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COMPARISON OF PREOPERATIVE NEBULIZATION WITH MAGNESIUM SULPHATE AND KETAMINE IN REDUCTION OF INCIDENCE OF POSTOPERATIVE SORE THROAT - AN OBSERVATIONAL COMPARATIVE STUDY

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ABSTRACT
Postoperative sore throat (POST) is one of the complications, which manifests itself as some amount of discomfort in patients who have undergone an operation. This review aimed to evaluate the role of preoperative nebulization with either $MgSO_4$ or ketamine or the prevention of new POST formation. $MgSO_4$ and ketamine may lower pain and inflammation caused by the tube inserted into the throat. We discuss the action, efficacy, and safety of both $MgSO_4$ and ketamine nebulization intentionally. Remarkably, ±$MgSO_4$ and ketamine have been shown to decrease the incidence and severity of POST in comparison to the control groups combined with a low risk of side effects. Ketamine had a better pain relief measurement at virtually all the postoperative time points. The interaction between $MgSO_4$ and ketamine shows that there is likely synergism: further study is nevertheless sparse. Some of them are Sterile compounding of solutions for nebulization before anesthetic induction. Subsequent, prospective double-blinded randomized controlled trials, enumerating doses of combined therapy, and probable modes of administration should be performed. In totality, preoperative nebulization with $MgSO_4$ and/or ketamine reduces POST through anti-inflammatory and antinociceptive pathways, and there is a slightly higher therapeutic gain with ketamine.

Keywords: Postoperative sore throat, Nebulization, Magnesium sulfate, Ketamine, Intraoperative complications, Anesthesia

1. Introduction

1.1 Background on Postoperative Sore Throat (POST)

Postoperative sore throat (POST) is a common complaint after surgery under general anesthesia with endotracheal intubation with the incidence varying between 14.4% and 50% (1). The symptoms of POST are minor soreness or discomfort in the throat, swallowing problems, sore throat, and hoarseness or loss of voice (2). Although typically mild and time-limited, POST plays a major role in the patient's postoperative pain and their overall satisfaction with their surgical process (3). Preventing and minimizing the occurrence of POST has emerged as a desirable Anesthesia quality improvement goal. The precise mechanism of POST is not clearly defined fully but it is posited that pressure in combination with local inflammation as a result of irritation resulting from the position of the endotracheal tube on the pharyngolaryngeal mucosa is probably the cause (4). Tubing diameter, cuff structure, pressure, amount of handling during laryngoscopy and tube insertion, and suctioning are operative factors that can raise mucosal trauma (5).

Other pertinent patient factors that may predispose to increased incidence and severity of POST include gender, smoking status, previous pathological laryngopharyngeal disease, and when the patient has a nasogastric tube in situ (6). POST reduction has especially been focused on among those using pharmacologic interventions with much emphasis. Drugs given orally before surgery in the form of a mouthwash solution, lozenge, or nebulized inhalant have the advantage of offering local anesthesia and anti-inflammatory action (7). POST could be reduced with the use of ketamine and magnesium sulfate; as established by previous research. Ketamine is the N-methyl-D-aspartate (NMDA) receptor antagonist that is normally employed as an analgesic and a sedative. Some randomized controlled trials demonstrated that preoperative ketamine gargle or lozenge decreases POST rates by 8-10 times (8–10). The proposed mechanisms are topical local anesthesia and anti-inflammatory and anti-NMDA effects on pharyngolaryngeal mucosa (11).

Magnesium sulfate thus decreases POST possibly through a relaxing effect on the smooth muscles, anti-inflammatory activity, and suppression of neuropathic pain and hyperexcitability (12). Several studies confirmed that the application of magnesium nebulization before surgery renders POST prophylaxis, although many of them involved a small number of patients (13,14).

1.2 Overview of Nebulization as a Preoperative Intervention

POST is frequent after general anesthesia with endotracheal intubation with incidence reported to be from 14.4% to 50% (15,16). POST results from mucosal injury during airway instrumentation and results in patient discomfort and dissatisfaction (17). Non-pharmacological and pharmacological modes of managing POST have over time been established with different degrees of efficacy (18). Of the pharmacological measures, nebulization of medicaments before intubation is becoming preferred, as it is not invasive, easily implemented, and results in elevated local drug concentrations with a faster rate of onset than in other systemic methods (19).

Nebulization may be defined as the process of administering drugs in a suspension form as aerosols that can be inhaled directly using a facemask or mouthpiece (20). If nebulized before intubation, the suspended drug particles can offer localized actions over the airway mucosa and submucosal areas that come into contact with the ETT and the blade of the laryngoscope. This leads to attenuation of the inflammatory trauma response induced by airway instrumentation (21). Two drugs that have appeared to have anti-inflammatory, analgesic, and anesthetic properties have been trialed as nebulizations before intubation including Magnesium sulfate and ketamine (22,23).

Endogenous opioids are known to interact with magnesium sulfate by increasing its activity and effects include inhibition of calcium ion transport across cell membranes, and inhibition of the release of neuropeptides that cause inflammation which act as analgesics (24). Nebulized magnesium given before intubation could well offer topical anesthesia, decrease airway reflexes during laryngoscopy, and lessen POST in these ways. The drug used in this study is ketamine, a dissociative anesthetic agent that also has analgesic effects brought about by non-competitive blockade of N-methyl-D-

aspartate (NMDA) receptors (25,26). Since ketamine is an NMDA receptor antagonist, it can cause pre-emptive analgesia if administered before noxious stimulation which could lessen POST (27).
Although previous works have assessed the outcomes of preoperative nebulization with magnesium sulfate or ketamine on POST, few permit a comparison between the two drugs as mentioned in Figure 1. Critical consideration will be placed on the incidences of POST in the two groups of study. Also, the baseline and intraoperative, postoperative, and prevalence of hemodynamic parameters and adverse effects will be assessed. The present review aims at offering empirically grounded suggestions about the selector which is preferable among nebulized magnesium sulfate and ketamine before intubation to lessen the frequency of POST.

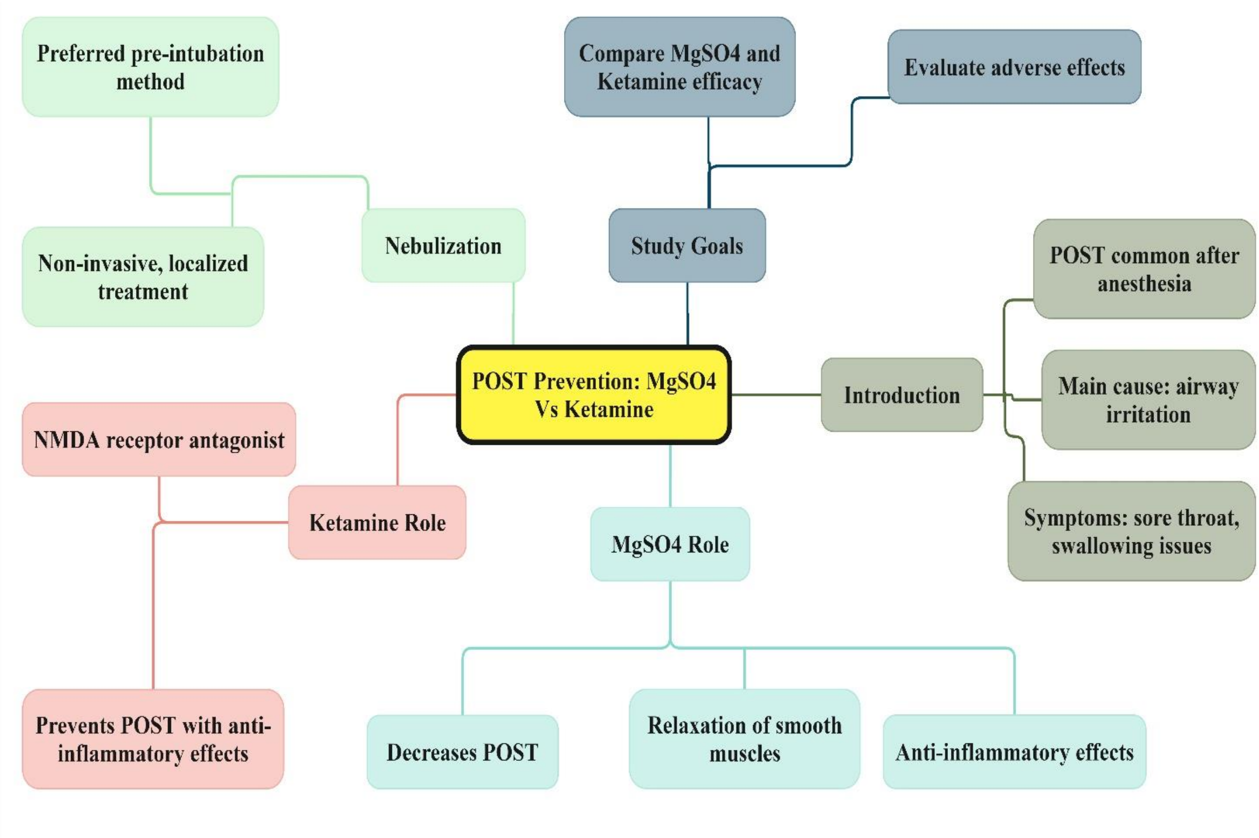

Figure 1: Postoperative Sore Throat (POST) Prevention: Comparison of $MgSO_4$ and Ketamine

