphoid nodules commonly enlarge and become adenoid which results in respiratory difficulties and nasal obstruction during childhood and often start to involute after 7 years of age or even atrophied in the adult.

The arterial supply of it comes from ascending pharyngeal artery, pharyngeal branch of the maxillary artery, artery of the pterygoid canal, basisphenoid artery, ascending palatine and tonsillar branch of the facial artery. It has a lymphatic drainage into upper deep cervical lymph nodes within the parapharyngeal space and retropharyngeal lymph nodes.

Chronic inflammation of the pharyngeal tonsil results in hyperplasia and hypertrophy of the lymphoid tissue known as adenoid.

TUBAL TONSIL

Eustachian tube (ET) tonsils, small aggregates of lymphoid tissue, form the upper lateral aspect of the ring and are located bilaterally around the pharyngeal ostium of the ET (torus tubarius) which is below and in front of the pharyngeal recess (fossa of rosenmuller) in the posterolateral wall of the nasopharynx. Because of their close relationship to the torus tubarius, they are called as tubal tonsils.

This triangular pharyngeal ostium has three prominences: anterior, posterior, and inferior. The anterior fold continues as plica salpingpalatina and descends into soft palate. The posterior fold is conspicuous and formed by the projecting cartilage of the auditory tube and also lies as plica salpingopharyngeus.

Tubal tonsils are covered by pseudo stratified ciliated columnar epithelium with no crypts. They receive arterial supply via the ascending pharyngeal artery. Their lymphatic drainage is same as the pharyngeal tonsil.

LINGUAL TONSIL

Lingual tonsils are the inferior most of the ring and composed of numerous lymphoid nodules in the posterior third of the tongue. The stratified squamous nonkeratinized epithelium covers this lymphoid tissue aggregates forming large, irregular protrusions. Also, they have less branching shallow crypts which are covered by the reticulated epithelium and mucous salivary glands which are drained through several ducts into these crypts which appear after birth.

The size of lingual tonsils varies from one to six milli meters. They rest on a basement membrane of fibrous tissue analogous to the capsule of faucial tonsils but not as developed as a tissue. A lateral section shows the nodules as discrete hemispheres, the mucosa at the bottom being free from lymphoid tissue, each representing two or three crypts. The epithelium is like that of the faucial tonsils, stratified and squamous, the lymphoid tissue differs in no way from faucial tonsils. Its arterial supply is from the dorsal lingual branch of the lingual artery. The venous drainage is part of the plexus draining the tongue.

PALATINE TONSIL

The palatine tonsils lie in the tonsillar fossa between two tonsillar pillars- the palatoglossal and the palatopharyngeal folds and can be variable in the depth to which they are embedded between the folds. Previous infections, particularly peritonsillar abscesses, can cause apparent asymmetry of the palatine tonsils. Palatine tonsils are characterized by multiple craters on their surface, which are formed by crypts passing deep into parenchyma of the tonsil.

Histologically unique, the palatine tonsils consist of lymphoid tissue covered by squamous epithelium. The floor of the tonsillar bed is formed by the superior constrictor, and is separated from the tonsil by a thick condensation of pharyngeal submucosa, the tonsillar capsule, which is, in essence, an extension of the pharyngobasilar fascia. This capsule is further separated from the superior constrictor by a thin film of loose areolar tissue.

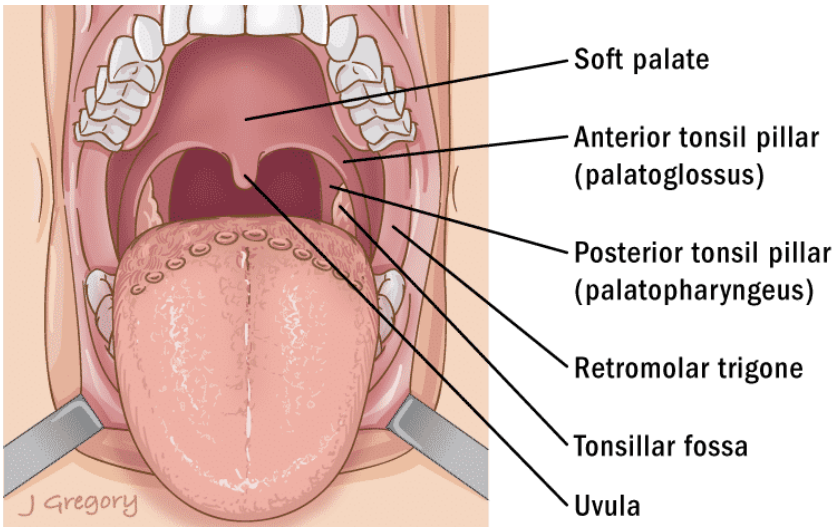


Figure 2: Palatine tonsil

BLOOD SUPPLY OF TONSIL

The palatine tonsils are supplied by the tonsillar artery, a branch of the facial artery that gains access to the tonsil by penetrating the superior constrictor to enter the inferior pole of the tonsil. There is an additional arterial supply from the ascending palatine, lingual, descending palatine and ascending pharyngeal arteries.

The venous drainage of the palatine tonsils is via a plexiform arrangement, deep to the tonsils, the pharyngeal venous plexus. The large external palatine vein descends from the soft palate and passes close to the lateral surface of the tonsillar capsule. This vain is most commonly dissected during tonsillectmy and is the likely culprit in persistent post-tonsillectomy bleeds. The lymphatics of the tonsil drain to the jugulodigastric lymph node area.

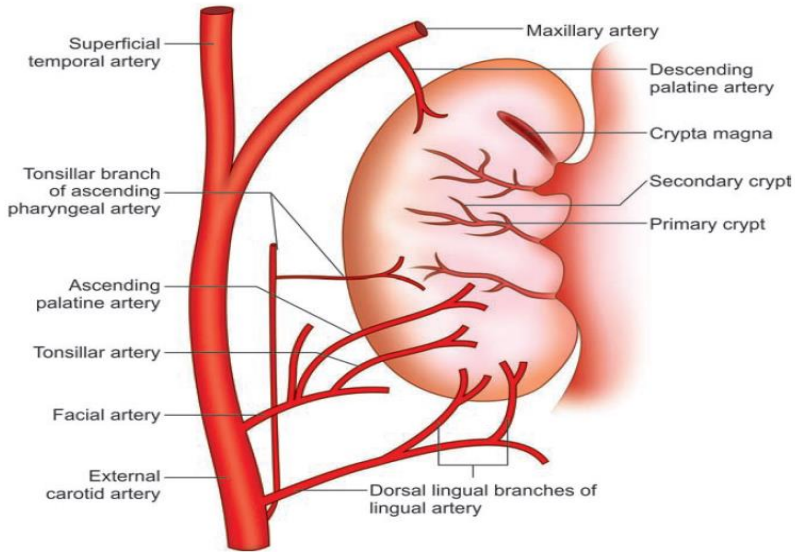


Figure 3: Blood supply of tonsil

NERVE SUPPLY OF TONSIL

The tonsils receive their nerve supply from the tonsillar plexus, a complex meshwork of nerves originating from the tonsillar branches of the maxillary nerve and the glossopharyngeal nerve. The fibres of the maxillary nerve are distributed to the lesser palatine nerves and via these nerves are then combined with the glossopharyngeal nerve to form their plexiform arrangement of nerves around the tonsils. An offshoot of the glossopharyngeal nerve, the tympanic nerve also supplies the tympanic cavity and the tympanic membrane. Consequently any pathology affecting the tonsils or the tonsillar fossa may present as pain referred to the ear.

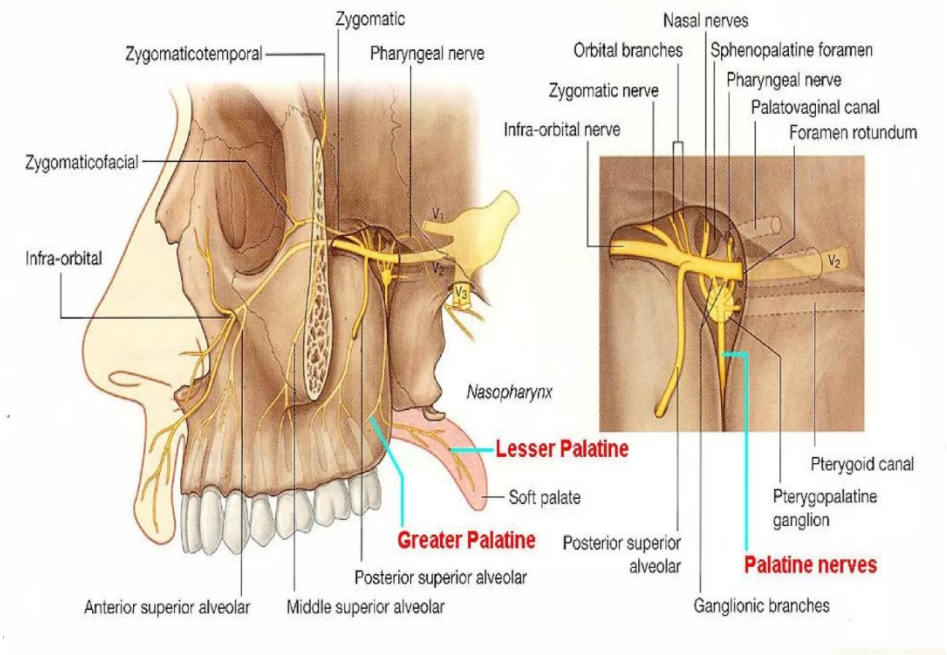


Figure 4: Nerve supply of tonsil

Structures related to bed of tonsil

- The tonsil is separated from its bed by loose areolar tissue.
- The structures forming the bed of tonsil are
    - Superior constrictor muscle
    - Styloglossus muscle
- The structures related to the bed of tonsil are
    - Styloid process
    - Glossopharyngeal nerve
    - Facial artery
    - Submandibular salivary gland
    - Posterior of digastric
    - Medial pterygoid muscle
    - Angle of mandible

Tonsillar crypts

The non keratinizing stratified squamous epithelium on medial surface of tonsil dips into the tonsillar mass and forms crypts. Opening of crypts can be seen on the medial surface of the tonsil.

- **Crypta magna or intra tonsillar cleft**: It is situated near the upper part of tonsil. It is very large and deep and represents the ventral part of second pharyngeal pouch.
- **Secondary crypts**: They arise from the main crypts within the substance of tonsil.

Contents of tonsillar crypts: Crypts may be filled with cheesy material, which consists of epithelial cells, bacteria and food debris and can be expressed out with pressure over the anterior tonsillar pillar.

The upper pole of tonsil extends into the soft plate. There is a semilunar fold of mucous membrane which covers the medial part of the upper pole. It encloses a potential space – supra tonsillar fossa. The lower pole of tonsil is attached to the tongue. A triangular fold of mucous membrane extends from anterior tonsillar pillar to the lower pole. It encloses a space – anterior tonsillar space. The lower pole is separated from tongue by the tonsillolingual sulcus. This sulcus may harbor carcinoma.

Capsule and peritonsillar space

Lateral surface of tonsil is covered by a well defined fibrous capsule, which is separated from the bed of tonsil by loose areolar tissue that allows easy dissection in this plane during tonsillectomy. In this peritonsillar space occurs the peritonsillar abscess. Some fibres of palatoglossus and palatopharyngeus muscles are attached to tonsillar capsule.

Elongated styloid process and stylalgia – the styloid process when enlarged may be palpated intraorally in the lower part of tonsillar fossa. The glossopharyngeal nerve and styloid process can be approached through the tonsil bed after tonsillectomy.

CLINICAL PHYSIOLOGY OF TONSIL[26][27]

To better understand the physiology of the palatine and pharyngeal tonsils, a brief embryologic review is necessary. The medial epithelial surface of the tonsil forms from the second branchial pouch, as solid epithelial cores invaginate into the surrounding mesenchyme. These cores eventually canalize and form crypts. Around week 16-17 of embryological development, lymphocytes and lymphoid stem cells invade the deeper lamina propria and begin to form follicles and what will eventually become germinal centers.

As these lymphoid elements grow, the deepest layers of the lamina propria eventually coalesce into a thin membrane that forms the tonsillar capsule. More superficial connective tissue fibers, primarily consisting of type III collagen, form septae that traverse between the crypts and become continuous with the deeper capsule.

In postnatal life, the branching crypts, totaling approximately 10-30 per tonsil, give the tonsils a "pitted" appearance on their medial free edge. The crypts resemble tubular diverticula and have a fibrovascular core surrounded by lymphoid tissue and the epithelial surface is comprised of non-keratinized stratified squamous epithelium along the medial (luminal) surface of the tonsil.

The crypts themselves are lined by a non-uniform distribution of stratified squamous epithelium and reticulated crypt epithelium. This latter epithelium, also referred to as lymphoepithelium, is similar to Peyer's patches found in the gastrointestinal tract. Reticulated epithelium is less orderly than stratified squamous epithelium and contains both epithelial and non-epithelial cells, particularly lymphoid cells.

This epithelial layer can be quite thin and even lack a basement membrane in some regions. With lymphocytes and dendritic cells just deep to the epithelial surface, this histologic arrangement allows for rapid transport and presentation of exogenous antigens to the lymphoid cells for efficient initiation of an immune response.

Furthermore, the invaginated structure of the tonsillar crypts significantly increases the total surface area that can participate in this process of antigen sampling and can facilitate direct trapping of foreign material entering the oropharynx. This is of particular importance because the palatine tonsils do not have an afferent lymphatic network as other lymphoid organs like lymph nodes and the spleen.

The pharyngeal tonsil has some similarities to the palatine tonsils in gross and histologic appearance. The free surface of the pharyngeal tonsil is characterized by mucosal folds that project anteriorly and laterally, with a much smaller number of crypts as compared to the palatine tonsils.

Histologically, the pharyngeal tonsil is composed primarily of pseudostratified ciliated columnar epithelium, with lymphoid follicles, fewer in number than the palatine tonsil, arranged throughout the mucosal folds. Superiorly, a capsule

separates the pharyngeal tonsil from the periosteum of the sphenoid and bony occiput; and connective tissue septa extend from this capsule into the tissue of the pharyngeal tonsil, separating it into 4-6 segments.

A complete discussion of the immunologic function of the palatine and pharyngeal tonsils is beyond the scope of this review and is detailed elsewhere. Briefly, exogenous antigens are "sampled" through an incompletely understood process thought to involve M (membrane)-cells, also found in Peyer's patches, whose structure facilitates antigen uptake from the nasal/oropharynx. Once these antigens cross the epithelium of the luminal tonsillar surface, they are processed by antigen-presenting cells (APCs), such as dendritic cells and macrophages, and then presented to T cells and B cells in the neighboring extrafollicular region.

If the antigen has been encountered previously, a secondary immune response is stimulated via T-cell proliferation and/or secondary antibody production by B cells. If the encountered antigen is novel and successfully recognized by a helper T cell, activation, proliferation, and differentiation into a T-cell population specific to this antigen ensues, as long as appropriate co-stimulatory signals are present. These T cells stimulate naive B cells, which then travel to nearby follicles and differentiate into antigen-specific plasma cells and memory B cells, eventually forming a germinal center.

These cells can then leave their respective lymphoid structures via high endothelial venules and travel to other mucosal sites, such as the nasal mucosa, where they

receive further signals to terminally differentiate into specific immunoglobulin-producing cells, with predominant production of IgG and IgA. Immunoglobulins are directly secreted by the pharyngeal tonsil and extravasate between palatine tonsil epithelial cells to reach their respective tonsillar surfaces for immune surveillance, preventing antigen attachment to host tissues and/or stimulating immune-mediated destruction.

Equally important to this immunologic response is apoptosis, or programmed cell death. This process helps to maintain homeostasis as the tonsils continually encounter new antigens, and also serves to eliminate autoreactive or non-specific immune cells within the organs. When functioning appropriately, apoptosis will minimize the risk for pathologies such as autoimmune disease, pathologic lymphoid organ hyperplasia, and/or decreased immune function due to decreased lymphocyte immunocompetence.

CLINICAL IMPLICATIONS OF TONSILLAR PHYSIOLOGY [28]

The immunologic function of the palatine and pharyngeal tonsils leads to their rapid growth during the early years of life. The exact mechanism of growth is not completely understood but is thought to occur as exogenous antigen presentation catalyzes germinal center development, lymphoid hyperplasia, and expansion of the tonsillar parenchyma. The pharyngeal and palatine tonsils typically reach their maximum size by age 6 and puberty, respectively. After this time, involution occurs via increased fibrous tissue production and eventually fatty atrophy, usually by 8-10 years of age and adulthood, respectively.

As the palatine and pharyngeal tonsils undergo their initial rapid growth phase through antigen sampling, some individuals develop pathologic immune-related processes, such as chronic adenoiditis or tonsillitis, recurrent otitis media, rhinosinusitis, and even allergic disease. Other individuals develop complications associated with anatomic obstruction of the oropharynx and nasopharynx, such as sleep-disordered breathing/obstructive sleep apnea (OSA) from adeno tonsillar hypertrophy and nasal obstruction, rhinosinusitis, and recurrent otitis media from adenoid hypertrophy and choanal and/or Eustachian tube obstruction.

The mechanisms underlying these pathologies, particularly adeno tonsillar hypertrophy, are not fully understood, with theories involving genetic predisposition, infections, environmental exposures, and aberrant immune responses. Given the immunologic function of Waldeyer's ring, a number of groups have focused their attention on investigating immunologic phenomena that may underlie these processes. While the pharyngeal and palatine tonsils can protect from

foreign pathogens, current evidence suggests that tonsillitis or adenoiditis occurs when foreign antigens escape immune defenses, become trapped in crypts, and proliferate before the immune system can mount a sufficient response.

In cases of recurrent infection, current evidence suggests that changes in the reticulated epithelium can impair efficient antigen uptake, while immaturity of antigen-presenting cells can lead to decreased capability in effectively activating the immune response, sometimes referred to as local immunosuppression.

In comparison, cellular senescence predominated in the germinal centers (predominantly among macrophages) and interfollicular area in patients with tonsillar hypertrophy. Cellular senescence suggests an impaired immune response that can lead to impaired phagocytosis and pathogen killing, as well overgrowth of follicles due to lymphoid cell accumulation.

SURGICAL CONSIDERATIONS[29]

Surgical removal of tonsil is called tonsillectomy. Its indications include recurrent chronic tonsillitis, hemorrhagic tonsillitis, peritonsillar abscess. Tonsils are surgically removed by dissecting between the tonsillar capsule and the superior constrictor muscle using either the hot or cold technique.

In the hot tonsillectomy technique, electrocautery is employed to dissect and coagulate simultaneously. In the cold technique, a superior incision is made through

the mucosal layers, and blunt dissection is used to separate the tonsils from the underlying tonsillar bed. Tonsils are then separated along their inferior border using the snare method. Studies have shown a superiority of the cold technique when looking at the outcome of postoperative pain.

However, electrocautery minimizes intraoperative blood loss. Newer techniques currently in practice employ the use of CO2 lasers, ultrasound, as well as radiofrequency ablation citing reduced postoperative pain.

Complications following a tonsillectomy classified into three categories: acute, subacute and delayed. Acute complications include airway obstruction due to edema, bleeding, and post obstructive pulmonary edema. Sub acute complications include postoperative hemorrhage, dehydration. Delayed complications include velopharyngeal insufficiency and nasopharyngeal stenosis.

PHYSIOLOGY OF PAIN[30]

Pain can be acute or chronic. Pain can be a result of any injury, underlying morbidity, abnormal function of any organ. Long standing disease usually cause chronic pain. The visceral pain which is experienced at a location away from its actual site is called as referred pain due to the same embryological origin.

Pain has four components-

- Sensory-conscious perception
- Motor- withdrawal reflex
- Autonomic-tachycardia, perspiration
- Affective-anger

Changes in each organ system due to pain are-

- Heart-tachycardia, hypertension, arrhythmias
- Lungs-oxygen consumption is increased, increase in respiratory rate
- Blood-thrombosis
- Gut- decreased gut motility, ulceration, urinary retention
- Endocrine-increased catecholamines
- Immunology-increased total count
- Psychology-anger, anxiety, decreased sleep

GATE THEORY

Ronald Melzack and Patrick wall, explained this theory. Here, the pain stimulus is not experienced if there is simultaneous stimulation by inhibitory impulses as well. Pain is delivered by A-delta and C fibers. A-beta fibres can override the pain stimulus by delivering information about touch and pressure simultaneously. Brain can decrease the pain intensity by activating endogenous pain suppression pathways.

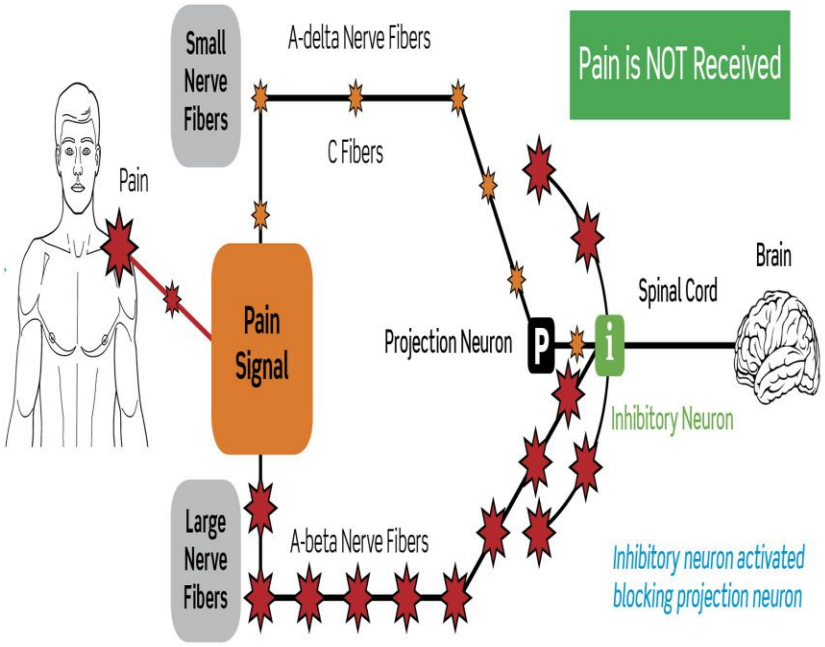


Figure 5: Gate theory of pain

PHARMACOLOGY

Ketamine [31][32]

Ketamine is a phencyclidine derivative that produces dissociative anesthesia, which is characterized by evidence on the EEG of dissociation between the thalamocortical and limbic systems. Dissociative anesthesia resembles a cataleptic state in which the eyes remain open with a slow nystagmic gaze. The patient is non communicative, although wakefulness may appear to be present. The patient is amnesic and analgesia is intense. Ketamine has advantage over propofol and etomidate in not requiring a lipid emulsion vehicle for dissolution and in producing profound analgesia at sub anesthetic doses.

Figure 6: Ketamine

STRUCTURAL ACTIVITY

Ketamine is a water soluble molecule that structurally resembles phencyclidine. The presence of an asymmetric carbon atom results in the existence of two optical isomers of ketamine. The left handed optical isomer of ketamine is designated S(+) ketamine and the right handed optical isomer is designated R(-) ketamine. The racemic form of ketamine has been the most frequently used preparation although S(+) is clinically available. When studied separately, S (+) ketamine produces more intense analgesia, more rapid metabolism and thus recovery. The fact that individual optical isomers of ketamine differ in their pharmacologic properties suggests that this drug interacts with specific receptors to induce these behaviors. The preservative used for ketamine is benzethonium chloride.

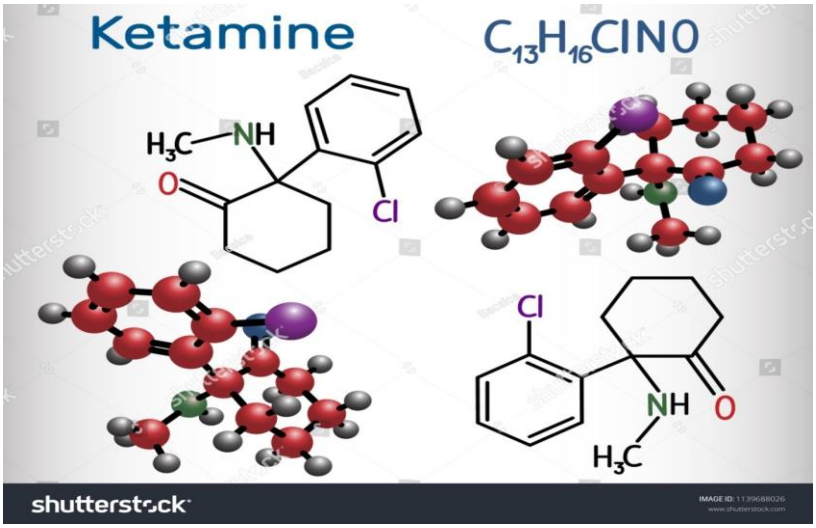


Figure 7: Structure of ketamine

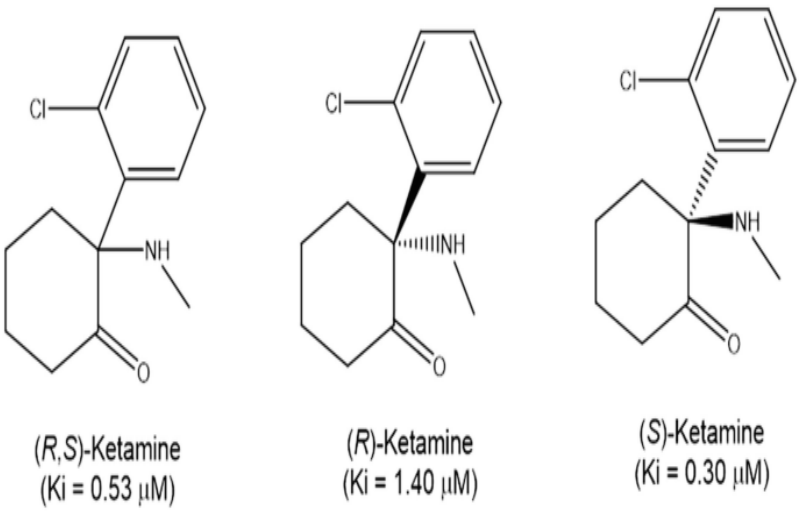


Figure 8: Isomers of ketamine

Mechanism of action

The mechanism of action of ketamine induced analgesia and dissociative anesthesia is unknown. Ketamine is known to interact with multiple CNS receptors but clear association has not been established. Ketamine binds non-competitively to the phencyclidine recognition site on NMDA (n methyl d aspartate) receptors.

In addition ketamine exerts effects at other sites including opioid receptors, monoaminergic receptors and muscarinic receptors and voltage sensitive sodium and L- type calcium channels neuronal nicotinic acetylcholine receptors. Ketamine suppresses neutrophil production of inflammatory mediators and improves blood flow. Direct inhibition of cytokines in blood by ketamine may contribute to the analgesic effects of this drug.

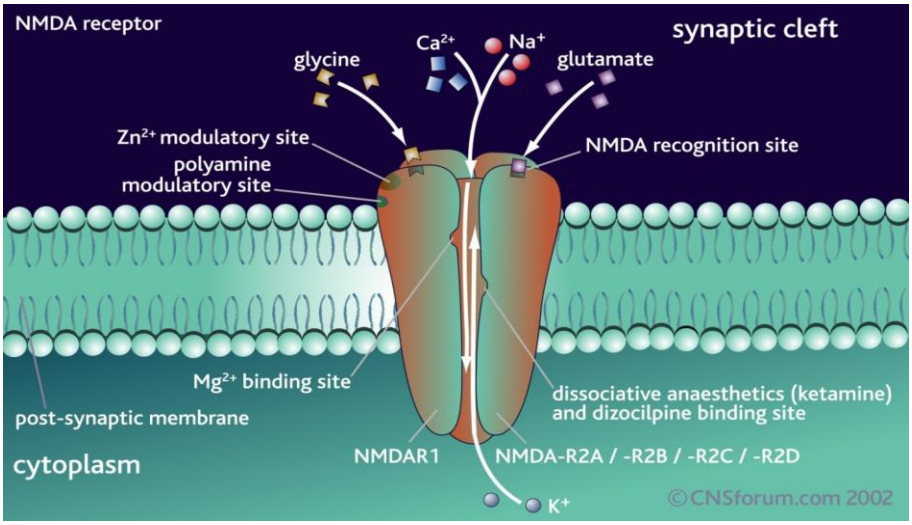


Figure 9: Mechanism of ketamine

N METHYL D ASPARTATE RECEPTOR ANTAGONISM

NMDA receptors (members of the glutamate receptors family) are ligand gated ion channels that are unique in that channel activation requires binding of the excitatory neurotransmitter, glutamate with glycine as an obligatory co-agonist. Ketamine inhibits activation of NMDA receptors by glutamate and decreases pre synaptic release of glutamate. The interaction with phencyclidine binding sites appears to be stereo selective, with the S (+) isomer having the greatest affinity.

OPIOID RECEPTORS

Ketamine has been ported to directly interact with mu, delta and kappa opioid receptors. In contrast other studies have suggested ketamine may be an antagonist at mu receptor and agonist at kappa receptors. Ketamine also weakly interacts with delta receptors.

Monoaminergic receptors

The antinociceptive action of ketamine may involve activation of descending inhibitory monoaminergic pain pathways.

Muscarinic receptors

Ketamine anesthesia is partially antagonized by anti cholinesterase drugs. The fact that ketamine produces anticholinergic symptoms (emergence delirium, bronchodilation) suggests that an antagonist effect of ketamine at muscarinic receptors is more likely than an agonist effect

Neuronal nicotinic acetylcholine receptors

Ketamine interacts with both heteromeric and homomeric alpha-7 nicotinic acetylcholine receptors. In alpha-7 receptors, a single subunit has been identified as a binding site in the extracellular loop between trans-membrane segments 2 and 3. Nicotinic inhibition by ketamine does not appear to affect sedation or immobility but may play a role in its analgesic effects.

PHARMACOKINETICS

The pharmacokinetics of ketamine is similar to thiopental in rapid onset of action, relatively short duration of action and high lipid solubility. Ketamine has a pKa of 7.5 at physiologic ph. Peak plasma concentrations of ketamine occur within 1 minute

after IV administration and within 5 minutes after IM injection. Ketamine is not significantly bound to plasma proteins and leaves the blood rapidly to be distributed into tissues.[32]

Initially ketamine is distributed to highly perfused tissues such as the brain, where the peak concentration may be four or five times that present in plasma. The extreme lipid solubility of ketamine (5 to 10 times that of thiopental) ensures its rapid transfer across blood brain barrier.

Furthermore, ketamine induced increase in cerebral blood flow could facilitate delivery of drug and thus enhance rapid achievement of high brain concentrations. Subsequently, ketamine is redistributed from the brain and other highly perfused tissues to less well perfused tissues, the release of which results in psychodynamic effects after emergence. Ketamine has a high hepatic clearance rate and a large volume of distribution resulting in an elimination half time of 2 to 3 hours.

METABOLISM

Ketamine is metabolized extensively by hepatic microsomal enzymes. An important pathway of metabolism is demethylation of ketamine by cytochrome P450 enzymes to form nor ketamine. This nor ketamine is one third as potent as ketamine. This active metabolite may contribute to prolonged effects of ketamine (analgesia), especially with repeated doses or a continuous infusion. Nor ketamine is eventually hydroxylated and then conjugated to form more water soluble and inactive glucuronide metabolites that are excreted by kidneys.

After IV administration, less than 4% of a dose of ketamine can be recovered from urine as unchanged drug. Fecal excretion accounts for less than 5% of an injected dose of ketamine. Chronic administration of ketamine stimulates the activity of enzymes responsible for its metabolism.

Accelerated metabolism of ketamine as a result of enzyme induction could explain, in part, the observation of tolerance to the analgesic effects of ketamine that occurs in patient receiving repeated doses of this drug. Indeed, tolerance may occur in burn patients receiving more than two short interval exposures to ketamine. Development of tolerance is also consistent with reports of ketamine dependence.

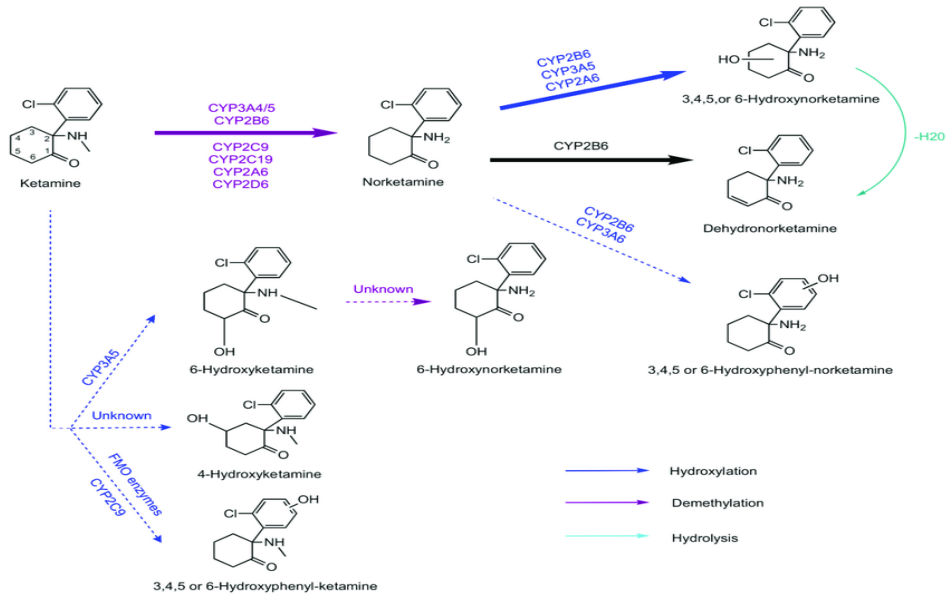


Figure 10: Metabolism of ketamine

CLINICAL USES

Ketamine is a unique drug evoking intense analgesia at subanesthetic doses and producing prompt induction of anesthesia when administered IV at higher doses. Inclusion of an anti sialogogue in the preoperative is often recommended to decrease the likelihood of coughing and laryngospasm due to ketamine induced salivary secretions. Glycopyrrolate may be preferable, as atropine can easily cross the blood brain barrier and could theoretically increase the incidence of emergence delirium.