1.3 Role of Magnesium Sulfate (MgSO4) and Ketamine in POST Prevention

Postoperative sore throat is a recognized side effect of general anesthesia with endotracheal intubation, the incidence of which is between 14.4% and 50% (28,29). It was established from pharyngeal inflammation and irritation from intubations that made the patients uncomfortable, dissatisfied, and; had long recovery periods (30,31)). Several pharmacological and nonpharmacological strategies have been considered in the treatment of POST. There’s still no efficient approach to this problem (32). Of the medications used, inhaled magnesium sulfate ($MgSO_4$) and ketamine have been shown to work in recent investigations. $MgSO_4$ is believed to act on POST through inflammation inhibition, pain-relieving, and muscle relaxation (33). $MgSO_4$ thus prevents mood-congruent release of pro-inflammatory neuropeptides from peripheral nociceptive nerves and modifications of peritracheal inflammation and edema formations that may trigger POST development (34,35).
Several randomized trials have also proved postoperative nebulization with $MgSO_4$ reduces the chance and intensity of sore throat (36,37). Meanwhile using the topical application of ketamine, a dissociative anesthetic agent that has social distancing, anti-inflammatory, as well as an anti-nociceptive effect may help in the management of the inflammatory component of POST (38). The

local application reduces inflammation through the down-regulation of nitric oxide synthase and decreases the production of inflammatory cytokines and blockage of peripheral pain pathways (39).
Recent research employed placebo-controlled trials that demonstrated that preoperative ketamine nebulization can decrease the POST incidence (40,41). To the best of our knowledge, no available studies are comparing the effectiveness of preoperative nebulized $MgSO_4$ vs ketamine in the prevention of POST. Whether one of them acts better anti-inflammatory, analgesic, or neuromuscular blockade when applied directly to the mucous membrane of the trachea is still unclear. It is necessary to realize how these two pharmacological interventions differ or are similar to gain a better understanding of POST as well as to obtain greater knowledge as to how this PTSD symptom may be further weakened.
Thus, the objective of the current systematic review and meta-analysis is to compare the efficacy of preoperative $MgSO_4$ aerosolization with ketamine in POST risk reduction as the primary outcome. Secondary end-points will be POST severity scores up to 24 hours after extubation, POST onset time, postoperative opioid requirements, and incidence of adverse respiratory events. Outcomes will assist in determining whether one nebulized medication should be preferred over the other to be included in clinical practice recommendations on POST prevention.

2. Mechanisms of Postoperative Sore Throat

Postoperative sore throat is a recognized side effect of general anesthesia with endotracheal intubation, the incidence of which is between 14.4% and 50% (42). It was established from pharyngeal inflammation and irritation from intubations that made the patients uncomfortable, dissatisfied, and had long recovery periods (43). Several pharmacological and nonpharmacological strategies have been considered in the treatment of POST (44). Of the medications used, inhaled magnesium sulfate ($MgSO_4$) and ketamine have been shown to work in recent investigations. $MgSO_4$ is believed to act on POST through inflammation inhibition, pain-relieving, and muscle relaxation (45). $MgSO_4$ thus prevents mood-congruent release of pro-inflammatory neuropeptides from peripheral nociceptive nerves and modifications of peritracheal inflammation and edema formations that may trigger POST development (46,47).
Several randomized trials have also proved postoperative nebulization with $MgSO_4$ reduces the chance and intensity of sore throat (48-49).The mechanism of postoperative sore throat is clearly mentioned in Table 1. Meanwhile using the topical application of ketamine, a dissociative anesthetic agent that has social distancing, anti-inflammatory, as well as an anti-nociceptive effect may help in the management of the inflammatory component of POST (50). The local application reduces inflammation through down-regulation of nitric oxide synthase, decreases the production of inflammatory cytokines, and blockage of peripheral pain pathways (51,52).
Recent research employed placebo-controlled trials that demonstrated that preoperative ketamine nebulization can decrease the POST incidence (53-55). To the best of our knowledge, no available studies are comparing the effectiveness of preoperative nebulized $MgSO_4$ vs ketamine in the prevention of POST. Whether one of them acts better anti-inflammatory, analgesic, or neuromuscular blockade when applied directly to the mucous membrane of the trachea is still unclear. It is necessary to realize how these two pharmacological interventions differ or are similar to gain a better understanding of POST as well as to obtain greater knowledge as to how this PTSD symptom may be further weakened.
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Table 1: Mechanisms of Postoperative Sore Throat

Category	Pathophysiology of POST	Description	Contributing Factors in POST	Description
Inflammation	Mucosal injury and inflammation	Mechanical irritation or trauma	Intubation duration	Longer exposure leads to greater irritation
Nerve Injury	Damage to pharyngeal and laryngeal nerves	Nerve compression or stretching during intubation	Tube size	Larger tubes increase the likelihood of trauma
Airway Irritation	Dryness and dehydration of the airway	Breathing dry or cold gases	Cuff pressure	High cuff pressure increases the risk of mucosal damage
Mucosal Damage	Direct trauma to the airway mucosa	Friction from endotracheal tube	Repeated intubation attempts	Multiple attempts cause cumulative injury
Muscle Strain	Tension in vocal cords and surrounding muscles	Overextension during intubation	Insertion technique	Improper technique can lead to muscle strain
Infection	Microbial colonization in the airway	Inadequate aseptic conditions during intubation	Preexisting respiratory conditions	Respiratory infections increase POST susceptibility
Edema Formation	Swelling in the laryngeal region	Trauma-induced inflammatory response	Allergies or hypersensitivity reactions	Increased risk of airway edema
Chemical Irritation	Reaction to anesthetic agents	Local irritation due to chemical exposure	Use of certain anesthetics	Some agents increase the risk of airway irritation
Hypoxia	Reduced oxygen supply to tissues	Airway obstruction or improper ventilation	Hypoventilation during surgery	This leads to oxygen deprivation and increased damage

3. Preoperative Nebulization with Magnesium Sulfate (MgSO4)

3.1 Mechanism of Action of MgSO4

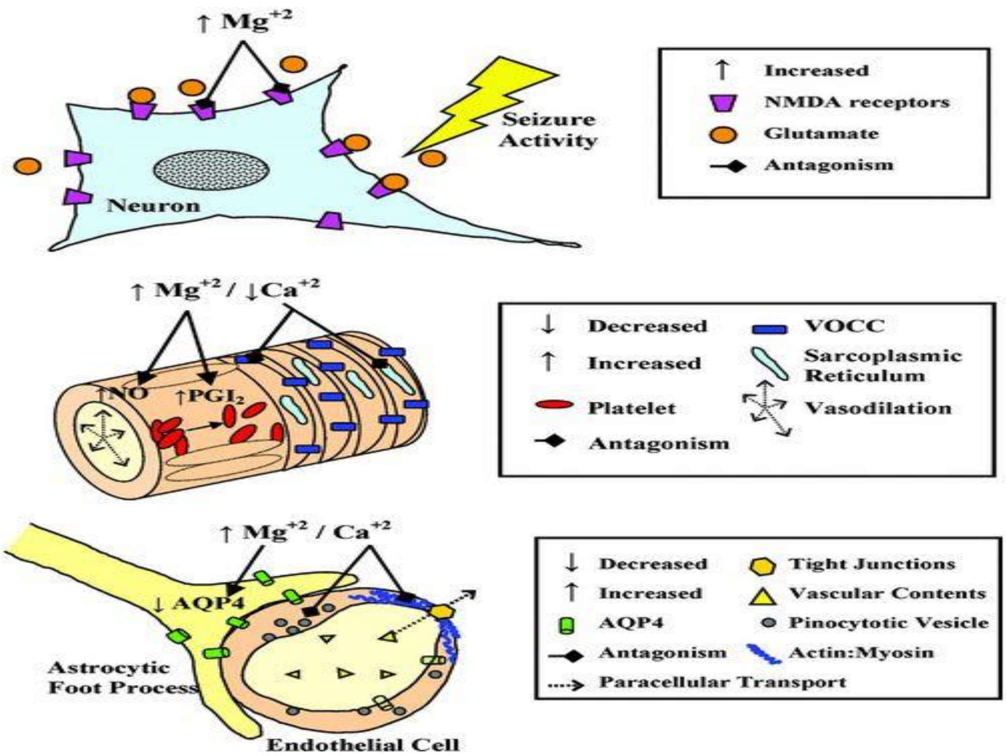

Figure 2: Mechanism of Action of MgSO4 (Epomedicine. Pritchard regimen (MgSO4) in PIH [Internet]. Epomedicine; 2014 Aug 29 [cited 2024 Sep 30]. Available from: https://epomedicine.com/emergency-medicine/pritchard-regimen-magnesium-sulphate/)