ANALGESIA

Intense analgesia can be achieved with subanesthetic doses of ketamine, 0.2 to 0.5 mg/kg IV. Plasma concentrations of ketamine that produce analgesia are lower after oral than IM concentrations, presumably reflecting a higher nor ketamine concentration due to hepatic first pass metabolism that occurs after oral administration. Analgesia is thought to be greater for somatic than for visceral pain. The analgesic effects of ketamine are likely due to its activity in the thalamic and limbic systems, which are responsible for the interpretation of painful signals. Small doses of ketamine are also useful adjuvant to opioid analgesia.

Spinal cord sensitization is responsible for pain associated with touching or moving an injured body part that would normally not be painful. Central to the development of spinal cord sensitization is activation of NMDA receptors, which are located in the spinal cord dorsal horn. NMDA receptors are excitatory amino acid receptors that are important in pain processing and modulation of pain. Excitatory amino acids,

particularly glutamate, acting at NMDA receptors play an important role in spinal nociceptive pathways. Inhibition of spinal NMDA receptors by drugs such as ketamine, magnesium, and dextromethorphan is useful in the management of postoperative pain including decrease in analgesic consumption. Ketamine is useful as an analgesic adjuvant in patients with preexisting chronic pain syndromes who require surgery.

INDUCTION OF ANESTHESIA

Induction of anesthesia is produced by administration of 1 to 2 mg/kg IV or 4 to 8mg/kg IM. Consciousness is lost in 30 to 60 seconds after IV administration and in 2 to 4 minutes after IM injection. Unconsciousness is associated with maintenance of normal or only slightly depressed pharyngeal or laryngeal reflexes. Return of consciousness usually occurs in 10 to 20 minutes after an injected induced dose of ketamine, but return to full orientation, may require an additional 60 to 90 minutes.

Because of its rapid onset of action, ketamine has been used as an IM induction drug in children and difficult to manage mentally challenged patients regardless of age. Due to its intense analgesic activity, ketamine has been used extensively for burn dressing changes, debridement and skin grafting procedures. The excellent analgesia and ability to maintain spontaneous ventilation in an airway are important advantages of ketamine in these patients.

The administration of ketamine to patients with coronary artery disease is complicated by increased myocardial oxygen requirements that may accompany this drug's sympathomimetic effects on the heart. The beneficial effects of ketamine on airway resistance due to drug induced bronchodilation make this a potentially useful drug for rapid IV induction of anesthesia in patients with asthma. Ketamine should be used cautiously or avoided in patients with systemic or pulmonary hypertension or increased ICP.

IMPROVEMENT OF PSYCHIATRIC DISORDERS

NMDA receptors for glutamate are thought to be involved in the pathophysiology of mental depression and the mechanism of action of antidepressants. Ketamine in small doses improved the postoperative depressive state in patients with mental depression. Intermittent treatment with low dose ketamine also results in long- term suppression of obsessions and compulsion in patients with obsessive compulsive disorder.

SIDE EFFECTS

CENTRAL NERVOUS SYSYTEM

Ketamine is traditionally considered to increase cerebral blood flow and $CMRO_2$, although there is also evidence suggesting that this may not be a valid generalization.

Intracranial pressure

Ketamine is reported to be a potent cerebral vasodilator capable of increasing cerebral blood flow by 60% in the presence of normocapnia. As a result, patients with intracranial pathology are commonly considered vulnerable to sustained increases in ICP after administration of ketamine. In patients requiring craniotomy for brain tumor or cerebral aneurysm resection, administration of ketamine 1mg/kg IV, did not increase middle cerebral artery blood flow velocity and ICP decreased modestly.

In patients with traumatic brain injury, the administration of ketamine 1.5, 3.0 and 5.0mg/kg IV, during mechanical ventilation of the lungs resulted in significant decrease in ICP regardless of the dose of ketamine. These results in patients suggest that ketamine can be administered to patients with mildly increased ICP if administered with mild hyperventilation without adversely altering cerebral hemodynamics. Prior administration of thiopental, diazepam, or midazolam has been shown to blunt ketamine induced increase in cerebral blood flow.

Neuroprotective effects

Activation of NMDA receptors has been implicated in cerebral ischemic damage. The antagonist effect of ketamine on NMDA receptors suggest possible neuroprotective role for this drug although this remains an unproved hypothesis. Indeed, S (+) ketamine offers no greater neuroprotection than remifentanil.

Electroencephalogram

Ketamine's effect on the EEG is characterized by abolition of alpha rhythm and dominance of theta activity. Onset of delta activity coincides with loss of consciousness. At high doses, ketamine produces a burst suppression pattern. Ketamine induced excitatory activity occurs in both the thalamus and limbic systems without evidence of subsequent spread of seizure activity to cortical areas. Ketamine does not alter the seizure threshold in epileptic patients. Although myoclonic and seizure like activity may occur in normal patients, EEG evidence of cortical epileptic activity is absent and ketamine is considered to possess anticonvulsant activity.

Somatosensory evoked potentials

Ketamine increase the cortical amplitude of somatosensory evoked potentials. The ketamine induced increase in amplitude is attenuated by nitrous oxide. Auditory and visual evoked responses are decreased by ketamine.

CARDIOVASULAR SYSTEM

Ketamine produces cardiovascular effects that resemble sympathetic nervous system stimulation. Indeed, a direct negative cardiac inotropic is usually overshadowed by central sympathetic stimulation.

Hemodynamic effects

Systemic and pulmonary arterial blood pressure, heart rate, cardiac output, cardiac work and myocardial oxygen requirements are increased after IV administration of ketamine. The increase in systolic blood pressure in adults receiving clinical doses of ketamine is 20 to 40 mm Hg, with a slightly smaller increase in diastolic blood pressure. Typically, systemic blood pressure increases progressively during the first 3 to 5 minutes after IV injection of ketamine and then decreases to pre drug levels over the next 10 to 20 minutes. Ketamine has been shown to decrease the need for inotropic support in septic patients, perhaps reflecting an inhibition of catecholamine reuptake.

Cardiac rhythm

The effect of ketamine on cardiac rhythm is inconclusive. There is evidence that ketamine enhances the dysrhythmogenicity of epinephrine. The mechanisms for ketamine induced cardiovascular effects are complex. Direct stimulation of the CNS leading to increased sympathetic nervous system outflow seems to be the most important mechanism for cardiovascular stimulation.

Increase in plasma concentrations of epinephrine and norepinephrine rise occur as early as 2 minutes after IV administration of ketamine and return to control levels 15 minutes later. In vitro, ketamine produces direct myocardial depression, emphasizing the importance of an intact sympathetic nervous system for the cardiac stimulating effect of this drug. [31]

Ventilation and airway

Ketamine does not produce significant depression of ventilation. The ventilator response to carbon dioxide is maintained during ketamine anesthesia and the $Paco_2$ is unlikely to increase more than 3 mm Hg. Upper airway reflexes remain relatively intact and upper airway skeletal muscle tone is well maintained after administration of ketamine. Salivary and tracheobronchial mucous gland secretions are increased by IM or IV administration of ketamine, leading to the frequent recommendation of anti-sialagogue be included in the preoperative medication when use of this drug is anticipated.

Ketamine has a broncho dilatory activity and has been successfully used to treat bronchospasm in the operating room and ICU. The mechanism by which ketamine produces airway relaxation is unclear, although several mechanisms have been suggested, including increased levels of circulating catecholamine concentration, inhibition of catecholamine uptake, voltage-sensitive calcium channel block, and inhibition of postsynaptic nicotinic or muscarinic receptors.[32]

Emergence delirium

Emergence from ketamine anesthesia in the postoperative period may be associated with visual, auditory, proprioceptive and confusional illusions, which may progress to delirium. Emergence delirium occurs secondary to ketamine induced depression of the inferior colliculus and medial geniculate nucleus, leading to misinterpretation of auditory and visual stimuli. Furthermore, the loss of skin and musculoskeletal

sensations result in decreased ability to perceive gravity, thereby producing a sensation of bodily detachment or floating in space.

LOCAL ANESTHETICS [33][34][35]

Local anesthetics are used to provide analgesia and anesthesia for various surgical and nonsurgical procedures. These drugs are also used for acute and chronic pain management, to reduce perioperative stress, to improve perioperative outcomes, and to treat dysrhythmias. Local anesthetics produce reversible conduction blockade of impulses along central and peripheral pathways. With progressive increases in concentrations of local anesthetics, the transmission of autonomic, somatic, sensory, and somatic motor impulses is interrupted, producing autonomic nervous system blockade, sensory anesthesia, and skeletal muscle paralysis in the area innervated by the affected nerve.

Molecular structure

Local anesthetics consist of a lipophilic and a hydrophilic portion separated by a connecting hydrocarbon chain. The hydrophilic group is usually a tertiary amine, such as diethylamine, whereas the lipophilic group is usually an unsaturated aromatic ring, such as paraminobenzoic acid. The lipophilic portion is essential for anesthetic activity and therapeutically useful local anesthetic require a delicate balance between lipid solubility and water solubility.

In almost all instances, an ester or an amide bond links the hydrocarbon chain to the lipophilic aromatic ring. The nature of this bond is the basis for classifying drugs that produce conduction blockade of nerve impulses as ester local anesthetics or amide local anesthetics.

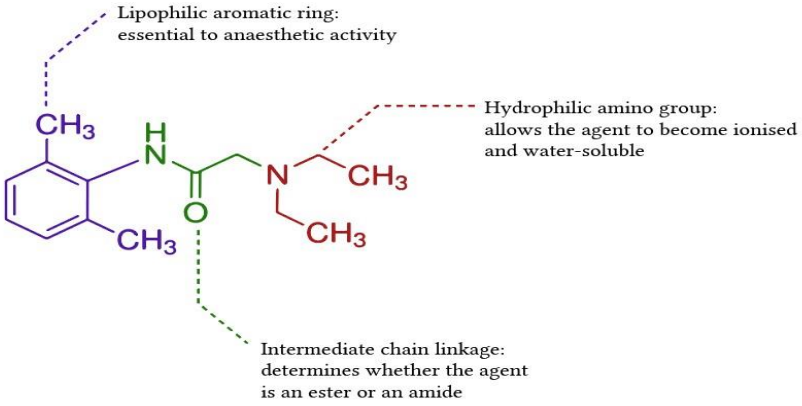


Figure 11: Molecular structure of local anesthetics

Structure activity relationships

Modifying the chemical structure of a local anesthetic alters its pharmacologic effects. For example, lengthening the connecting hydrocarbon chain or increasing the number of carbon atoms on the tertiary amine or aromatic ring often results in a local anesthetic with a different lipid solubility, potency, rate, rate of metabolism, and duration of action.

Substituting a butyl group for the amine group on the benzene ring of procaine results in tetracaine. Compared with procaine, tetracaine is more lipid soluble, is 10 times more potent, and has a longer duration of action corresponding to 4 to 5 fold decrease in the rate of metabolism.

Mepivacaine, bupivacaine, and ropivacaine are characterized as pipecoloxylidides. Mepivacaine has a methyl group on the piperidine nitrogen atom of the molecule. Addition of a butyl group to the piperidine nitrogen of mepivacaine results in bupivacaine, which is 35 times more lipid soluble and has a potency and duration of action 3 to 4 times that of mepivacaine.

Ropivacaine structurally resembles bupivacaine and mepivacaine, with a propyl group on the piperidine nitrogen atom of the molecule. The pipecoloxylidide local anesthetics are chiral drugs because their molecule posses an asymmetric carbon atom. As such these drugs have a left(S) or right (R) handed configuration.

Various formulation and drug delivery system including liposomes, cyclodextrins, and biopolymers are studied to prolong the duration and to limit the toxicity of local anesthetics. Liposomes, hydrophobic-based polymer particles such as Poly(lactic-co-glycolic) microspheres and solid polymers such as Poly (sebaic-co-ricinoleic acid) P(SA:RA) and their combination with synthetic and natural local anesthetic are examples of delivery systems currently in clinical use. Drugs such as lidocaine, tetracaine, and bupivacaine have been incorporated into liposomes to prolong the duration of action and decrease toxicity.

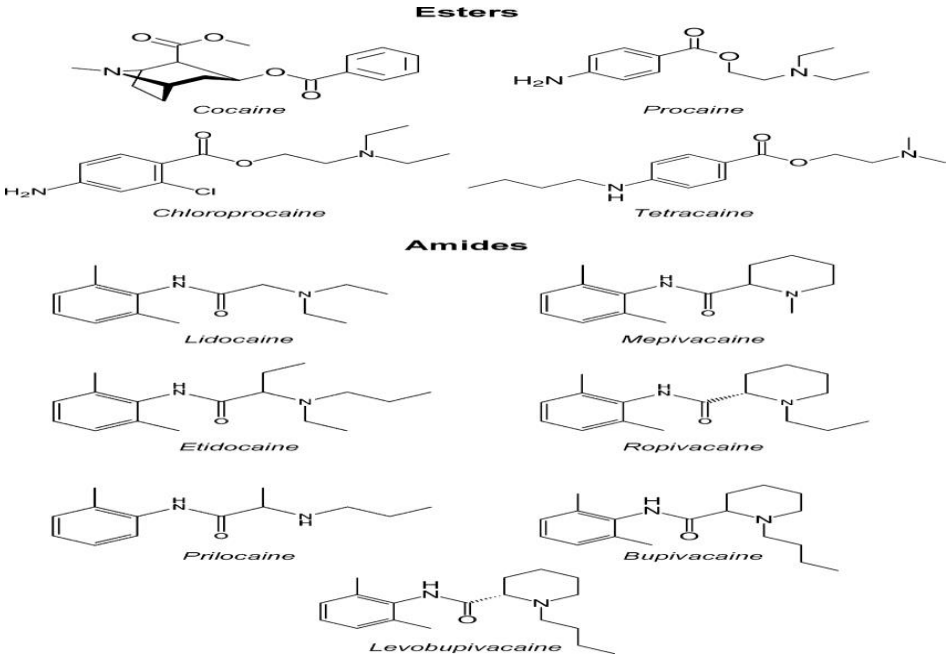


Figure 12: Types of local anesthetics

MECHANISM OF ACTION

Local anesthetics bind to specific sites in voltage-gated Na^+ channels. They block Na^+ current, thereby reducing excitability of neuronal, cardiac or central nervous system tissue. Local anesthetics prevent transmission of nerve impulses (conduction blockade) by inhibiting passage of sodium ions through ion-selective sodium channels in nerve membranes.

The sodium channel itself is a specific receptor local anesthetic molecules. Failure of sodium ion channel permeability to increase slows the rate of depolarization such that threshold potential is not reached and thus an action potential is not propagated. Local anesthetics do not alter the resting transmembrane potential or threshold potential.

In addition to sodium ion channels, local anesthetics block voltage-dependent potassium ion channels. Compared with sodium ion channels, local anesthetics exhibit a much lower affinity for potassium channels. However, blockade of potassium ion channels might explain broadening of the action potential in the presence of local anesthetics. Although local anesthetics are considered principally ion channel blockers, there is evidence that these drugs may also on G protein-coupled receptors.

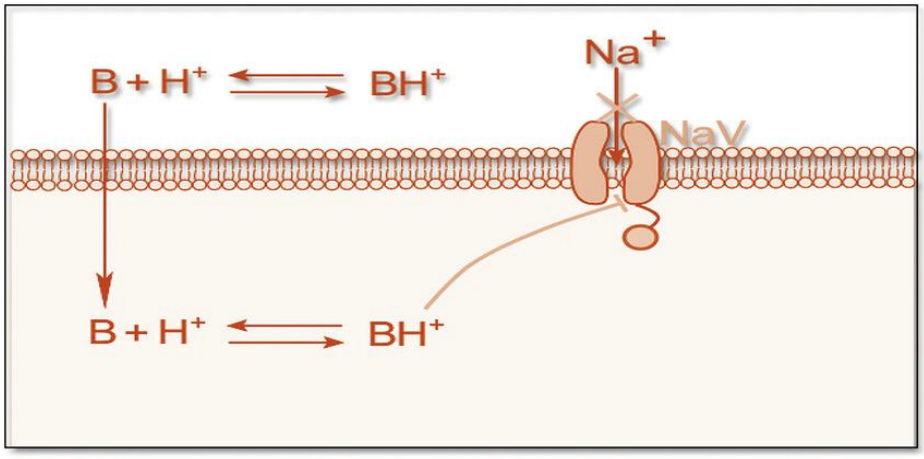


Figure 13: Mechanism of local anesthetics

Pharmacokinetics

Local anesthetics are weak bases that have pK values somewhat above physiologic pH. As a result, <50% of the local anesthetic exists in a lipid-soluble nonionized form at physiologic pH. Local anesthetics with pKa nearest to physiologic pH have the most rapid onset of action, reflecting the presence of an optimal ratio of ionized to nonionized drug fraction. Intrinsic vasodilator activity will also influence apparent potency and duration of action.

Absorption and Distribution

Absorption of a local anesthetic from its site of injection into the systemic circulation is influenced by the site of injection and dosage, use of epinephrine, and pharmacologic characteristics of the drug. The ultimate plasma concentration of a local anesthetic is determined by the rate of tissue distribution and the rate of clearance of the drug.

For example, the infusion of lidocaine for 1 minute is followed by a rapid decrease in the drug's plasma concentration that is paralleled by an initial high uptake into lungs and distribution of the local anesthetic to highly perfused tissues. Lipid solubility of the local anesthetic is important in this redistribution as well as being a primary determinant of intrinsic local anesthetic potency.

After distribution to highly perfused tissues, the local anesthetic is redistributed to less well perfused tissues, including skeletal muscles and fat. In addition to the tissue blood flow and lipid solubility of the local anesthetic, patient-related factors such as age, cardiovascular status, and hepatic function will also influence the absorption and plasma concentration of local anesthetics. Protein binding parallels lipid solubility of the local anesthetics and is inversely related to the plasma concentration of the drug.

Metabolism of Local Anesthetics

Amide local anesthetics undergo varying rates of metabolism by microsomal enzymes located primarily in the liver. The initial step is conversion of the amide base to aminocarboxylic acid and a cyclic aniline derivative. Complete metabolism

usually involves additional steps, such as hydroxylation of the aniline moiety and N-dealkylation of the aminocarboxylic acid.

Compared with that of ester local anesthetics, the metabolism of amide local anesthetics is more complex and slower. This slower metabolism means that sustained increase of the plasma concentrations of amide local anesthetics, and thus systemic toxicity, are more likely than with ester local anesthetics.

LIDOCAINE [34][35][36]

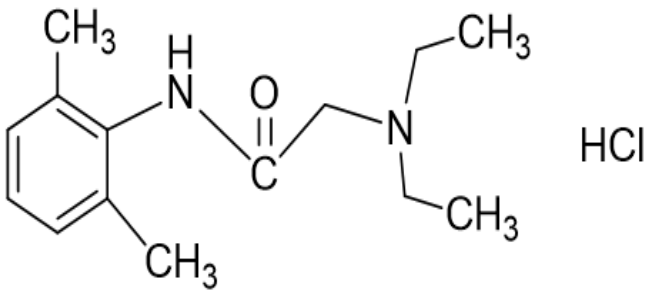


Figure 14: Structure of lidocaine

The principal metabolic pathway of lidocaine is oxidative dealkylation in the liver to monoethylglycinexylidide followed by hydrolysis of this metabolite to xylidide. Monoethylglucinexylidide has approximately 80% of the activity of lidocaine for protecting against cardiac dysrhythmias. This metabolite has a prolonged elimination half-time, accounting for its efficacy in controlling cardiac dysrhythmias after the infusion of lidocaine is discontinued.

Xylidide has only 10% of the cardiac antidysrhythmic activity of lidocaine. In humans, approximately 75% of xylidide is excreted in the urine as 4-hydroxy-2,6-dimethylaniline. Hepatic disease or decrease in hepatic blood flow, which may occur during anesthesia, can decrease the rate of metabolism of lidocaine. For example, the elimination half-time of lidocaine is increased more than fivefold in patients with liver dysfunction compared with normal patients.

Decreased hepatic metabolism of lidocaine should be anticipated when patients are anesthetized with volatile anesthetics. Maternal clearance of lidocaine is prolonged in presence of pregnancy-induced hypertension, and repeated administration of lidocaine can result in higher plasma concentrations than in normotensive parturients.

PHARMACODYNAMICS

Excessive blood levels in lidocaine can cause change in cardiac output, total peripheral resistance, and mean arterial pressure. With central neural blockade these changes may be attributable to the block of autonomic fibres, a direct depressant effect of the local anesthetic agent on various components of the cardiovascular system. The net effect is normally a modest hypotension when the recommended doses are not exceeded.

In particular, such cardiac effects are likely associated with the principal effect that lidocaine elicits when it binds and blocks sodium channels, inhibiting the ionic fluxes required for the initiation and conduction of electrical action potential impulses necessary to facilitate muscle contraction.

Moreover, lidocaine possesses a dissociation constant (pKa) of 7.7 and is considered a weak base. As a result, about 25% of lidocaine molecules will be unionized and available at physiologic pH of 7.4 to translocate inside nerve cells, which means lidocaine elicits an onset of action more rapidly than other local anesthetics.

Route of elimination

The excretion of unchanged lidocaine and its metabolites occurs predominantly via the kidney with less than 5% in the unchanged form appearing in the urine. The renal clearance is inversely related to its protein binding affinity and the pH of the urine. This suggests that excretion of lidocaine occurs by non ionic diffusion.

Half-life

The elimination half-life of lidocaine hydrochloride following an intravenous bolus injection is typically 1.5 to 2.0 hours. Because of the rapid rate at which lidocaine hydrochloride is metabolized, any condition that affects liver function may alter lidocaine kinetics. The half-life may be prolonged two-fold or more in patients with liver dysfunction. The mean systemic clearance observed for intravenously administered lidocaine is approximately 0.64 +/- 0.18 L/min.

Toxicity

Symptoms of overdose or acute systemic toxicity involve central nervous system toxicity that presents with symptoms of increasing severity. Patients may present

initially with circumoral paraesthesia, numbness of the tongue, light-headedness, hyperacusis, and tinnitus. Visual disturbance and muscular tremors or muscle twitching are more serious and precede the onset of generalized convulsions . These signs must not be mistaken for neurotic behavior. Unconsciousness and grand mal convulsions may follow, which may last from a few seconds to several minutes.

Hypoxia and hypercapnia occur rapidly following convulsions due to increased muscular activity, together with the interference with normal respiration and loss of the airway. In severe cases, apnoea may occur. Acidosis increases the toxic effects of local anesthetics. Effects on the cardiovascular system may be seen in severe cases. Hypotension, bradycardia, arrhythmia and cardiac arrest may occur as a result of high systemic concentrations, with potentially fatal outcome .

Pregnancy Category B has been established for the use of lidocaine in pregnancy, although there are no formal, adequate, and well-controlled studies in pregnant women. General consideration should be given to this fact before administering lidocaine to women of childbearing potential, especially during early pregnancy when maximum organogenesis takes place. Ultimately, although animal studies have revealed no evidence of harm to the fetus, lidocaine should not be administered during early pregnancy unless the benefits are considered to outweigh the risks.

Lidocaine readily crosses the placental barrier after epidural or intravenous administration to the mother. The ratio of umbilical to maternal venous concentration is 0.5 to 0.6. The fetus appears to be capable of metabolizing lidocaine at term. The elimination half-life in the newborn of the drug received in utero is

about three hours, compared with 100 minutes in the adult. Elevated lidocaine levels may persist in the newborn for at least 48 hours after delivery. Fetal bradycardia or tachycardia, neonatal bradycardia, hypotonia or respiratory depression may occur.[35]

Local anesthetics rapidly cross the placenta and when used for epidural, paracervical, pudendal or caudal block anesthesia, can cause varying degrees of maternal, fetal and neonatal toxicity. The potential for toxicity depends upon the procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus and neonate involve alterations of the central nervous system, peripheral vascular tone, and cardiac function.

Maternal hypotension has resulted from regional anesthesia. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and positioning her on her left side will help prevent decreases in blood pressure. The fetal heart rate also should be monitored continuously, and electronic fetal monitoring is highly advisable.

Epidural, spinal, paracervical, or pudendal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. In one study, paracervical block anesthesia was associated with a decrease in the mean duration of first stage labor and facilitation of cervical dilation. However, spinal and epidural anesthesia have also been reported to prolong the second stage of labor by

removing the parturient's reflex urge to bear down or by interfering with motor function. The use of obstetrical anesthesia may increase the need for forceps assistance.

The use of some local anesthetic drug products during labor and delivery may be followed by diminished muscle strength and tone for the first day or two of life. The long-term significance of these observations is unknown. Fetal bradycardia may occur in 20 to 30 percent of patients receiving paracervical nerve block anesthesia with the amide-type local anesthetics and may be associated with fetal acidosis. Fetal heart rate should always be monitored during paracervical anesthesia. The physician should weigh the possible advantages against risks when considering a paracervical block in prematurity, toxemia of pregnancy, and fetal distress. Careful adherence to the recommended dosage is of the utmost importance in obstetrical paracervical block.

Failure to achieve adequate analgesia with recommended doses should arouse suspicion of intravascular or fetal intracranial injection. Cases compatible with unintended fetal intracranial injection of local anesthetic solution have been reported following intended paracervical or pudendal block or both. Babies so affected present with unexplained neonatal depression at birth, which correlates with high local anesthetic serum levels, and often manifest seizures within six hours. Prompt use of supportive measures combined with forced urinary excretion of the local anesthetic has been used successfully to manage this complication.

MATERIALS AND METHODS

SOURCE OF DATA

This study was carried out in the Department of Anesthesiology, BLDE (Deemed to be University), Shri. B. M. Patil Medical College, Hospital and Research center, Vijayapura.

METHOD OF COLLECTION OF DATA:

Study method: The study population of 105 with age, weight, and sex-matched have been assigned using computerized random table numbers into three groups with 35 patients in each group.

Sample size: Based on a previous study, The Mean±SD of time to Extubation (min) is 7.6±1.3, 6.3±1.43, and 6.1±1.50 in control, K-N1 AND K-N2 groups resp. (ref)(1) Using a type 2 error of 0.05 and power of 90%, the calculated sample size 35 per group ((i.e., a total sample size of 105 assuming equal group sizes) with an effect size of 0.355 for detecting a difference in means between three groups. Using G* power software 3.1.9.7.

STUDY POPULATION

This study have been done on pediatric patients aged 5-12 years undergoing tonsillectomy under general anesthesia.

INCLUSION CRITERIA:

- ASA I and II class of patients
- Age between 5-12 years.
- Both gender pediatric patients.
- Patients undergoing adenoidectomy.

EXCLUSION CRITERIA:

- Patient having a congenital abnormality
- Children with cardiac, respiratory, and neuropsychiatric disorders
- Patients having a history of allergy to drugs
- Use of lidocaine spray intraoperatively

METHODOLOGY:

Pre-anesthetic evaluation:

Pre-anesthetic evaluation included the following

History:

History of underlying medical illness, previous history of surgery, anesthetic exposure, and hospitalization elicited.

Physical examination

General condition of the patient

Vital signs -heart rate, blood pressure, respiratory rate,

Height and weight

Examination of the respiratory system, cardiovascular system, central nervous system, and vertebral system.

Airway assessment by Mallampatti grading

Procedure will be explained to the patient and patient attender.

INVESTIGATIONS

Investigations required in this study were routine standardized procedures like: Complete blood count, bleeding time, clotting time, HIV, HbsAg, urine routine, chest radiograph.

PROCEDURE

The patients enrolled in this study were randomly divided into three groups by computer generated randomization table depending on the pre-emptive nebulized drug. The groups are:

- **GROUP K** - Patients received ketamine (2mg/kg) + normal saline 0.9% nebulization- 4ml
- **GROUP L** - Patients received lidocaine2% (4mg/kg) + normal saline 0.9% nebulization - 4ml
- **GROUP C** - Control group, patients received saline 0.9% nebulization (4ml)

The pre-anesthetic checkup was done in the ward and faces pain scale have been explained to the patient and their attender. Patients were kept nil by mouth 6 hours before surgery. Patients were selected for the study based on the inclusion and exclusion criteria.

The procedure had been explained to the patient, and informed consent was taken. The study population were randomly arranged for nebulization, and vitals such as Spo2, respiratory rate, heart rate, and blood pressure were recorded before nebulization. These were the baseline vitals. Nebulization have been provided by a standard hospital jet nebulizer.

Fifteen minutes before induction of general anesthesia, all the patients were nebulized with ketamine or lidocaine, or saline. Spo2, respiratory rate, heart rate, and blood pressure were recorded after nebulization. The anesthesia technique was standardized for all groups. Anesthesia was induced with propofol 2-3 mg/kg, fentanyl 1microgram/kg, atracurium 0.5mg/kg.

The size of the endotracheal tube was selected according to age. Anesthesia and muscle relaxant have been maintained with sevoflurane in a 50%oxygen /air mixture and 0.15mg/kg atracurium at fixed intervals. At the end of the procedure, neuromuscular blockade was reversed with standard doses of neostigmine and glycopyrrolate. Patients was extubated awake in recovery position and transported to the post-anesthesia care unit.

Faces pain scale revised scoring have been recorded on admission to the post-anesthesia care unit and at 30min,1,2,3,4,5 and 6 hours postoperatively. Patients

received IV paracetamol 15mg/kg as rescue analgesia if requested, and the total consumption of postoperative rescue analgesia was recorded.

Any perioperative adverse events were treated and recorded, such as hypotension, hypertension, bradycardia, tachycardia, desaturation (<95%), postoperative vomiting, agitation, excess salivation, and hallucination. The target of the study was to estimate the total consumption of rescue analgesics in the first 6-hour postoperative period.

If there was fall in saturation post operatively, those patients were given oxygen at the rate of 4l/min to maintain saturation. Those patients who complained of hallucinations were given injection midazolam with a minimum dose of 0.05 to 0.1mg per kg to alleviate the symptoms.

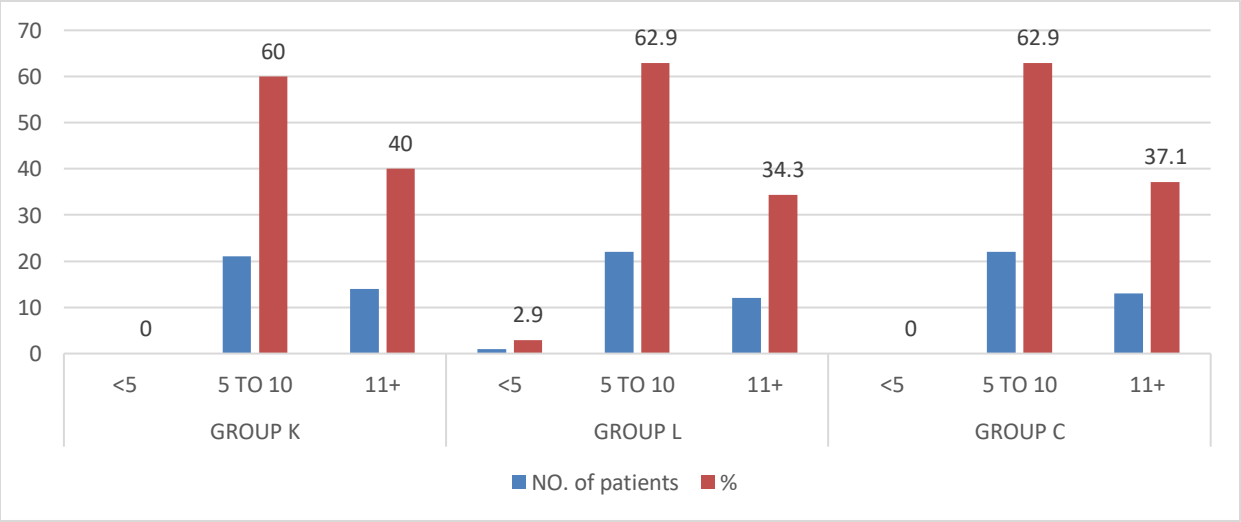
RESULTS

1. AGE

Table 1: Age distribution between the groups.