3.1.1 Neuron

Awareness of the pioneer's contribution to the science will intensify exploring the role of magnesium ion ($Mg^{2+)}$ in regulating the excitability of neurons by interacting with the N-methyl-D-aspartate channel. The NMDA receptor mechanisms involve an activation of neural impulses due to glutamic acid. In normal conditions, the pore of the NMDA receptor is occupied by the extracellular Mg^{2+} as illustrated by Figure 2 that blocks the receptor channel depending on the membrane potential. When glutamate levels rise above a certain threshold during a seizure situation Mg^{2+} deserts the NMDA receptor. This enables calcium to flood the neuron resulting in excessive neuron activation.

The raised levels of extraneuronal Mg^{2+} lead to the prevention of neuronal excitation through the restoration of the Mg^{2+} block of the NMDA receptors. In this context, increased Mg^{2+} reduces NMDA receptor activation and calcium influx by preventing the binding of glutamate to the receptor further helping to depress hyperexcitable neuronal circuits as well as suppressing seizures. The NMDA receptor's pore is occupied by Mg^{2+} and it completely shuts out the arrival of glutamate. If supplemental Mg^{2+} were to reduce NMDA receptor function in this manner, then the drug could be of value in treating disorders related to neuronal hyperexcitability such as epilepsy.

3.1.2 Vascular Smooth Muscle Cell

The actions of magnesium are to cause relaxation of the vascular smooth muscles of blood vessels. It modulates voltage-operated calcium channels (VOCCs) present in these cells and decreases calcium entry which leads to the relaxation of smooth muscles and vasodilation. Also, it has been found that magnesium augments the action of endogenous PGI2 and NO in promoting vasodilation. Thus, inhibition of VOCCs and augmentation of PGI2 and NO by magnesium provides robust vasodilation. These cellular changes are depicted in the diagram: blue color stands for decreased VOCC, indicating that calcium flues have been reduced; blood vessels are larger symbolizing vasodilation; and decreased platelet clumps which imply reduced aggregation.

Furthermore, it inhibits platelets from sticking together thereby favoring antithrombotic processes in artery walls. Thus, multiple pathways and enhanced positive vasodilatory signaling, while attenuating thrombotic promotion from platelet activity, result in favorable effects of augmenting intracellular magnesium levels. In conclusion is a summary of critical details concerning cell operations and the role of magnesium in vessel expansion.

3.1.3 Astrocyte-Endothelial Cell Interaction

Endbrain magnesium serves as a regulatory factor in astrocyte-endothelial cell signaling that is crucial in blood-brain barrier homeostasis. Upon raising intracellular Mg^{2+} concentration, AQP4 water channels in astrocytic end-feet processes are found to be upregulated. AQP4 is involved in water transport across cell membranes and its overexpression is thought to help maintain brain fluid homeostasis and decrease permeability of blood vessels.

The higher concentrations of Mg^{2+} provide a decline in tight junctions of the endothelial cells in cerebral microvessels. This has a positive effect on raising the rate of paracellular transport of solutes and water by passive diffusion. These effects of Mg^{2+} are illustrated diagrammatically in the figure 2. The larger intracellular spaces within the blood vessels point towards increased vascular contents due to increased water movement through AQP4 across the blood vessel wall. The green squares represent upregulated and functioning AQP4 water channels in astrocytic End-feet processes which minimize the content in the brain parenchyma. In combination, Mg^{2+} modulation of astrocyte-endothelial cell crosstalk sustains proper water and ionic balance in the neurovascular unit.

4. Preoperative Nebulization with Ketamine

It is worth noting that the nebulized preoperative ketamine has bronchodilating, anti-inflammatory, analgesic, neuro and hemodynamic stabilizing, bronchial protective, locally anesthetic, sedative, and cognitive impacts (56,57). These therapeutic effects are posited to occur through the NMDA receptor antagonism which is caused by ketamine. This results mentioned in Table 2 in suppression of cytokines formation lowered sensitization to pain, regulation of glutamate and suppression of sympathetic flow, diminished broncho spasm, and NMDA receptors inhibition centrally and peripherally (58,59).

Ketamine does have its side effects which are associated with the use of this drug. However, there are reports of respiratory depression, which, in this case, is moderate at most in response to the sedative impact (60). Most often, local irritation at the site of administration may be mild especially when using low concentrations (61). The effects are sometimes sedative, sometimes similar to morphine, and increased doses can lead to hallucinations and delirium. It is also possible to experience tachycardia, increased salivation, dizziness, and memory deficits (62).

When ketamine is delivered as nebulized medication in a controlled manner issues such as side effects turn out to be tolerable. Notice changes in oxygen saturation levels because of the danger of respiratory depression. Concentrations should be reduced locally to reduce skin and eye irritation. Sedative effects are dose-related, but, if it is necessary, other medications may be added as an adjunct to the CII therapy. Again, most of the other side effects such as an increase in the rate of heartbeat and hypersalivation are of moderate impact. Therefore, preoperative ketamine nebulization seems to be relatively safe in cases of medical attention and intervention (63).

Table 2: Summary of Mechanism of Action and Safety Profile of Preoperative Nebulization with Ketamine

Aspect	**Category**	**Mechanism of Action**	**Adverse Effect**	**Severity**	**Safety Profile**
Respiratory	Bronchodilation	NMDA Receptor Antagonism	Respiratory Depression	Mild to Moderate	Monitor Oxygen Saturation
Anti-inflammatory	Anti-inflammatory Effect	Inhibition of Cytokine Release	Local Irritation	Mild	Safe with Low Concentration
Analgesic	Pain Reduction	Reduces Pain Perception	Sedation	Moderate	Dose-Dependent
Neurological	Neuroprotection	Modulation of Glutamate	Hallucinations	Severe in High Doses	Administer with Caution
Hemodynamic	Stabilization	Inhibition of Sympathetic Flow	Increased Heart Rate	Mild	Tolerable at Therapeutic Doses
Bronchial Protection	Airway Protection	Reduction in Bronchoconstriction	Hypersalivation	Mild to Moderate	Ensure Airway Management
Local Anesthesia	Pain Block	Local NMDA Receptor Blockade	Dizziness	Mild	Effective in Lower Doses
Psychological	Sedative Effect	NMDA Block in CNS	Delirium	Moderate	Manage with Adjunct Medications
Cognitive	Cognitive Impact	Altered Consciousness	Memory Impairment	Mild	Safe with Proper Monitoring

5. Comparison of MgSO4 and Ketamine

Postoperative sore throat (POST) is a common complaint after general anesthesia with endotracheal intubation involvement in up to 90 % of patients. Both nebulized magnesium sulfate ($MgSO_4$) and ketamine have been examined as potential preventive measures in POST due to their topical analgesic and anti-inflammatory actions on airway tissues (64). Regarding safety effectiveness in several trials, it was noted that nebulized $MgSO_4$ set a significantly lower incidence or intensity of POST compared to placebo (65,66). The sample size required to treat with $MgSO_4$ nebulization to avoid one case of POST was 2.3.