AGE		NO OF PATIENTS	%	CHI SQUARE TEST	P VALUE
GROUP K	<5	0	0	2.185	0.702
	5 TO 10	21	60		
	>11	14	40		
GROUP L	<5	1	2.9		
	5 TO 10	22	62.9		
	>11	12	34.3		
GROUP C	<5	0	0		
	5 TO 10	22	62.9		
	>11	13	37.1		
Statistically insignificant as P value is more then 0.05					

Mean age distribution between the groups were statistically not significant, it was comparable between the groups as shown in the table.



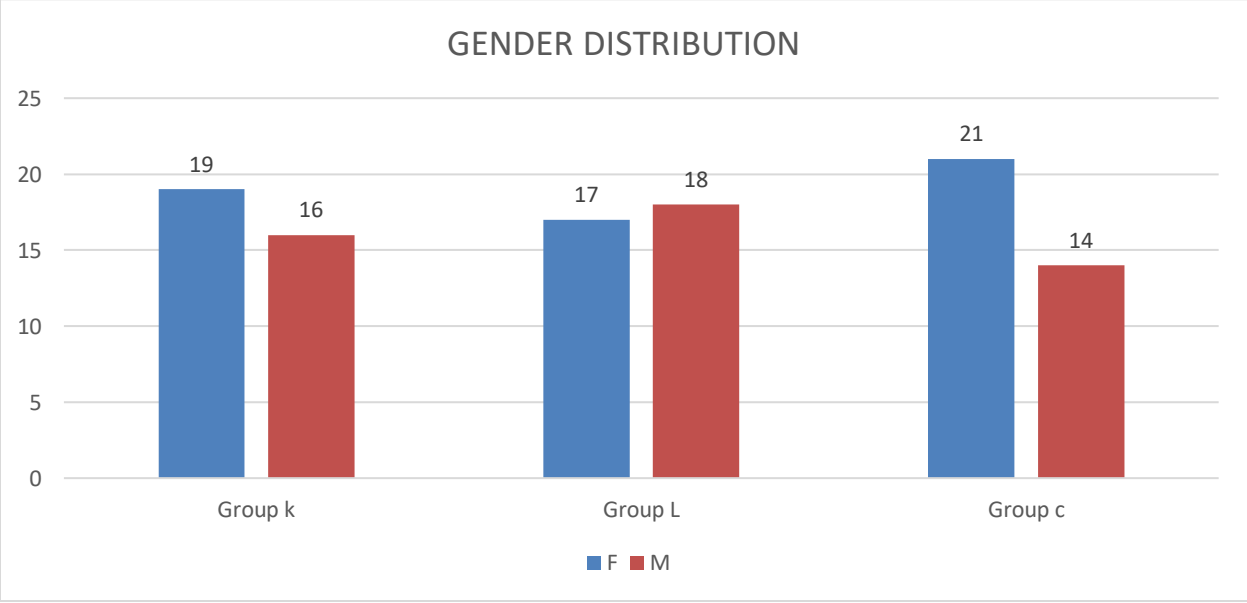
Graph 1: Age distribution between the groups

2. GENDER

Table 2: Gender distribution between the groups.

GENDER		No of patients	%	Chi-Square	P- value
GROUP K	F	19	54.3%	0.921	0.631
	M	16	45.7%		
GROUP L	F	17	48.6%		
	M	18	51.4%		
GROUP C	F	21	60.0%		
	M	14	40.0%		
Statistically insignificant as P value more than 0.05					

There is no significant difference in gender between the groups, gender was comparable between the groups and there were majorly females present in the study.



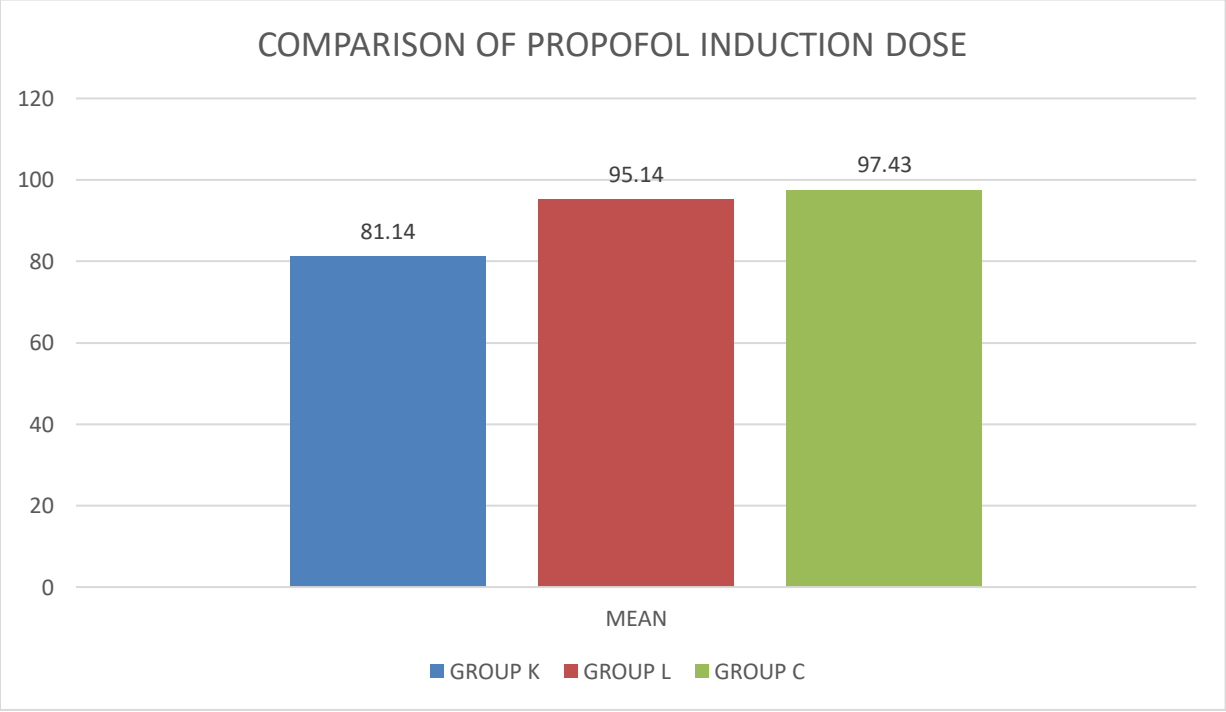
Graph 2: Gender distribution between the groups.

3. PROPOFOL INDUCTION DOSE

Table 3: Comparison of propofol induction dose among groups

PROPOFOL INDUCTION DOSE	No of patients	MEAN	SD	KRUSKALWALLIS TEST	P VALUE
GROUP K	35	81.14	11.054	42.276	0
GROUP L	35	95.14	9.813		
GROUP C	35	97.43	6.108		
Statistically significant as P value is less than 0.05					

There is significant difference between all the groups in propofol induction dose with group K patients received lesser Propofol dose.



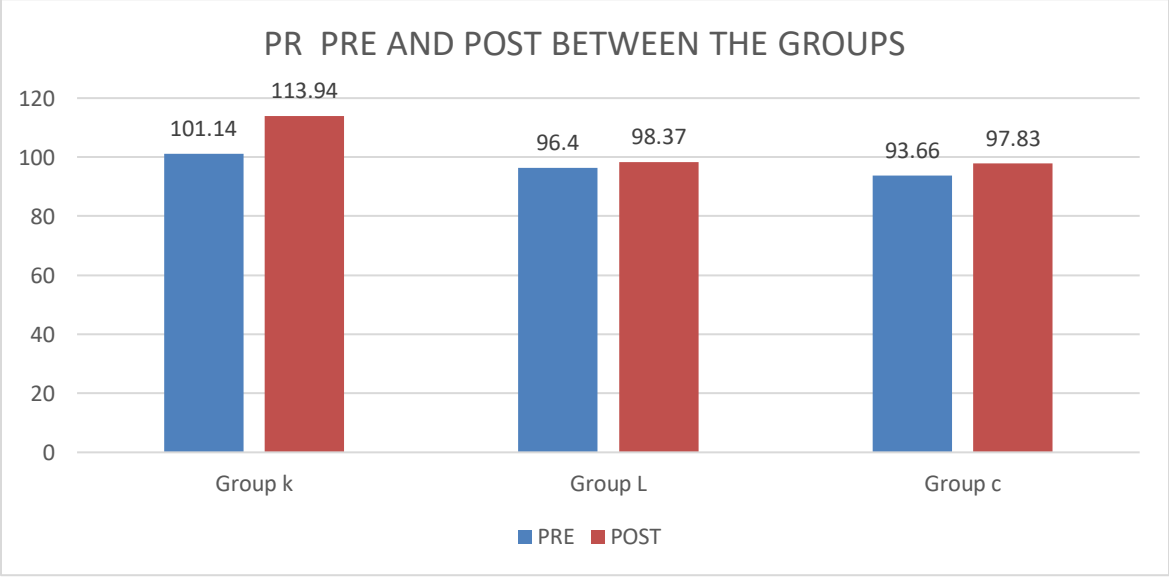
Graph 3: Comparison of propofol induction between groups

4. PULSE RATE

Table 4: Comparison of preoperative and postoperative pulse rate among groups

	PULSE RATE	MEAN	SD	P VALUE
GROUP K	PRE	101.14	6.912	0.000
	POST	113.94	8.728	
GROUP L	PRE	96.40	6.495	0.000
	POST	98.37	9.117	
GROUP C	PRE	93.66	5.207	0.000
	POST	97.83	5.032	
Statistically significant as P value is less than 0.05				

There is significant difference in pulse rate among all groups before and after nebulization, with more number of patients in group K having increased pulse rate after receiving nebulization.



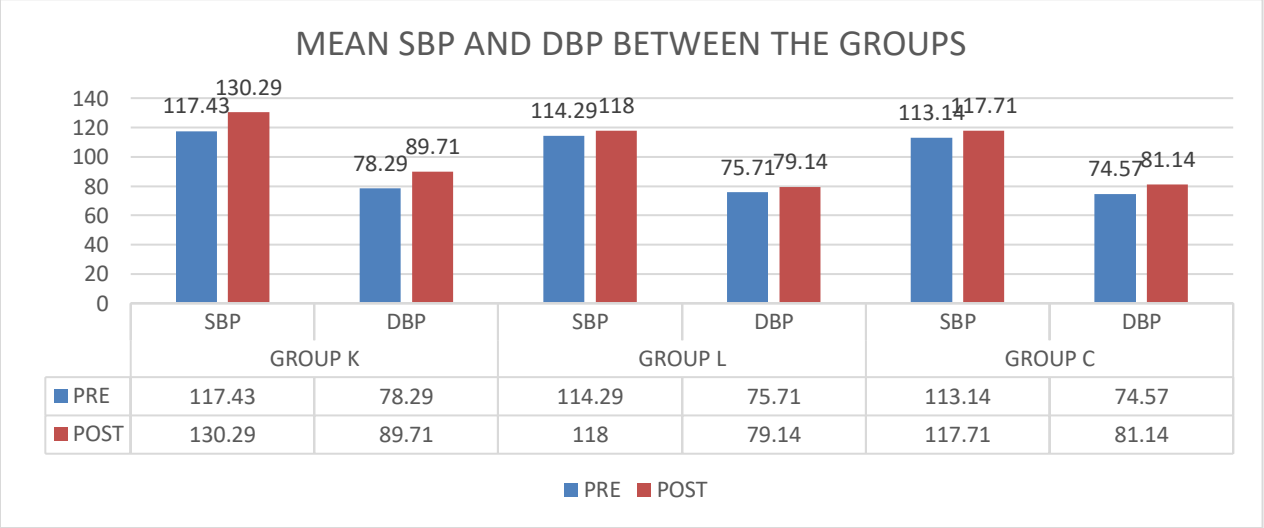
Graph 4: Comparison of pulse rate between pre operative and post operative between groups

5. BLOOD PRESSURE

Table 5: Comparison of pre operative and post operative SBP and DBP values among the groups

			MEAN	SD	P VALUE
GROUP K	SBP	PRE	117.43	7.005	0.000
		POST	130.29	8.907	
	DBP	PRE	78.29	5.137	0.000
		POST	89.71	5.137	
GROUP L	SBP	PRE	114.29	6.081	0.000
		POST	118.00	6.325	
	DBP	PRE	75.71	6.547	0.005
		POST	79.14	7.017	
GROUP C	SBP	PRE	113.14	5.827	0.001
		POST	117.71	5.983	
	DBP	PRE	74.57	5.606	0.000
		POST	81.14	6.311	
Statistically significant as P value is less than 0.05					

There is difference in SBP and DBP in all groups which is statistically significant, indicating a rise in bp after nebulization.



	GROUP K		GROUP L		GROUP C	
	SBP	DBP	SBP	DBP	SBP	DBP
PRE	117.43	78.29	114.29	75.71	113.14	74.57
POST	130.29	89.71	118	79.14	117.71	81.14

Graph 5: Comparison of pre operative and post operative SBP and DBP values among the groups

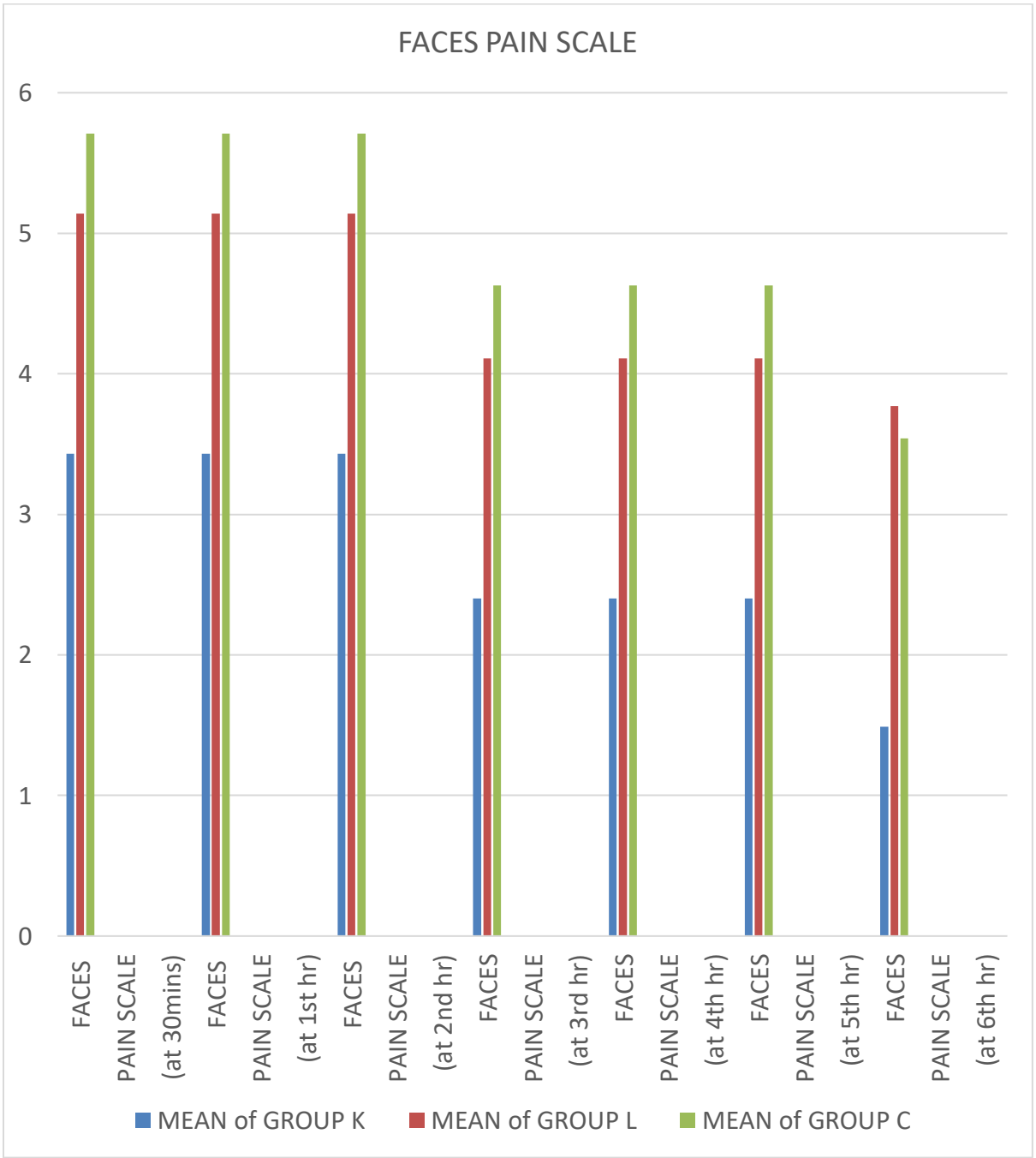
6. FACES PAIN SCALE

Table 6: Comparison of faces pain scale among groups

	MEAN ± SD			
	GROUP K	GROUP L	GROUP C	P-VALUE
FACES PAIN SCALE (at 30mins)	3.43 ± 1.42	5.14 ± 1.11	5.71± 1.20	0.000
FACES PAIN SCALE (at 1st hr)	3.43 ± 1.42	5.14 ± 1.11	5.71± 1.20	0.000
FACES PAIN SCALE (at 2nd hr)	3.43 ± 1.42	5.14 ± 1.11	5.71± 1.20	0.000
FACES PAIN SCALE (at 3rd hr)	2.4 ± 1.66	4.11 ± 1.18	4.63 ± 1.23	0.000
FACES PAIN SCALE (at 4th hr)	2.4 ± 1.66	4.11 ± 1.18	4.63 ± 1.23	0.000
FACES PAIN SCALE (at 5th hr)	2.4 ± 1.66	4.11 ± 1.18	4.63 ± 1.23	0.000
FACES PAIN SCALE (at 6th hr)	1.49 ± 1.56	3.77 ± 1.26	3.54 ± 1.19	0.000
Statistically significant as P value is less than 0.05				

The faces pain scale scores have a significant difference among all the groups with scores lesser in group K patients.

Graph 6: Comparison of faces pain scale among groups

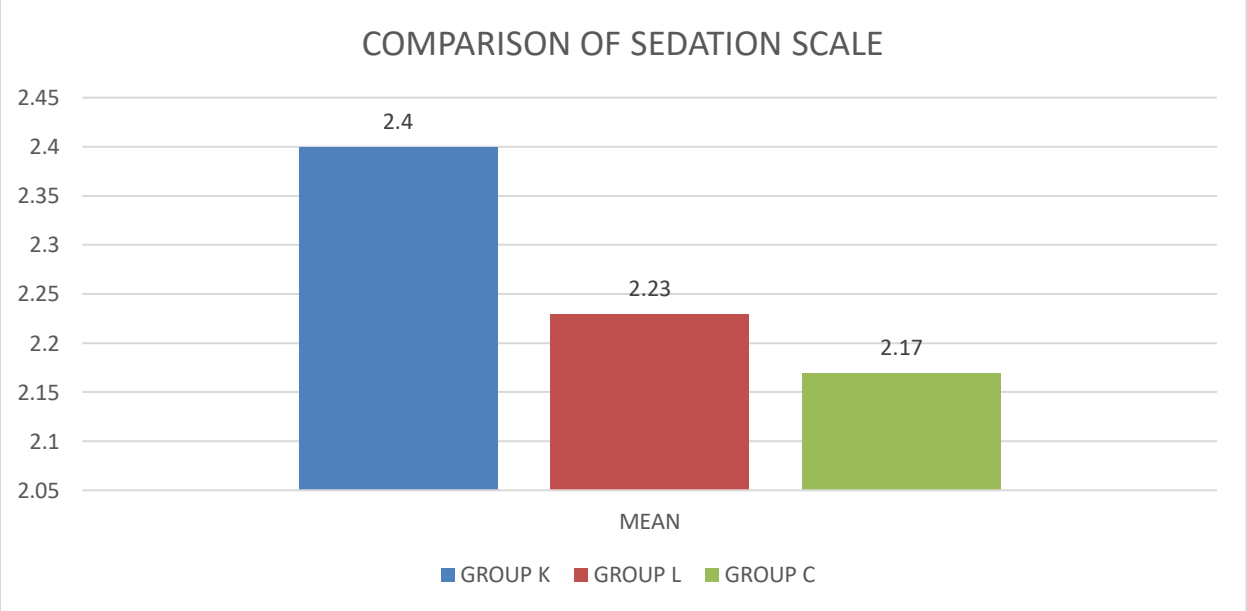


7. SEDATION SCALE

Table 7: Comparison of sedation scale among group

SEDATION SCALE	No of patients	MEAN	SD	KRUSKALWALLIS TEST	P VALUE
GROUP K	35	2.4	0.881	1.497	0.473
GROUP L	35	2.23	0.426		
GROUP C	35	2.17	0.382		
Statistically insignificant as P value is more than 0.05					

There is no significant difference among all groups in sedation scale scores after nebulization.



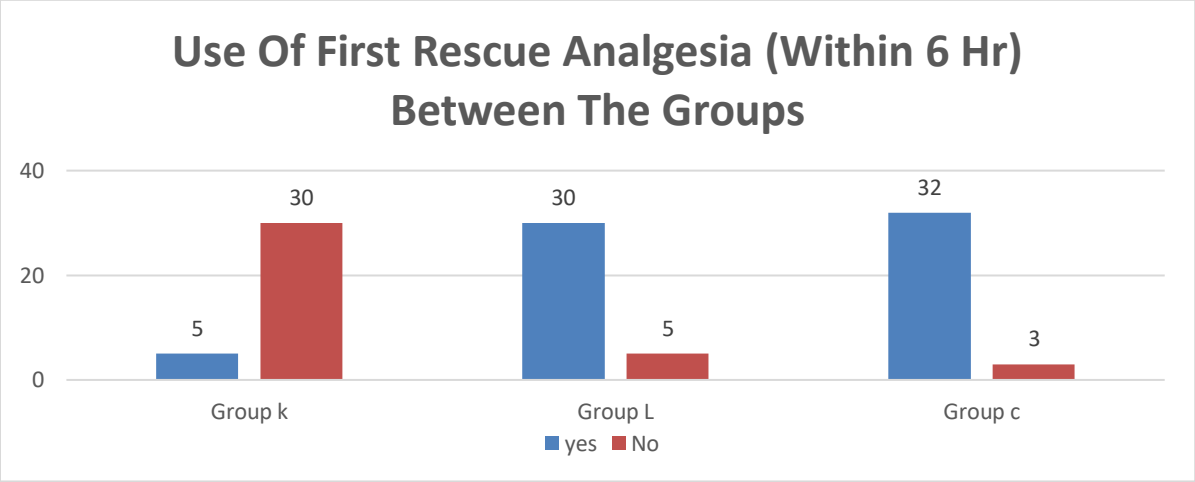
Graph 7: Comparison of sedation scale among group

8. RESCUE ANALGESIA

Table 8: Comparison of rescue analgesia among groups

GENDER		Number Of Patients	%	CHI SQUARE TEST	P VALUE
GROUP K	yes	5	14.3%	56.005	<0.001
	No	30	85.7%		
GROUP L	yes	30	85.7%		
	No	5	14.3%		
GROUP C	yes	32	91.4%		
	No	3	8.6%		
Statistically significant as P value is less than 0.05					

There is significant difference in patients receiving rescue analgesia as only 14.3% patients received in group K which is comparatively lower to other groups receiving 85.7% and 91.4% respectively.



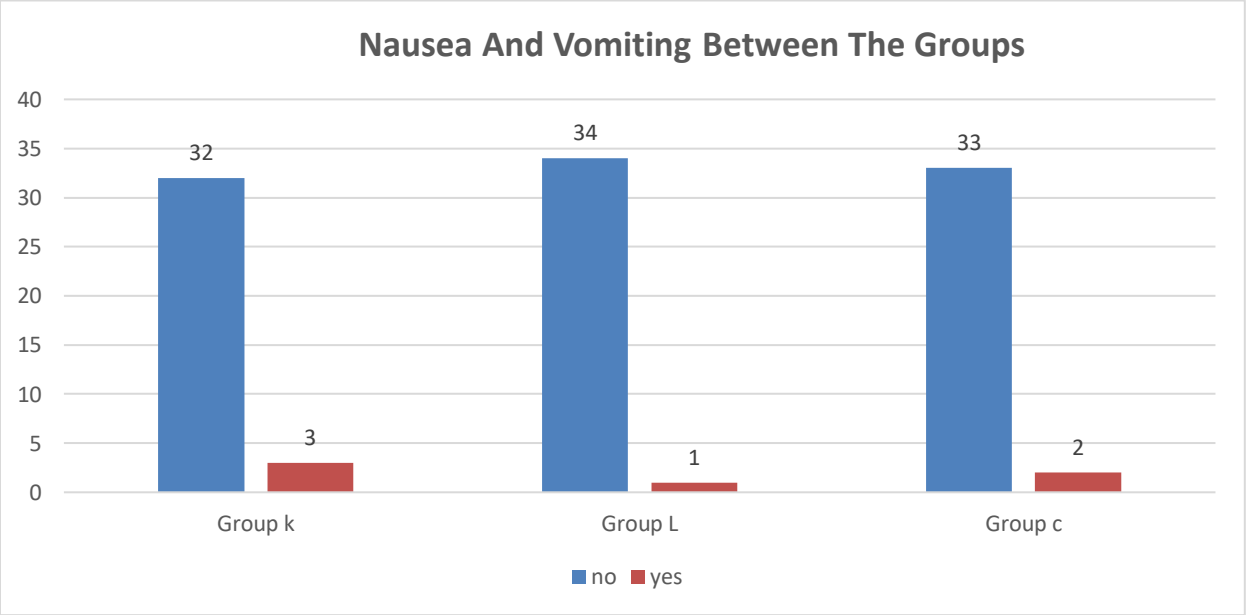
Graph 8: Comparison of rescue analgesia among groups

9. NAUSEA AND VOMITING

Table 9: Comparison of nausea and vomiting among groups

NAUSEA AND VOMITING		Number of patients	%	CHI SQUARE TEST	P- VALUE
GROUP K	no	32	91.40%	1.061	0.588
	yes	3	8.60%		
GROUP L	no	34	97.10%		
	yes	1	2.90%		
GROUP C	no	33	94.30%		
	yes	2	5.70%		
Statistically insignificant as P value is more than 0.05					

There is no difference in post operative nausea and vomiting in all three groups as all the group patients complained of nausea and vomiting.



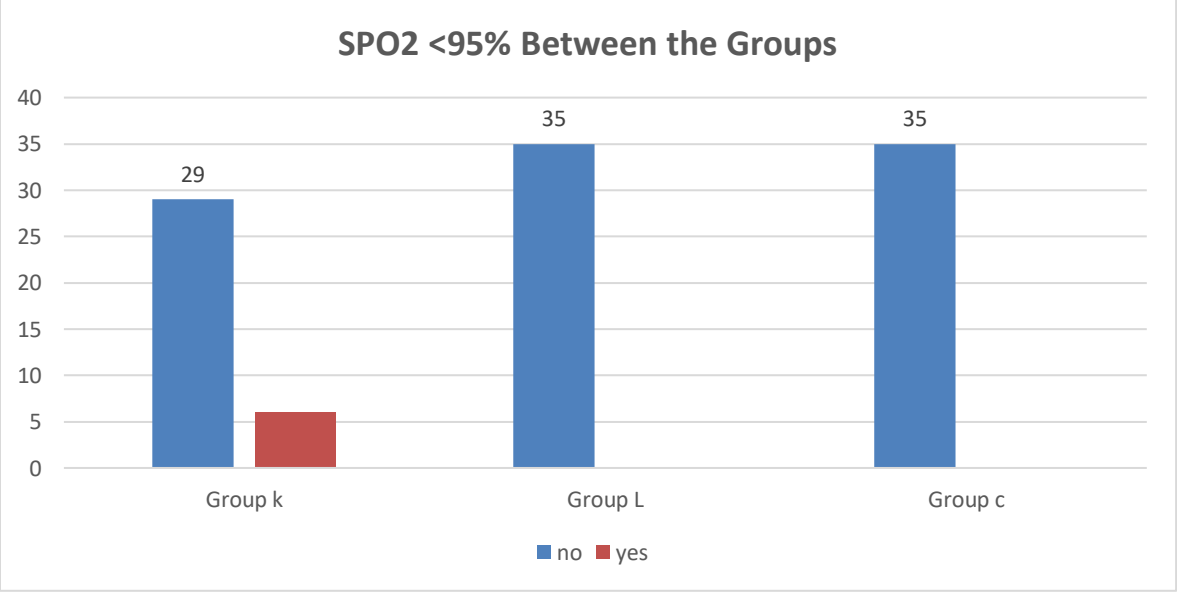
Graph 9: Comparison of nausea and vomiting among groups

10. SATURATION <95%

Table 10: Comparison of saturation <95% among groups

SPO2 <95%		NO OF PATIENTS	%	CHI SQAURE TEST	P VALUE
GROUP K	NO	29	82.90%	12.727	0.002
	YES	6	17.10%		
GROUP L	NO	35	100.00%		
	YES	0	0.00%		
GROUP C	NO	35	100.00%		
	YES	0	0.00%		
Statistically significant as P value is less than 0.05					

There is difference in fall in saturation after nebulization post operatively with group K patients complained of fall in saturation which is less than 95%



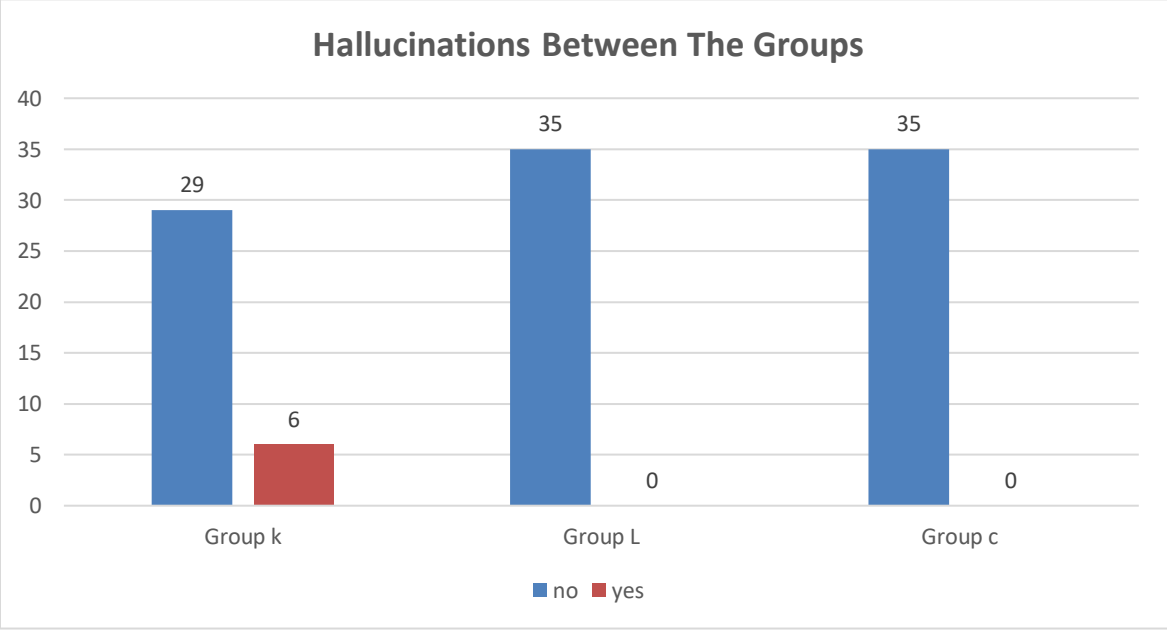
Graph 10: Comparison of saturation <95% among groups

11. HALLUCINATIONS

Table 11: Comparison of hallucinations among groups

SPO2 <95%		NO OF PATIENTS	%	CHI SQUARE TEST	P VALUE
GROUP K	no	29	82.90%	12.727	0.002
	yes	6	17.10%		
GROUP L	no	35	100.00%		
	yes	0	0.00%		
GROUP C	no	35	100.00%		
	yes	0	0.00%		
Statistically significant as P value is less than 0.05					

There is significant difference in comparison of hallucinations with group K patients complaining of presence of hallucinations postoperatively.