In contrast, a similar review on nebulized ketamine has produced a higher variety with some researchers noting that it may be beneficial mentioned in Figure 3. However, others were quite the opposite noting that there was no difference between ketamine and placebo (67,68). There are few direct comparisons between the given two medications. There was one study in the subclass of patients undergoing lumbar discectomy in which there were no significant differences in POST occurring between the groups that received $MgSO_4$ 40mg, ketamine 25mg, or ketamine 50mg nebulization. With regards to side effects as well as complications, nebulized $MgSO_4$ was reported to have a favorable safety profile by not claiming numerous complications in many of the existing studies. Adverse effects are usually mild and self-limited and include bitter taste, nausea and/or vomiting, and dry mouth (64). Compared to nebulized ketamine some side effects may include psychotic-like symptoms, for example, visual disturbances or vivid dreams in some patients, but several studies have not reported any significant side effects compared to placebo or $MgSO_4$ (69,70).

The determination of the best dose for both drugs has not been confirmed. For MgSO4, doses under investigation include 25 to 100mg; 40 to 50mg appear to be reasonably effective according to the current studies (63). For ketamine, 25 to 50mg have been assessed with confusing dose-response (67,69) both medications are nebulized as a single dose 20 to 30 minutes before the induction of anesthesia along with other anesthetic agents (64). Thus, nebulized $MgSO_4$ seems to be more effective than ketamine in preventing POST with an acceptable safety profile. Ketamine nebulization should not be construed as lacking potential efficacy: however, there is higher variability in the results between the studies and sometimes minor adverse psychotomimetic effects. More study is needed, including controlled trials and identification of the specific doses of both preoperative agents.

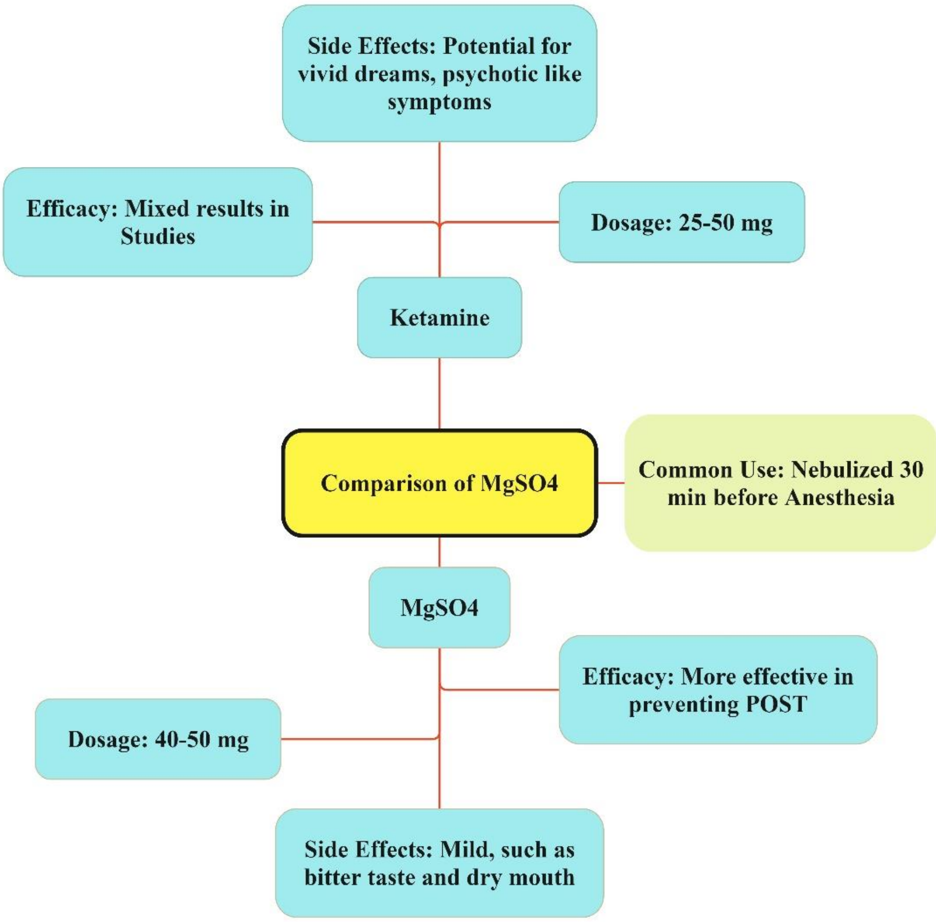

Figure 3: Comparison of $MgSO_4$ and Ketamine for POST

6. Combination Therapy: MgSO4 and Ketamine

Table 3 aims to compare the effects of Magnesium Sulfate ($MgSO_4$) and Ketamine particularly when used as preoperative nebulization in the prevention of POST. The usual dose of magnesium sulfate is between 50-100 mg; its mechanism of action is NMDA receptor antagonism and calcium channel blocking, which decrease POST by about 65% (71,72). It is well appreciated because of its very rapid onset of action, which is within the period of 10 to 15 minutes, and the period of action which lasts for a period of 4 to 6 hours. However, side effects consist of hypotension and flushing which are normally mild and easily controlled (73). The safety profile of $MgSO_4$ has been established and thus it can be used as a general grade (74,75). The $MgSO_4$ increases the effectiveness of Ketamine and decreases side effects, which is considered desirable for achieving a cumulative effect in the treatment of POST (76). Ketamine, however, is given in a dose of 0.5 – 1 mg/kg and works through the NMDA receptor thus giving a slightly higher efficacy of about 70% in managing the POST (77,78). It possesses first-degree action and efficacy and offers results within the surgical environment almost instantly. However, the duration of Ketamine is less and it remains in the body for 2-4 hours only (79). Side effects related to Ketamine include psychotomimetic effects or simply dissociation, which the patients may not find pleasant (80). It is safe when used in moderation especially when supervised, hence it is safe in a controlled environment (81). The table also shows the possible additive effects when using $MgSO_4$ and Ketamine in the preoperative nebulization. This interaction between the drugs results to a synergy that can enhance the management of POST, the overall advantage being more than the individual drawbacks (82). The dosage for both combination therapies should be 50 mg of $MgSO_4$ together with 0.5 mg/kg of Ketamine, which provides the best therapeutic effect along with minimal side effects. Each agent is useful for POST management, and their combined actions justify their application in clinical practice.

Table 3: Comparison of Magnesium Sulfate (MgSO4) and Ketamine in Preoperative Nebulization for Postoperative Sore Throat and Potential Synergistic Effects

Parameter	Magnesium Sulfate (MgSO4)	Ketamine	Mechanism of Action	Efficacy (MgSO4)	Efficacy (Ketamine)
Dosage (mg)	50-100 mg	0.5-1 mg/kg	NMDA Receptor Antagonism	65% Reduction in POST	70% Reduction in POST
Onset of Action	Rapid (10-15 min)	Immediate	Calcium Channel Blocker	Moderate	High
Duration of Effect (hours)	4-6 hours	2-4 hours	Anti-inflammatory Action	Sustained	Short
Adverse Effects	Hypotension, Flushing	Dissociation	Neuroprotective	Minimal	Mild
Synergistic Potential	Enhanced Block of POST	Increased Efficacy	Cumulative Effects	High	High
Safety Profile	Safe for General Use	Safe with Caution	Minimal Interactions	Safe	Safe
Combination Dosage	50 mg	0.5 mg/kg	Dual Action Synergy	Increased Efficacy	Reduced Side Effects
Recommended Uses	Preoperative Nebulization	Preoperative Nebulization	POST Management	Effective for POST	Effective for POST
Conclusion	Synergistic with Ketamine	Synergistic with MgSO4	Complementary Actions	Recommended	Recommended

7. Clinical Implications and Recommendations

7.1 Best Practices for Preoperative Nebulization

The clinical implications and best practice recommendations for two studies on nebulized magnesium sulfate and ketamine for postoperative sore throat: In the first study, the findings show that preoperative nebulization using either drug reduces the occurrence and intensity of POST in comparison with placebo (83,84). There are no serious complications of a sore throat and hence the number needed to treat is acceptable meaning this is an appropriate intervention (85). Second, there is no difference in efficacy between magnesium sulfate and ketamine (86). Both show the similar trends regarding the POST reduction.

In this case, the preference and feasibility of the practitioner in a given setting may also define the choice between these drugs. However, in the case of using magnesium sulfate or ketamine in preoperative nebulization, standard guidelines should be followed. The nebulization process should be performed 30 – 60 minutes before the induction to have time for topical absorption and coating of the airway surface (87,88). To avoid any emergent necessity for an IV infusion, nebulization should be initiated after a patient has had IV access placed in anticipation of possible paradoxical bronchospasm. The patient should observe the side effects of nebulization during and after the treatment. When utilizing nebulization practitioners need to record in the patient record the medication administered, dosage, route, period of treatment, tolerance of the patient, and any other comments regarding the treatment. Enhancing patient compliance and perception of nebulization will be important if the patients are educated on the essence of nebulization and the feeling of the process.