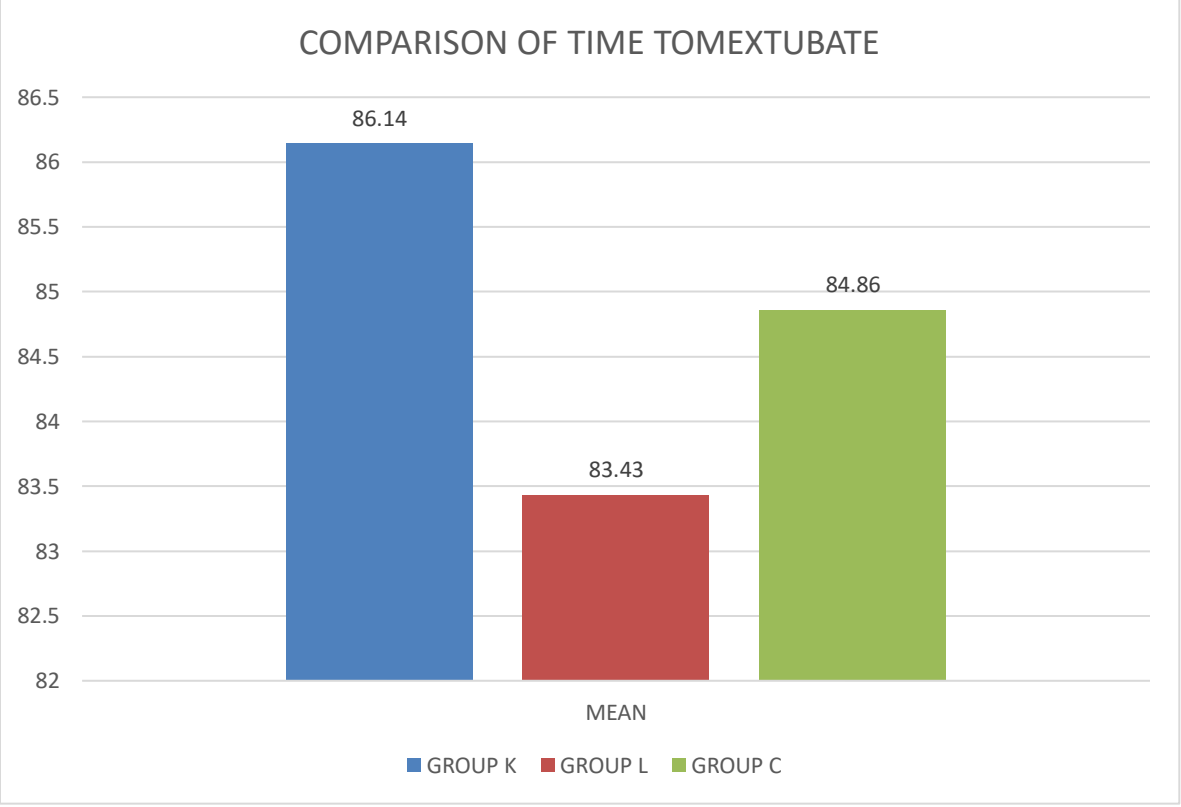
Graph 11: Comparison of hallucinations among groups

12. TIME TO EXTUBATE

Table 12: Comparison of time to extubate among groups

TIME TO EXTUBATE	No of patients	MEAN	SD	KRUSKALWALLIS TEST	P VALUE
GROUP K	35	86.14	5.298	1.738	0.419
GROUP L	35	83.43	6.505		
GROUP C	35	84.86	2.264		
Statistically insignificant as P value is more than 0.05					

There is no difference in time to extubate among all the three groups.



Graph 12: Comparison of time to extubate among groups

DISCUSSION

In this study, we tried to evaluate the role of pre-emptive nebulized ketamine and nebulized lidocaine to enhance and prolong postoperative analgesia for patients undergoing tonsillectomy. Pre-emptive administration of the drugs was done trying to study the effects on the hemodynamics during the intubation and intraoperatively. Using nebulization of the drugs instead of other routes was primarily to ensure equal and effective distribution of the drug in the respiratory tract.

Our results showed that the induction doses of propofol were markedly decreased in ketamine group with a mean of 81.14 compared to lidocaine and control group whose mean values are 95.14 and 97.43 respectively. This is in accordance with Erden et al [37] who found that addition of low dose intravenous ketamine to propofol-fentanyl combination decreased the need for supplemental propofol dosage in pediatric patients.

Topical and intravenous lidocaine has been used to abolish the pressor response to laryngoscopy and intubation. Numerous studies have shown that lidocaine spray is effective in preventing pressor response to tracheal intubation. Mostafa et al [38] in their study confirmed that topical lidocaine sprayed before induction of anesthesia was more effective than after induction in attenuating the pressor response. Abd El Hamid et al [39] found that preoperative lidocaine nebulizer decreased the pressor response to laryngoscopy and intubation. This is in agreement with our results that

confirmed the least hemodynamic changes in response to tracheal intubation occurred in lidocaine nebulized group compared with ketamine and control groups.

Mostafa et al [38] in their study to evaluate the effects of intranasal midazolam, ketamine and dexmedetomidine when administered as preanesthetic medication for children undergoing bone marrow biopsy, found no significant decrease in HR, SBP and respiratory rate among three groups. Rajan et al [40] who compared the effects of preemptive ketamine and magnesium sulfate nebulization on the incidence and severity of postoperative sore throat found no significant difference regarding MAP mean values when baseline and pre nebulization readings were compared with those at postintubation time in all groups.

Our results found to be consistent with Abdel Ghaffar et al [36], who found that intranasal ketamine significantly increased HR, SBP and DBP monitored after induction of anesthesia at 3 and 5 min than intranasal fentanyl, with no difference at 10 and 15 min after intubation. This could be attributed to the larger volume of ketamine dose used in this study compared to other studies.

In our study, observed pain profile of our patients showed that faces pain scale score values were significantly lower with nebulized ketamine and lidocaine than in control group for the first 6 hour postoperatively. However, in comparing the group K and group L, there was significant difference in faces pain scale scores with group K having low pain scores whose mean value at 6^{th} hour postoperative is 1.49 which

is statistically significant. Whereas group L mean value at 6th hour is 3.77 which is slightly higher compared to group K.

Our results were found to be matched with Abdel Ghaffar et al [36], who reported significant lower VAS scores in intranasal ketamine and fentanyl groups in the first 4h compared with placebo group, with trend towards lower values at all time points. In a study conducted by Mehrotra et al [41], they compared the preoperative nebulization of either ketamine, lidocaine, budesonide, or distilled water on the incidence and severity of POST that over all VAS scores were decreased in ketamine and lidocaine groups.

The reduction in faces pain scale scores in our patients could be explained by the deposition of ketamine droplets in the upper airways producing topical analgesia and reducing the inflammatory reactions together with the NMDA receptor antagonism of ketamine nebulization, but possibility of systemic absorption cannot be excluded.

In our study, results had confirmed the postoperative analgesic effects of nebulized ketamine and lidocaine, as the time required for the request of first analgesia significantly longer compared to control groups. In comparison with lidocaine, patients who received ketamine nebulization, the requirement of first rescue analgesia is longer. These findings are supported by the study of Abdel-Ghaffar et al [36], in which they have concluded that pre-emptive intranasal ketamine at a dose of 1.5 mg/kg can effectively reduce postoperative pain after endoscopic nasal surgery.

In this study, hallucinations occurred in six patients who received ketamine nebulization. but hallucinations were not seen in patients of group L and group C. this is in accordance with the study conducted by Abdel-Ghaffar et al [36]in which hallucinations were reported in patients who received ketamine nebulization rather than in patients who received fentanyl nebulization. In this study, we found that postoperative complication such as nausea and vomiting were not statistically significant in all the three groups whereas there was significant decrease in saturation in patients who received ketamine nebulization.

Rao et al [42] reported nebulized lidocaine to be well tolerated except for transient oropharyngeal numbness and bitter taste in the mouth. Slaton et al [43] mentioned in their study that nebulized lidocaine has been documented to cause initial bronchoconstriction in those patients with bronchial hyperactivity such as chronic obstructive pulmonary disease and asthma, unlike ketamine, which is known to be a good bronchodilator. So, it is better to mention that in the presence of such obstacles, nebulized ketamine can play a good role as an alternative drug to nebulized lidocaine.

A drawback of this study was the absence of the measurements of plasma levels of ketamine, so we cannot rule out the influence of the systemic effect of ketamine. Moreover, timing and safety doses of nebulization before intubation need further evaluation.

CONCLUSION

Nebulization with ketamine before induction of general anesthesia is efficacious and enhances postoperative analgesia following tonsillectomy surgeries. This is an easy, simple, cost-effective method to reduce postoperative pain and total doses of rescue analgesics used. Ketamine is also useful in patients where lidocaine is contraindicated in conditions such as lidocaine allergy and where the patients have bronchial hyperactivity.

SUMMARY

This randomized comparative study titled "**PRE-EMPTIVE NEBULIZED KETAMINE VERSUS PRE-EMPTIVE NEBULIZED LIDOCAINE FOR PAIN CONTROL AFTER TONSILLECTOMY IN CHILDREN WITH CONCURRENT CONTROLS"** was carried out from September 2022 to May 2024 in the department of anesthesiology at Shri BM Patil medical college and hospital, BLDE University, Vijayapura.

This study was designed to compare the efficacy of nebulized ketamine and lidocaine when given pre-emptively for pain control postoperatively in children undergoing tonsillectomy. The objectives of the study were to compare the pain scores and the requirement of rescue analgesia postoperatively.

The study population of 105 patients were selected randomly between age groups of 5 to 12 years under ASA I and II. They were divided into three groups of Group K (received ketamine nebulization), Group L (received lidocaine nebulization), Group C (received saline nebulization). Vitals before and after nebulization were recorded for each group of patients. Postoperative pain scores and requirement of rescue analgesia were noted.

The results were found to be in patients who received ketamine nebulization, postoperative pain scores and the requirement of rescue analgesia doses were less

compared to the patients who received lidocaine nebulization. In group K, where patients received ketamine nebulization, only 14.3% patients required rescue analgesia which is lower when compared to other groups. Whereas in group L and group C, a total of 85.7% and 91.4% patients required rescue analgesia which is significant.

Thus, nebulized ketamine can be used as a pre-emptive analgesia for children who are undergoing tonsillectomy for postoperative pain management.

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ANNEXURE I

Institutional ethical clearance certificate

BLDE
(DEEMED TO BE UNIVERSITY)
Declared as Deemed to be University u/s 3 of UGC Act, 1956
Accredited with 'A' Grade by NAAC (Cycle-2)
The Constituent College
SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, VIJAYAPURA

BLDE (DU)/IEC/ 782/2022-23 30/8/2022

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this University met on **Friday, 26th August, 2022 at 3.30 p.m. in the Department of Pharmacology** scrutinizes the Synopsis of Post Graduate Student of BLDE (DU)'s Shri B.M.Patil Medical College Hospital & Research Centre from ethical clearance point of view. After scrutiny, the following original/ corrected and revised version synopsis of the thesis/ research projects has been accorded ethical clearance.

TITLE: "Pre-emptive nebulized ketamine versus pre-emptive Nebulized lidocaine for pain control after tonsillectomy in children with concurrent controls".

NAME OF THE STUDENT/PRINCIPAL INVESTIGATOR Dr.Manikandan S

NAME OF THE GUIDE: Dr.Sridevi M, **Dept. of Anaesthesiology**

Dr. Santoshkumar Jeevangi
Chairperson
IEC, BLDE (DU),
VIJAYAPURA

Chairman,
Institutional Ethical Committee,
BLDE (Deemed to be University)
Vijayapura

Dr.Akram A. Naikwadi
Member Secretary
IEC, BLDE (DU),
VIJAYAPURA

MEMBER SECRETARY
Institutional Ethics Committee
BLDE (Deemed to be University)
Vijayapura-586103. Karnataka

Following documents were placed before Ethical Committee for Scrutinization.

- Copy of Synopsis/Research Projects
- Copy of inform consent form
- Any other relevant document

Smt. Bangaramma Sajjan Campus, B. M. Patil Road (Sholapur Road), Vijayapura - 586103, Karnataka, India.
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ANNEXURE – II

SAMPLE INFORMED CONSENT FORM

B.L.D.E.(DU) SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPURA – 586103, KARNATAKA

TITLE OF THE PROJECT : **"PRE-EMPTIVE NEBULIZED KETAMINE VERSUS PRE-EMPTIVE NEBULIZED LIDOCAINE FOR PAIN CONTROL AFTER TONSILLECTOMY IN CHILDREN WITH CONCURRENT CONTROLS"**

PRINCIPAL INVESTIGATOR: Dr. MANIKANDAN S

Post graduate

Department of Anesthesiology

smk27279@gmail.com

P. G. GUIDE : Dr. Sridevi Mulimani

Professor,

Dept of Anesthesiology, B.L.D. E(DU)
Shri B.M. Patil Medical College Hospital
Vijayapura

PURPOSE OF RESEARCH

I have been informed that this study is "**PRE-EMPTIVE NEBULIZED KETAMINE VERSUS PRE-EMPTIVE NEBULIZED LIDOCAINE FOR PAIN CONTROL AFTER TONSILLECTOMY IN CHILDREN WITH CONCURRENT CONTROLS"**

I have been well explained in the language I best understand about the procedure, purpose of the study, effects and possible adverse effects of the drugs by the doctor.

I hereby voluntarily give my consent for the participation in the study. I have been explained that I have the right to withdraw the participation from the study at any point I want. And the treatment will not be changed from the standard treatment being followed in the hospital for the denial of participation in the study.

I allow the clinical information related to me to be used for research and academic purpose. I have been explained that my name and identity was concealed throughout the process and the clinical information related to me will not be shared with or given to anyone except _____ and the concerned clinician.

I have been well explained that I will not be provided with any incentives or compensation in any form for the participation in this study.

I have been explained about the reason for doing this study and selecting me/my ward as a subject for this study. I have also been given free choice for either being included or not in the study.

CONFIDENTIALITY:

I understand that medical information produced by this study was come a part of this Hospital records and was subjected to the confidentiality and privacy regulation of this hospital. If the data are used for publication in the medical literature or for teaching purpose, no names was used and other identifiers such as photographs and audio or video tapes was used only with my special written permission. I understand that I may see the photograph and videotapes and hear audiotapes before giving this permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time. Dr. MANIKANDAN S is available to answer my questions or concerns. I understand that I was informed of any significant new findings discovered during the course of this study, which might influence my continued participation.

If during this study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me.

And that a copy of this consent form was given to me for careful reading.

REFUSAL OR WITHDRAWL OF PARTICIPATION:

I understand that my participation is voluntary and I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital.

I also understand that Dr. MANIKANDAN S will terminate my participation in this study at any time after he has explained the reasons for doing so and has

helped arrange for my continued care by my own physician or therapist, if this is appropriate

INJURY STATEMENT:

I understand that in the unlikely event of injury to me/my ward, resulting directly due to my participation in this study, such injury was reported promptly, then medical treatment would be available to me, but no further compensation was provided.

I understand that by my agreement to participate in this study, I am not waiving any of my legal rights.

I have explained to _____ the purpose of this research, the procedures required and the possible risks and benefits, to the best of my ability in patient's own language.

Patient's Name: Age/Sex:

Parents name:

Date: DR. MANIKANDAN S

(Investigator)

Signature of the Parents:

Name:

Relation:

Address: Witness to above signature

Phone Number:

STUDY SUBJECT CONSENT STATEMENT:

I confirm that **Dr. MANIKANDAN S** has explained to me the purpose of this research, the study procedure that I will undergo and the possible discomforts and benefits that I may experience, in my own language.

I have been explained all the above in detail in my own language and I understand the same. Therefore, I agree to give my consent to participate as a subject in this research project.

_____ _____

(Patient) Date

_____ _____

(Witness to above signature) Date

PROFORMA

STUDY: PRE-EMPTIVE NEBULIZED KETAMINE VERSUS PRE-EMPTIVE NEBULIZED LIDOCAINE FOR PAIN CONTROL AFTER TONSILLECTOMY IN CHILDREN WITH CONCURRENT CONTROLS

PATIENT DETAILS

Name Age Gender Weight IP NO DATE

Group allotted by randomization: ketamine/lidocaine/saline

Diagnosis:

Comorbidities:

Surgical procedure:

Past history:
General physical examination:

Pallor icterus cyanosis clubbing lymphadenopathy edema

Mallampati Grade:

Vital parameters:

Pulse blood pressure respiratory rate temperature

Systemic Examination

CVS RS

PA PA

INVESTIGATIONS:

HB TC Paltelet count: Urine routine:

HIV: HbsAg:

Other Investigations:

ASA GRADE

PRE AND POST NEBULISATION VITALS :

GROUPS	PULSE RATE (PER MIN)		SYSTOLIC BP (MM OF HG)		DIASTOLICBP (MM OF HG)		RESPIRATORY RATE (PER MIN)		SPO2 (%)	
	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST
K										
L										
C										

COMPLICATIONS:

SYMPTOMS	GROUP K	GROUP L	GROUP C
SPO2 <95%			
NAUSEA AND VOMITING			
HALLUCINATIONS			

SCALE	GROUP K	GROUP L	GROUP C
FACES PAIN SCALE REVISED (0 2 4 6 8 10)	TIMING 30min 1 2 3 4 5 6 hrly	TIMING 30min 1 2 3 4 5 6 hrly	TIMING 30min 1 2 3 4 5 6 hrly
SEDATION SCALE (+4 TO -5)			
TIME TO EXTUBATE(MINS)			
TIME OF FIRST RESCUE ANALGESIA(MINS)			

SIGN

BIODATA

GUIDE

NAME	:	Dr. SRIDEVI MULIMANI
DATE OF BIRTH:	:	11/11/1966
EDUCATION:	:	MBBS-1990 KIMS, HUBLI DIPLOMA IN ANAESTHESIOLOGY-1993 KIMS, HUBLI MD ANAESTHESIOLOGY-2007 SHRI B M PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTER, VIJAYAPURA, KARNATAKA
DESIGNATION:	:	PROFESSOR DEPARTMENT OF ANAESTHESIOLOGY

TEACHING: : UG TEACHING-27YRS

PG TEACHING-15YRS

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9449534216.

INVESTIGATOR

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QUALIFICATION : M.B.B.S,

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B.M. PATIL MEDICAL COLLEGE

HOSPITAL AND RESEARCH,

KARNATAKA- 586103

9994901960.

MASTER CHART

SL NO	NAME	PT NO	AGE (years)	SEX	WEIGHT (KG)	GROUP	PRE SYS BP (mm hg)	PRE DIA BP (mm hg)	POST SYS BP (mm hg)	POST DIA BP (mm hg)	PRE PR (bpm)	POST PR (bpm)	FACES PAIN SCA	FACES PAIN SCA	FACES PAIN SCALE	FACES PAIN SCALE	FACES PAIN SCALE	FACES PAIN SCALE	FACES PAIN SCALE	SEDATION SCALE	TIME TO EXTUBATE (mins)	USE OF FIRST RESCUE	PROPOFOL INDUCTION DOSE	NAUSEA AND VOMITING	O2 <95%	LUCINATIONS
1	Mahade	##	7	M	20	K	110	70	120	80	92	110	2	2	2	4	4	4	2	2	85	NO	80	NO	NO	NO
2	indhus	##	8	F	33	K	110	80	120	90	105	120	4	4	4	4	4	4	2	2	90	NO	100	NO	NO	NO
3	harsha	##	7	M	24	K	110	80	130	100	110	130	4	4	4	4	4	4	2	3	85	NO	80	NO	NO	NO
4	Bhoom	##	7	F	18	K	100	70	130	90	105	128	2	2	2	0	0	0	0	2	90	NO	80	NO	YES	NO
5	gyalak	##	9	F	24	K	110	80	120	90	112	132	4	4	4	4	4	4	0	3	85	NO	80	NO	NO	NO
6	mad S	##	9	M	28	K	120	80	140	90	98	110	4	4	4	2	2	2	2	4	80	NO	80	NO	NO	YES
7	Pallavi	##	5	F	16	K	120	80	130	80	102	116	6	6	6	6	6	6	4	1	85	YES	60	YES	YES	YES
8	Dinesh	##	12	M	25	K	130	80	150	90	96	110	2	2	2	0	0	0	0	2	85	NO	100	NO	NO	NO
9	Karan	##	12	M	30	K	120	80	130	90	110	128	2	2	2	2	2	2	0	3	95	NO	100	NO	NO	NO
10	itashre	##	6	F	15	K	120	80	140	90	98	108	4	4	4	2	2	2	2	2	110	NO	60	NO	NO	NO
11	nivana	##	5	M	15	K	120	80	130	90	106	108	6	6	6	4	4	4	4	2	90	YES	60	YES	YES	NO
12	Akash	##	8	M	21	K	120	80	130	90	110	120	2	2	2	2	2	2	2	2	85	NO	80	NO	NO	NO
13	Vandita	##	11	F	22	K	120	80	130	80	98	102	2	2	2	0	0	0	0	3	85	NO	80	NO	NO	NO
14	oramm	##	12	F	22	K	110	70	130	90	90	110	4	4	4	2	2	2	2	2	80	NO	100	NO	NO	NO
15	Sriniva	##	10	M	20	K	110	80	130	90	95	102	2	2	2	2	2	2	0	2	85	NO	80	NO	NO	YES
16	Shobha	##	12	F	24	K	120	80	140	90	92	108	2	2	2	2	2	2	2	4	90	NO	100	NO	YES	NO
17	Shreya	##	12	F	22	K	120	80	130	80	102	115	4	4	4	2	2	2	2	3	85	NO	80	NO	NO	NO
18	Jyothi	##	11	F	20	K	110	70	130	90	90	100	4	4	4	2	2	2	0	2	85	NO	80	NO	NO	NO
19	Pooja	##	12	F	22	K	120	80	130	90	92	103	2	2	2	0	0	0	0	4	85	NO	80	NO	NO	NO
20	anushr	##	8	F	18	K	110	70	130	90	101	113	4	4	4	4	4	4	2	3	85	NO	80	NO	NO	NO

21	Sachita	##	6	F	22	K	120	80	130	100	110	123	6	6	6	4	4	4	2	2	90	NO	80	NO	NO	NO
22	Manoj	##	8	M	19	K	110	70	110	90	115	118	4	4	4	2	2	2	2	2	85	NO	80	NO	NO	NO
23	Sidapp	##	5	M	15	K	120	80	130	90	102	118	6	6	6	6	6	6	6	1	85	YES	60	NO	NO	YES
24	wastik	##	10	F	22	K	130	90	140	90	98	116	4	4	4	2	2	2	2	2	85	NO	80	NO	NO	NO
25	Nihant	##	8	F	20	K	110	70	110	80	110	112	2	2	2	2	2	2	0	2	90	NO	80	NO	NO	NO
26	Renu	##	9	F	25	K	110	70	130	90	102	116	2	2	2	0	0	0	0	3	85	NO	80	NO	NO	NO
27	ilambi	##	12	F	24	K	130	90	140	90	98	102	2	2	2	2	2	2	0	2	85	NO	80	NO	NO	NO
28	Laxmi	##	12	F	26	K	120	80	130	90	96	112	4	4	4	2	2	2	0	3	85	NO	100	NO	NO	NO
29	Aditya	##	11	M	25	K	120	80	120	90	98	110	4	4	4	2	2	2	4	1	80	YES	80	NO	YES	YES
30	arth B	##	9	M	18	K	120	80	130	90	102	121	2	2	2	2	2	2	0	2	80	NO	80	NO	YES	NO
31	een Ch	##	12	M	26	K	120	80	130	90	108	116	2	2	2	2	2	2	0	2	85	NO	80	NO	NO	NO
32	Shruthi	##	11	F	26	K	120	80	150	100	95	99	2	2	2	0	0	0	0	4	85	NO	80	YES	NO	NO
33	ruputr	##	6	M	13	K	130	80	130	90	110	126	4	4	4	2	2	2	2	4	85	NO	70	NO	NO	NO
34	Pankaj	##	10	M	18	K	120	80	120	90	96	108	6	6	6	6	6	6	4	1	80	YES	80	NO	NO	YES
35	Umesh	##	12	M	25	K	120	80	140	100	96	118	4	4	4	2	2	2	2	2	85	NO	90	NO	NO	NO
36	rish M	##	12	M	28	L	120	80	120	80	92	96	6	6	6	4	4	4	4	3	85	YES	100	NO	NO	NO
37	Ganesh	##	10	M	20	L	110	70	110	70	98	100	6	6	6	4	4	4	4	2	85	YES	100	NO	NO	NO
38	Seema	##	11	F	19	L	110	70	110	80	88	92	4	4	4	4	4	4	4	2	90	YES	100	NO	NO	NO
39	Laxmi	##	10	F	20	L	100	80	110	80	89	88	6	6	6	4	4	4	4	2	90	YES	100	NO	NO	NO
40	aj Shri	##	10	M	22	L	100	70	110	70	101	106	4	4	4	2	2	2	2	3	80	NO	100	NO	NO	NO
41	Jingara	##	8	M	18	L	110	70	110	70	96	98	4	4	4	4	4	4	4	2	85	YES	90	NO	NO	NO
42	Tejas	##	9	M	19	L	120	80	120	80	102	105	6	6	6	4	4	4	4	2	85	YES	90	NO	NO	NO
43	ithivir	##	8	M	20	L	120	70	120	70	103	110	6	6	6	6	6	6	4	2	85	YES	90	NO	NO	NO
44	shamm	##	8	M	21	L	110	70	120	90	102	116	6	6	6	6	6	6	6	2	85	YES	90	NO	NO	NO
45	avikum	##	10	M	22	L	120	80	120	80	88	90	6	6	6	4	4	4	4	2	85	YES	100	NO	NO	NO

46	Sanjivn	##	12	F	24	L	120	90	120	80	96	98	4	4	4	2	2	2	2	2	80	NO	100	NO	NO	NO
47	Arjun	##	5	M	15	L	110	70	110	70	112	118	4	4	4	4	4	4	4	3	90	YES	80	NO	NO	NO
48	umithr	##	10	F	22	L	120	80	120	80	98	102	6	6	6	4	4	4	4	2	85	YES	100	NO	NO	NO
49	avamal	##	6	M	16	L	110	60	110	70	88	90	4	4	4	4	4	4	2	2	85	YES	80	NO	NO	NO
50	Rekha	##	7	F	15	L	110	70	110	70	90	90	4	4	4	4	4	4	4	2	85	YES	100	NO	NO	NO
51	Shoban	##	9	F	18	L	120	80	120	80	90	92	6	6	6	6	6	6	4	2	80	YES	100	YES	NO	NO
52	manap	##	4	M	12	L	120	80	120	90	102	105	4	4	4	2	2	2	2	2	85	NO	60	NO	NO	NO
53	Ilango	##	7	M	16	L	110	70	110	80	88	96	6	6	6	6	6	6	6	2	85	YES	100	NO	NO	NO
54	Pooja	##	11	F	20	L	120	80	120	80	92	92	6	6	6	6	6	6	4	2	85	YES	100	NO	NO	NO
55	ayanar	##	7	M	19	L	120	90	130	90	98	96	6	6	6	4	4	4	4	2	75	YES	80	NO	NO	NO
56	oramm	##	8	F	18	L	110	80	120	90	110	70	4	4	4	4	4	4	4	3	85	YES	100	NO	NO	NO
57	Yesuba	##	9	F	17	L	110	70	110	70	92	93	4	4	4	2	2	2	2	3	85	NO	100	NO	NO	NO
58	ayshre	##	6	F	16	L	120	80	120	80	99	99	8	8	8	6	6	6	4	2	85	YES	100	NO	NO	NO
59	iddara	##	5	M	14	L	120	80	120	70	110	118	6	6	6	4	4	4	4	2	60	YES	70	NO	NO	NO
60	antamm	##	7	F	16	L	110	70	110	70	95	96	4	4	4	4	4	4	2	2	85	YES	100	NO	NO	NO
61	Anand	##	12	M	20	L	110	80	120	80	98	98	6	6	6	6	6	6	6	2	85	YES	100	NO	NO	NO
62	anamm	##	11	F	21	L	120	80	120	80	88	92	6	6	6	4	4	4	4	3	85	YES	100	NO	NO	NO
63	Priya	##	12	F	20	L	120	80	130	90	96	102	6	6	6	4	4	4	4	2	85	YES	100	NO	NO	NO
64	Umera	##	10	F	19	L	110	70	120	80	99	103	4	4	4	4	4	4	6	2	60	YES	100	NO	NO	NO
65	wartik	##	11	F	20	L	120	80	130	80	98	98	4	4	4	4	4	4	4	2	85	YES	100	NO	NO	NO
66	Dhanes	##	12	M	22	L	120	80	130	90	101	105	6	6	6	4	4	4	4	2	85	YES	100	NO	NO	NO
67	ivanap	##	11	M	25	L	110	70	120	80	92	94	4	4	4	4	4	4	4	3	90	YES	100	NO	NO	NO
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69	Radha	##	11	F	19	L	110	70	120	80	95	96	6	6	6	4	4	4	4	2	85	YES	100	NO	NO	NO
70	appa W	##	12	M	26	L	120	80	120	90	90	98	4	4	4	2	2	2	0	3	85	NO	100	NO	NO	NO

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72	umithr	##	11	F	20	C	110	70	110	70	98	106	8	8	8	6	6	6	4	2	85	YES	100	NO	NO	NO
73	agyash	##	10	F	19	C	110	70	110	80	88	90	6	6	6	4	4	4	4	2	85	YES	100	NO	NO	NO
74	Amit	##	7	M	18	C	110	80	110	80	92	92	6	6	6	6	6	6	4	2	85	YES	90	NO	NO	NO
75	allamu	##	12	F	22	C	120	80	120	80	99	102	6	6	6	4	4	4	4	3	85	YES	100	NO	NO	NO
76	Rahul	##	7	M	16	C	120	70	120	70	102	106	4	4	4	4	4	4	4	2	90	YES	100	NO	NO	NO
77	Shilpa	##	8	F	17	C	110	70	110	80	98	99	6	6	6	4	4	4	4	2	85	YES	100	NO	NO	NO
78	rathib	##	11	F	22	C	110	80	120	80	99	102	4	4	4	2	2	2	2	2	85	NO	100	NO	NO	NO
79	hit Ba	##	10	M	20	C	120	80	120	80	88	92	6	6	6	4	4	4	4	2	85	YES	100	NO	NO	NO
80	urukir	##	7	M	18	C	110	70	110	80	86	90	6	6	6	4	4	4	4	2	90	YES	90	NO	NO	NO
81	Yuvan	##	8	M	19	C	120	80	120	90	89	93	4	4	4	4	4	4	2	3	85	YES	100	NO	NO	NO
82	Farhan	##	8	M	21	C	110	70	110	90	90	95	4	4	4	4	4	4	4	2	85	YES	100	NO	NO	NO
83	hreeha	##	7	M	16	C	120	80	120	80	92	98	6	6	6	6	6	6	4	2	85	YES	100	NO	NO	NO
84	Arhan	##	7	M	18	C	110	70	120	80	96	99	6	6	6	6	6	6	6	2	85	YES	100	NO	NO	NO
85	ratibh	##	12	F	20	C	120	80	120	80	89	98	6	6	6	6	6	6	4	2	90	YES	100	NO	NO	NO
86	Pooja	##	7	F	18	C	110	70	110	70	92	98	6	6	6	4	4	4	4	2	85	YES	80	NO	NO	NO
87	Aadhya	##	10	F	19	C	100	80	110	80	98	102	8	8	8	6	6	6	6	2	85	YES	100	NO	NO	NO
88	Muskan	##	11	F	20	C	110	70	120	80	96	98	6	6	6	4	4	4	4	3	85	YES	100	NO	NO	NO
89	yalaks	##	10	F	19	C	120	80	120	90	102	105	4	4	4	2	2	2	2	2	80	NO	100	NO	NO	NO
90	aduma	##	8	F	17	C	110	70	120	80	98	99	6	6	6	6	6	6	4	2	85	YES	90	NO	NO	NO

90	aduma	##	8	F	17	C	110	70	120	80	98	99	6	6	6	6	6	6	4	2	85	YES	90	NO	NO	NO
91	asavar	##	12	M	22	C	110	80	120	90	102	105	6	6	6	4	4	4	4	2	85	YES	100	NO	NO	NO
92	ouramr	##	12	F	21	C	120	80	120	80	98	102	4	4	4	4	4	4	2	2	85	YES	100	NO	NO	NO
93	Akasha	##	10	F	20	C	110	70	130	90	88	92	4	4	4	4	4	4	4	3	85	YES	100	NO	NO	NO
94	aishna	##	12	F	21	C	110	70	130	80	92	96	6	6	6	6	6	6	6	2	85	YES	100	NO	NO	NO
95	Maheer	##	8	M	19	C	120	80	120	80	88	90	6	6	6	4	4	4	4	2	80	YES	100	NO	NO	NO
96	Jyoti	##	12	F	20	C	120	80	120	90	96	98	6	6	6	6	6	6	2	2	85	YES	100	NO	NO	NO
97	ayashr	##	11	F	22	C	110	80	120	90	88	98	6	6	6	6	6	6	2	2	85	YES	100	YES	NO	NO
98	Lalitha	##	12	F	21	C	120	70	120	80	92	96	6	6	6	6	6	6	2	2	85	YES	100	NO	NO	NO
99	athiksl	##	8	F	18	C	110	60	110	70	90	96	6	6	6	6	6	6	4	2	85	YES	80	NO	NO	NO
100	akshm	##	9	F	17	C	110	70	120	80	102	106	4	4	4	4	4	4	2	3	85	YES	100	NO	NO	NO
101	Nehal	##	6	M	15	C	120	80	110	70	98	102	4	4	4	2	2	2	2	2	80	NO	80	NO	NO	NO
102	anushr	##	10	F	20	C	110	70	130	90	90	103	6	6	6	4	4	4	2	3	85	YES	100	NO	NO	NO
103	Swati	##	9	F	18	C	100	70	110	80	88	96	8	8	8	6	6	6	4	2	85	YES	100	YES	NO	NO
104	sanap	##	12	M	22	C	110	70	120	80	86	90	6	6	6	4	4	4	2	2	85	YES	100	NO	NO	NO
105	Alli	##	10	M	20	C	110	80	120	90	89	91	8	8	8	6	6	6	4	2	80	YES	100	NO	NO	NO

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