However, as this intervention gains popularity, several areas of importance need more research. The comparison of higher and lower doses of magnesium in contrast to ketamine in various surgical patients would present clearer demarcations of the two agents' therapeutic value (89). Further studies comparing the type of medication, dose, and duration of nebulization suitable for POST are needed. More optimal intraoperative variables such as anthropometric measures could be expanded on by analyzing the impact of preoperative nebulization (90). Perhaps if this becomes the standard of care cost-benefit should also be done. In conclusion, given the current level of evidence, preoperative nebulization with magnesium sulfate and ketamine is both beneficial and worthwhile to prevent POST in certain at-risk patient populations (91). Adhering to protocol guidelines and other best practices is a logical and reasonable way for clinicians to incorporate these methods into their practice. More analysis can further refine remaining uncertainties on direct comparisons, concerning different protocols, incidental outcomes, and cost-utility. With the appropriate selection of patients and proper use of nebulizers, the technique is safe, effective, and warranted its clinical use preoperatively.

7.2 Recommendations for Future Clinical Trials

Sore throat is one of the most prevalent complications in patients with general anesthesia via endotracheal intubation which arises in 21-65% and affects patient satisfaction (92). It suggests that the nebulization of $MgSO_4$ or ketamine can minimize the risk of POST through topical anesthesia along with anti-inflammatory features when inhaled before intubation (93). The understanding and identifying an efficient method of preoperative use of nebulized $MgSO_4$ or ketamine for minimizing POST is the clinical relevance of this present review. Suggestions for subsequent clinical research concerning this subject are making the dose and time of administration of treatment groups uniform. The reported dose of $MgSO_4$ varied from 150 – 500 mg and that of ketamine from 20- 50 mg across the included studies (94). The time interval between nebulisation to intubation also varied across the studies ranging from 10 minutes to 1 hour (93). It recommended that a standardized nebulization protocol must be set to determine the optimal doses and time to ne Furthermore, POST should be assessed using uniformly reliable scales by future research across different patient populations, including the Visual Analogue Scale or Numerical Rating Scale so that the effects of treatments can be compared. Some of the current studies only have a yes/no response from the patient regarding sore throat after the surgery instead of rating the severity of POST (95). If standard and valid surveys are used the amount of data analysis regarding the degree of relief between the $MgSO_4$ and ketamine groups will be higher. It must initiate more extensive randomized studies with wider inclusion criteria to boost the validity and strength of the results.

Previously published studies are largely of modest size with less than 100 participant patients and significantly exclude patients with predicted difficult intubation, a history of smoking, or recent respiratory tract infection, which must lower generalizability to the highest risk of POST surgical population (96).

Peculiarly, no POST reduction trials were flagged for public interest, and larger multi-center trials that excluded fewer patients would more adequately represent POST reduction benefits across patient groups. It is recommended that nebulized $MgSO_4$ and ketamine dosages, as well as the choice of POST severity survey, should be further optimized and that the sample size and inclusion criteria of trials should be enlarged. Greater standardization of the allowed methodology and increased generalization of results will contribute to the detailed definitions of coupling the application of $MgSO_4$ and ketamine nebulization with the decrease in POST incidence and the state of postoperative recovery.

8. CONCLUSION

This analysis compared the benefits of treating postoperative sore throat with preoperative nebulization plus $MgSO_4$ against ketamine. Ketamine and $MgSO_4$ successfully diminish pain and evoke neuroactivity. In summary, the findings seem relatively favorable, with several RCT (Randomized Controlled Trial) trials indicating that nebulized doses of $MgSO_4$ and ketamine administered preoperatively can meaningfully lower the rates of POST and patient pain scores compared to the placebo. Between the two agents, ketamine appears to be slightly more efficacious and with a more robust effect size – current data suggest an average reduction in POST incidence rates of roughly 50%. $MgSO_4$ also helps minimize POST but has significant inter-study variability. In particular, all the used drugs demonstrated acceptable tolerability of side effects at nebulized proper concentrations. It is, however, necessary for readers to know that double-barrel therapy using both may have additional benefits and would like to call for larger, better-quality clinical trials. Thus, the nebulization with $MgSO_4$ and/or ketamine before surgery is a rather easy, nonpharmacological preconditioning method for the prevention of POST. Additional studies are still required to fine-tune optimal dosing regimens, assess combination versus single-agent therapy, explore patient characteristics that may be useful in predicting outcomes, and consolidate guidelines that would help clinicians practice what has been discovered to be best practice. This study has identified various approaches that could enhance postoperative recovery and patient satisfaction for many who undergo airway instrumentation. Further, more properly conducted RCTs in other surgical populations will assist with the further development of the evidence as it pertains to this research area in the future.

REFERENCES

1. Elhakim M, Ali NM, Rashed I, Riad MK, Refat M. Dexamethasone reduces postoperative vomiting and pain after pediatric tonsillectomy. Can J Anaesth. 2003 Apr;50(4):392-7. English, French. doi: 10.1007/BF03021038. PMID: 12670818.
2. Macario A, Weinger M, Carney S, Kim A. Which clinical anesthesia outcomes are important to avoid? The perspective of patients. Anesth Analg. 1999 Sep;89(3):652-8. doi: 10.1097/00000539-199909000-00022. PMID: 10475299.
3. Chen KT, Tzeng JI, Lu CL, Liu KS, Chen YW, Hsu CS, Wang JJ. Risk factors associated with postoperative sore throat after tracheal intubation: an evaluation in the postanesthetic recovery room. Acta Anaesthesiol Taiwan. 2004 Mar;42(1):3-8. PMID: 15148688.
4. Muzi M, Robinson BJ, Ebert TJ, O'Brien TJ. Induction of anesthesia and tracheal intubation with sevoflurane in adults. Anesthesiology. 1996 Sep;85(3):536-43. doi: 10.1097/00000542-199609000-00012. PMID: 8853083.

5. Hara K, Maruyama K. Effect of additives in lidocaine spray on postoperative sore throat, hoarseness and dysphagia after total intravenous anaesthesia. Acta Anaesthesiol Scand. 2005 Apr;49(4):463-7. doi: 10.1111/j.1399-6576.2005.00632.x. PMID: 15777293.
6. Tanaka Y, Nakayama T, Nishimori M, Tsujimura Y, Kawaguchi M, Sato Y. Lidocaine for preventing postoperative sore throat. Cochrane Database Syst Rev. 2015 Jul 14;2015(7):CD004081. doi: 10.1002/14651858.CD004081.pub3. PMID: 26171894; PMCID: PMC7151755.
7. Agarwal A, Nath SS, Goswami D, Gupta D, Dhiraaj S, Singh PK. An evaluation of the efficacy of aspirin and benzydamine hydrochloride gargle for attenuating postoperative sore throat: a prospective, randomized, single-blind study. Anesth Analg. 2006 Oct;103(4):1001-3. doi: 10.1213/01.ane.0000231637.28427.00. PMID: 17000820.
8. Jee D, Park SY. Lidocaine sprayed down the endotracheal tube attenuates the airway-circulatory reflexes by local anesthesia during emergence and extubation. Anesth Analg. 2003 Jan;96(1):293-7, table of contents. doi: 10.1097/00000539-200301000-00058. PMID: 12505969.
9. Lucy C, Chan M, Lee M, Lo YL. Postoperative sore throat and ketamine gargle. Br J Anaesth. 2010;105(1):97. doi: 10.1093/bja/aeq152.
10. Thomas D, Bejoy R, Zabrin N, Beevi S. Preoperative ketamine nebulization attenuates the incidence and severity of postoperative sore throat: A randomized controlled clinical trial. Saudi J Anaesth. 2018 Jul-Sep;12(3):440-445. doi: 10.4103/sja.SJA_47_18. PMID: 30100844; PMCID: PMC6044170.
11. Barazanchi AWH, MacFater WS, Rahiri JL, Tutone S, Hill AG, Joshi GP; PROSPECT collaboration. Evidence-based management of pain after laparoscopic cholecystectomy: a PROSPECT review update. Br J Anaesth. 2018 Oct;121(4):787-803. doi: 10.1016/j.bja.2018.06.023. Epub 2018 Aug 7. PMID: 30236241.
12. Borazan H, Kececioglu A, Okesli S, Otelcioglu S. Oral magnesium lozenge reduces postoperative sore throat: a randomized, prospective, placebo-controlled study. Anesthesiology. 2012 Sep;117(3):512-8. doi: 10.1097/ALN.0b013e3182639d5f. PMID: 22797283.
13. Gupta SK, Tharwani S, Singh DK, Yadav G. Nebulized magnesium for prevention of postoperative sore throat. Br J Anaesth. 2012 Jan;108(1):168-9. doi: 10.1093/bja/aer437. PMID: 22157461.
14. Yadav M, Chalumuru N, Gopinath R. Effect of magnesium sulfate nebulization on the incidence of postoperative sore throat. J Anaesthesiol Clin Pharmacol. 2016 Apr-Jun;32(2):168-71. doi: 10.4103/0970-9185.173367. PMID: 27275043; PMCID: PMC4874068.
15. Jaensson M, Gupta A, Nilsson UG. Risk factors for development of postoperative sore throat and hoarseness after endotracheal intubation in women: a secondary analysis. AANA J. 2012 Aug;80(4 Suppl):S67-73. PMID: 23248834.
16. El-Boghdadly K, Bailey CR, Wiles MD. Postoperative sore throat: a systematic review. Anaesthesia. 2016 Jun;71(6):706-17. doi: 10.1111/anae.13438. Epub 2016 Mar 28. PMID: 27158989.
17. Liu J, Zhang X, Gong W, Li S, Wang F, Fu S, Zhang M, Hang Y. Correlations between controlled endotracheal tube cuff pressure and postprocedural complications: a multicenter study. Anesth Analg. 2010 Nov;111(5):1133-7. doi: 10.1213/ANE.0b013e3181f2ecc7. Epub 2010 Aug 24. PMID: 20736432.
18. Tanaka Y, Nakayama T, Nishimori M, Tsujimura Y, Kawaguchi M, Sato Y. Lidocaine for preventing postoperative sore throat. Cochrane Database Syst Rev. 2015 Jul 14;2015(7):CD004081. doi: 10.1002/14651858.CD004081.pub3. PMID: 26171894; PMCID: PMC7151755.
19. Hess DR. Nebulizers: principles and performance. Respir Care. 2000 Jun;45(6):609-22. PMID: 10894454.

20. Ahuja V, Mitra S, Sarna R. Nebulized ketamine decreases incidence and severity of post-operative sore throat. Indian J Anaesth. 2015 Jan;59(1):37-42. doi: 10.4103/0019-5049.149448. PMID: 25684812; PMCID: PMC4322100.
21. Ryu JH, Kang MH, Park KS, Do SH. Effects of magnesium sulphate on intraoperative anaesthetic requirements and postoperative analgesia in gynaecology patients receiving total intravenous anaesthesia. Br J Anaesth. 2008 Mar;100(3):397-403. doi: 10.1093/bja/aem407. PMID: 18276652.
22. Kwok RFK, Lim J, Chan MTV, Gin T, Chiu WKY. Preoperative ketamine improves postoperative analgesia after gynecologic laparoscopic surgery. Anesth Analg. 2004 Apr;98(4):1044-1049. doi: 10.1213/01.ANE.0000105911.66089.59. PMID: 15041596.
23. Chen C, Wen D, Wang Y, Li H, Yu Q, Li M. A spray-as-you-go airway topical anesthesia attenuates cardiovascular responses for double-lumen tube tracheal intubation. BMC Anesthesiol. 2022 Jul 2;22(1):203. doi: 10.1186/s12871-022-01749-8. PMID: 35780106; PMCID: PMC9250180.
24. Do SH. Magnesium: a versatile drug for anesthesiologists. Korean J Anesthesiol. 2013 Jul;65(1):4-8. doi: 10.4097/kjae.2013.65.1.4. Epub 2013 Jul 19. PMID: 23904932; PMCID: PMC3726845.
25. Peng YN, Sung FC, Huang ML, Lin CL, Kao CH. The use of intravenous magnesium sulfate on postoperative analgesia in orthopedic surgery: A systematic review of randomized controlled trials. Medicine (Baltimore). 2018 Dec;97(50):e13583. doi: 10.1097/MD.0000000000013583. PMID: 30558026; PMCID: PMC6319973.
26. Hirota K, Lambert DG. Ketamine: its mechanism(s) of action and unusual clinical uses. Br J Anaesth. 1996 Oct;77(4):441-4. doi: 10.1093/bja/77.4.441. PMID: 8942324.
27. Borazan H, Kececioglu A, Okesli S, Otelcioglu S. Oral magnesium lozenge reduces postoperative sore throat: a randomized, prospective, placebo-controlled study. Anesthesiology. 2012 Sep;117(3):512-8. doi: 10.1097/ALN.0b013e3182639d5f. PMID: 22797283.
28. Ahuja V, Mitra S, Sarna R. Nebulized ketamine decreases incidence and severity of post-operative sore throat. Indian J Anaesth. 2015 Jan;59(1):37-42. doi: 10.4103/0019-5049.149448. PMID: 25684812; PMCID: PMC4322100.
29. Xue FS, Zhang YM, Xiong J, Zhang PJ, Li XY, Liu Y, et al. Spray-as-you-go airway topical anesthesia in patients undergoing awake fibreoptic nasotracheal intubation: a randomised, double blind trial of lidocaine, ropivacaine, and a combination lidocaine/ ropivacaine solution. Anaesthesia. 2016;71(4):440-7.
30. McHardy FE, Chung F. Postoperative sore throat: cause, prevention and treatment. Anaesthesia. 1999 May;54(5):444-53. doi: 10.1046/j.1365-2044.1999.00780.x. PMID: 10995141.
31. Tanaka Y, Nakayama T, Nishimori M, Tsujimura Y, Kawaguchi M, Sato Y. Lidocaine for preventing postoperative sore throat. Cochrane Database Syst Rev. 2015 Jul 14;2015(7):CD004081. doi: 10.1002/14651858.CD004081.pub3. PMID: 26171894; PMCID: PMC7151755.
32. El-Boghdadly K, Bailey C, Wiles M. Postoperative sore throat: A systematic review. Anaesthesia. 2016;71: n/a-n/a. doi: 10.1111/anae.13438.
33. Kim YS, Kim YI, Seo KH, Kang HR. Optimal dose of prophylactic dexmedetomidine for preventing postoperative shivering. Int J Med Sci. 2013 Aug 13;10(10):1327-32. doi: 10.7150/ijms.6531. PMID: 23983593; PMCID: PMC3752720.
34. Zhu MM, Zhou QH, Zhu MH, Rong HB, Xu YM, Qian YN, Fu CZ. Effects of nebulized ketamine on allergen-induced airway hyperresponsiveness and inflammation in actively sensitized Brown-Norway rats. J Inflamm (Lond). 2007 May 4;4:10. doi: 10.1186/1476-9255-4-10. PMID: 17480224; PMCID: PMC1876456.
35. Hua X, Chen Y, Wu Z, Zheng G, Yang D, Li J, Wu Q, Fan W. Effects of intra-operative magnesium sulfate infusion on orthognathic surgery: A prospective and randomized controlled

trial. Heliyon. 2024 Apr 25;10(9):e30342. doi: 10.1016/j.heliyon.2024.e30342. PMID: 38707412; PMCID: PMC11066664.

36. Borazan H, Kececioglu A, Okesli S, Otelcioglu S. Oral magnesium lozenge reduces postoperative sore throat: a randomized, prospective, placebo-controlled study. Anesthesiology. 2012 Sep;117(3):512-8. doi: 10.1097/ALN.0b013e3182639d5f. PMID: 22797283.
37. Gupta SK, Tharwani S, Singh DK, Yadav G. Nebulized magnesium for prevention of postoperative sore throat. Br J Anaesth. 2012 Jan;108(1):168-9. doi: 10.1093/bja/aer437. PMID: 22157461.
38. Canbay O, Celebi N, Sahin A, Celiker V, Ozgen S, Aypar U. Ketamine gargle for attenuating postoperative sore throat. Br J Anaesth. 2008 Apr;100(4):490-3. doi: 10.1093/bja/aen023. Epub 2008 Mar 1. PMID: 18310675.
39. Xue FS, Liu HP, He N, Xu YC, Yang QY, Liao X, Xu XZ, Guo XL, Zhang YM. Spray-as-you-go airway topical anesthesia in patients with a difficult airway: a randomized, double-blind comparison of 2% and 4% lidocaine. Anesth Analg. 2009 Feb;108(2):536-43. doi: 10.1213/ane.0b013e31818f1665. PMID: 19151284.
40. Thomas D, Bejoy R, Zabrin N, Beevi S. Preoperative ketamine nebulization attenuates the incidence and severity of postoperative sore throat: A randomized controlled clinical trial. Saudi J Anaesth. 2018 Jul-Sep;12(3):440-445. doi: 10.4103/sja.SJA_47_18. PMID: 30100844; PMCID: PMC6044170.
41. Rudra A, Ray S, Chatterjee S, Ahmed A, Ghosh S. Gargling with ketamine attenuates the postoperative sore throat. Indian J Anaesth. 2009 Feb;53(1):40-3. PMID: 20640076; PMCID: PMC2900032.
42. McHardy FE, Chung F. Postoperative sore throat: cause, prevention and treatment. Anaesthesia. 1999 May;54(5):444-53. doi: 10.1046/j.1365-2044.1999.00780.x. PMID: 10995141.
43. Tanaka Y, Nakayama T, Nishimori M, Tsujimura Y, Kawaguchi M, Sato Y. Lidocaine for preventing postoperative sore throat. Cochrane Database Syst Rev. 2015 Jul 14;2015(7):CD004081. doi: 10.1002/14651858.CD004081.pub3. PMID: 26171894; PMCID: PMC7151755.
44. El-Boghdadly K, Bailey CR, Wiles MD. Postoperative sore throat: a systematic review. Anaesthesia. 2016 Jun;71(6):706-17. doi: 10.1111/anae.13438. Epub 2016 Mar 28. PMID: 27158989.
45. Mazzotta E, Soghomonyan S, Hu LQ. Postoperative sore throat: prophylaxis and treatment. Front Pharmacol. 2023 Nov 23;14:1284071. doi: 10.3389/fphar.2023.1284071. PMID: 38074131; PMCID: PMC10701272.
46. Kim YS, Kim YI, Seo KH, Kang HR. Optimal dose of prophylactic dexmedetomidine for preventing postoperative shivering. Int J Med Sci. 2013 Aug 13;10(10):1327-32. doi: 10.7150/ijms.6531. PMID: 23983593; PMCID: PMC3752720.
47. Zhu MM, Zhou QH, Zhu MH, Rong HB, Xu YM, Qian YN, Fu CZ. Effects of nebulized ketamine on allergen-induced airway hyperresponsiveness and inflammation in actively sensitized Brown-Norway rats. J Inflamm (Lond). 2007 May 4;4:10. doi: 10.1186/1476-9255-4-10. PMID: 17480224; PMCID: PMC1876456.
48. Hua X, Chen Y, Wu Z, Zheng G, Yang D, Li J, Wu Q, Fan W. Effects of intra-operative magnesium sulfate infusion on orthognathic surgery: A prospective and randomized controlled trial. Heliyon. 2024 Apr 25;10(9):e30342. doi: 10.1016/j.heliyon.2024.e30342. PMID: 38707412; PMCID: PMC11066664.
49. Borazan H, Kececioglu A, Okesli S, Otelcioglu S. Oral magnesium lozenge reduces postoperative sore throat: a randomized, prospective, placebo-controlled study. Anesthesiology. 2012 Sep;117(3):512-8. doi: 10.1097/ALN.0b013e3182639d5f. PMID: 22797283.
50. Gupta SK, Tharwani S, Singh DK, Yadav G. Nebulized magnesium for prevention of postoperative sore throat. Br J Anaesth. 2012 Jan;108(1):168-9. doi: 10.1093/bja/aer437. PMID: 22157461.

51. Himmelseher S, Durieux ME. Ketamine for perioperative pain management. Anesthesiology. 2005 Jan;102(1):211-20. doi: 10.1097/00000542-200501000-00030. PMID: 15618805.
52. Canbay O, Celebi N, Sahin A, Celiker V, Ozgen S, Aypar U. Ketamine gargle for attenuating postoperative sore throat. Br J Anaesth. 2008 Apr;100(4):490-3. doi: 10.1093/bja/aen023. Epub 2008 Mar 1. PMID: 18310675.
53. Xue FS, Liu HP, He N, et al. Spray-as-you-go airway topical anesthesia in patients undergoing awake fibreoptic intubation: a double blind cross over trial between 2% lidocaine gel and 5% lidocaine gel. Anaesthesia. 2015;70(5):538-44.
54. Thomas D, Bejoy R, Zabrin N, Beevi S. Preoperative ketamine nebulization attenuates the incidence and severity of postoperative sore throat: A randomized controlled clinical trial. Saudi J Anaesth. 2018 Jul-Sep;12(3):440-445. doi: 10.4103/sja.SJA_47_18. PMID: 30100844; PMCID: PMC6044170.
55. Rudra A, Ray S, Chatterjee S, Ahmed A, Ghosh S. Gargling with ketamine attenuates the postoperative sore throat. Indian J Anaesth. 2009 Feb;53(1):40-3. PMID: 20640076; PMCID: PMC2900032.
56. Lee EN, Lee JH. The Effects of Low-Dose Ketamine on Acute Pain in an Emergency Setting: A Systematic Review and Meta-Analysis. PLoS One. 2016 Oct 27;11(10):e0165461. doi: 10.1371/journal.pone.0165461. PMID: 27788221; PMCID: PMC5082866.
57. Elia N, Tramer MR. Ketamine and postoperative pain: a quantitative systematic review of randomised trials. 2005. In: Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet]. York (UK): Centre for Reviews and Dissemination (UK); 1995-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK71633.
58. Ma X, Yan J, Jiang H. Application of Ketamine in Pain Management and the Underlying Mechanism. Pain Res Manag. 2023 Aug 16;2023:1928969. doi: 10.1155/2023/1928969. PMID: 37622028; PMCID: PMC10447145.
59. Bell RF. Ketamine for chronic non-cancer pain. Pain. 2009 Feb;141(3):210-214. doi: 10.1016/j.pain.2008.12.003. Epub 2009 Jan 6. PMID: 19128879.
60. Jouguelet-Lacoste J, La Colla L, Schilling D, Chelly JE. The use of intravenous infusion or single dose of low-dose ketamine for postoperative analgesia: a review of the current literature. Pain Med. 2015 Feb;16(2):383-403. doi: 10.1111/pme.12619. Epub 2014 Dec 19. PMID: 25530168.
61. Suvvari P, Mishra S, Bhatnagar S, Garg R, Bharati SJ, Gupta N, Kumar V, Khan MA. Comparison of Intranasal Dexmedetomidine Versus Intranasal Ketamine as Premedication for Level of Sedation in Children Undergoing Radiation Therapy: A Prospective, Randomised, Double-Blind Study. Turk J Anaesthesiol Reanim. 2020 Jun;48(3):215-222. doi: 10.5152/TJAR.2019.45087. Epub 2019 Oct 4. PMID: 32551449; PMCID: PMC7279870.
62. Lee JH. Anesthesia for ambulatory surgery. Korean J Anesthesiol. 2017 Aug;70(4):398-406. doi: 10.4097/kjae.2017.70.4.398. Epub 2017 May 19. PMID: 28794834; PMCID: PMC5548941.
63. Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. Ann Emerg Med. 2011 May;57(5):449-61. doi: 10.1016/j.annemergmed.2010.11.030. Epub 2011 Jan 21. PMID: 21256625.
64. McHardy FE, Chung F. Postoperative sore throat: cause, prevention and treatment. Anaesthesia. 1999 May;54(5):444-53. doi: 10.1046/j.1365-2044.1999.00780.x. PMID: 10995141..
65. Wu CL, Rowlingson AJ, Partin AW, Kalish MA, Courpas GE, Walsh PC, Fleisher LA. Correlation of postoperative pain to quality of recovery in the immediate postoperative period. Reg Anesth Pain Med. 2005 Nov-Dec;30(6):516-22. doi: 10.1016/j.rapm.2005.07.190. PMID: 16326335..
66. Xue FS, Liu HP, He N, Xu YC, Yang QY, Liao X, Xu XZ, Guo XL, Zhang YM. Spray-as-you-go airway topical anesthesia in patients with a difficult airway: a randomized, double-blind comparison of 2% and 4% lidocaine. Anesth Analg. 2009 Feb;108(2):536-43. doi: 10.1213/ane.0b013e31818f1665. PMID: 19151284.

67. Yadav M, Chalumuru N, Gopinath R. Effect of magnesium sulfate nebulization on the incidence of postoperative sore throat. J Anaesthesiol Clin Pharmacol. 2016 Apr-Jun;32(2):168-71. doi: 10.4103/0970-9185.173367. PMID: 27275043; PMCID: PMC4874068.
68. Paula-Garcia WN, Oliveira-Paula GH, de Boer HD, Garcia LV. Lidocaine combined with magnesium sulfate preserved hemodynamic stability during general anesthesia without prolonging neuromuscular blockade: a randomized, double-blind, controlled trial. BMC Anesthesiol. 2021 Mar 27;21(1):91. doi: 10.1186/s12871-021-01311-y. PMID: 33773580; PMCID: PMC8004390.
69. Agarwal A, Nath SS, Goswami D, Gupta D, Dhiraaj S, Singh PK. An evaluation of the efficacy of aspirin and benzydamine hydrochloride gargle for attenuating postoperative sore throat: a prospective, randomized, single-blind study. Anesth Analg. 2006 Oct;103(4):1001-3. doi: 10.1213/01.ane.0000231637.28427.00. PMID: 17000820.
70. Park SY, Kim SH, Noh JI, Lee SM, Kim MG, Kim SH, Ok SY, Kim SI. The effect of intravenous low dose ketamine for reducing postoperative sore throat. Korean J Anesthesiol. 2010 Jul;59(1):22-6. doi: 10.4097/kjae.2010.59.1.22. Epub 2010 Jul 21. PMID: 20651994; PMCID: PMC2908222.
71. Peng YN, Sung FC, Huang ML, Lin CL, Kao CH. The use of intravenous magnesium sulfate on postoperative analgesia in orthopedic surgery: A systematic review of randomized controlled trials. Medicine (Baltimore). 2018 Dec;97(50):e13583. doi: 10.1097/MD.0000000000013583. PMID: 30558026; PMCID: PMC6319973.
72. Singh NP, Makkar JK, Wourms V, Zorrilla-Vaca A, Cappellani RB, Singh PM. Role of topical magnesium in post-operative sore throat: A systematic review and meta-analysis of randomised controlled trials. Indian J Anaesth. 2019 Jul;63(7):520-529. doi: 10.4103/ija.IJA_856_18. PMID: 31391614; PMCID: PMC6644199.
73. Abd-Elsalam KA, Fares KM, Mohamed MA, Mohamed MF, El-Rahman AMA, Tohamy MM. Efficacy of Magnesium Sulfate Added to Local Anesthetic in a Transversus Abdominis Plane Block for Analgesia Following Total Abdominal Hysterectomy: A Randomized Trial. Pain Physician. 2017 Nov;20(7):641-647. PMID: 29149143.
74. Hicks MA, Tyagi A. Magnesium Sulfate. [Updated 2023 May 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554553/
75. Kayem G, Mandelbrot L, Haddad B. Utilisation du sulfate de magnésium en obstétrique [Use of magnesium sulfate in obstetrics]. Gynecol Obstet Fertil. 2012 Oct;40(10):605-13. French. doi: 10.1016/j.gyobfe.2012.08.005. Epub 2012 Sep 18. PMID: 22995056.
76. El-Boghdadly K, Bailey CR, Wiles MD. Postoperative sore throat: a systematic review. Anaesthesia. 2016 Jun;71(6):706-17. doi: 10.1111/anae.13438. Epub 2016 Mar 28. PMID: 27158989.
77. Mion G, Villevieille T. Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). CNS Neurosci Ther. 2013 Jun;19(6):370-80. doi: 10.1111/cns.12099. Epub 2013 Apr 10. PMID: 23575437; PMCID: PMC6493357.
78. Bell RF, Kalso EA. Ketamine for pain management. Pain Rep. 2018 Aug 9;3(5):e674. doi: 10.1097/PR9.0000000000000674. PMID: 30534625; PMCID: PMC6181464.
79. Segaran S, Bacthavasalame AT, Venkatesh RR, Zachariah M, George SK, Kandasamy R. Comparison of Nebulized Ketamine with Nebulized Magnesium Sulfate on the Incidence of Postoperative Sore Throat. Anesth Essays Res. 2018 Oct-Dec;12(4):885-890. doi: 10.4103/aer.AER_148_18. PMID: 30662125; PMCID: PMC6319074.
80. Radvansky BM, Shah K, Parikh A, Sifonios AN, Le V, Eloy JD. Role of ketamine in acute postoperative pain management: a narrative review. Biomed Res Int. 2015;2015:749837. doi: 10.1155/2015/749837. Epub 2015 Oct 1. PMID: 26495312; PMCID: PMC4606413.

81. Segaran S, Bacthavasalame AT, Venkatesh RR, Zachariah M, George SK, Kandasamy R. Comparison of Nebulized Ketamine with Nebulized Magnesium Sulfate on the Incidence of Postoperative Sore Throat. Anesth Essays Res. 2018 Oct-Dec;12(4):885-890. doi: 10.4103/aer.AER_148_18. PMID: 30662125; PMCID: PMC6319074.
82. Delage N, Morel V, Picard P, Marcaillou F, Pereira B, Pickering G. Effect of ketamine combined with magnesium sulfate in neuropathic pain patients (KETAPAIN): study protocol for a randomized controlled trial. Trials. 2017 Nov 3;18(1):517. doi: 10.1186/s13063-017-2254-3. PMID: 29100524; PMCID: PMC5670712.
83. Zhu M, Zhou Q, Zhu M, Rong H, Xu YM, Qian Y, Fu C. Effects of nebulized ketamine on allergen-induced airway hyperresponsiveness and inflammation in actively sensitized Brown-Norway rats. J Inflamm (Lond). 2007;4:10. doi: 10.1186/1476-9255-4-10.
84. Puri A, Ghosh SK, Singh G, Madan A. Gargling with ketamine preoperatively decreases postoperative sore throat after endotracheal intubation in middle ear surgeries: A prospective randomized control study. Indian J Otolaryngol Head Neck Surg. 2022 Dec;74(Suppl 3):5739-5743. doi: 10.1007/s12070-021-03062-1. Epub 2022 Apr 28. PMID: 36742572; PMCID: PMC9895345.
85. Sirvinskas E, Laurinaitis R. Magnio sulfato panaudojimas anesteziologijai [Use of magnesium sulfate in anesthesiology]. Medicina (Kaunas). 2002;38(7):695-8. Lithuanian. PMID: 12474653.
86. Thomas D, Bejoy R, Zabrin N, Beevi S. Preoperative ketamine nebulization attenuates the incidence and severity of postoperative sore throat: A randomized controlled clinical trial. Saudi J Anaesth. 2018 Jul-Sep;12(3):440-445. doi: 10.4103/sja.SJA_47_18. PMID: 30100844; PMCID: PMC6044170.
87. Mazzotta E, Soghomonyan S, Hu LQ. Postoperative sore throat: prophylaxis and treatment. Front Pharmacol. 2023 Nov 23;14:1284071. doi: 10.3389/fphar.2023.1284071. PMID: 38074131; PMCID: PMC10701272.
88. Yadav M, Chalumuru N, Gopinath R. Effect of magnesium sulfate nebulization on the incidence of postoperative sore throat. J Anaesthesiol Clin Pharmacol. 2016 Apr-Jun;32(2):168-71. doi: 10.4103/0970-9185.173367. PMID: 27275043; PMCID: PMC4874068.
89. O'Flaherty JE, Lin CX. Does ketamine or magnesium affect posttonsillectomy pain in children? Paediatr Anaesth. 2003 Jun;13(5):413-21. doi: 10.1046/j.1460-9592.2003.01049.x. PMID: 12791115.
90. De Oliveira GS Jr, Castro-Alves LJ, Khan JH, McCarthy RJ. Perioperative systemic magnesium to minimize postoperative pain: a meta-analysis of randomized controlled trials. Anesthesiology. 2013 Jul;119(1):178-90. doi: 10.1097/ALN.0b013e318297630d. PMID: 23669270.
91. Borazan H, Kececioglu A, Okesli S, Otelcioglu S. Oral magnesium lozenge reduces postoperative sore throat: a randomized, prospective, placebo-controlled study. Anesthesiology. 2012 Sep;117(3):512-8. doi: 10.1097/ALN.0b013e3182639d5f. PMID: 22797283.
92. Higgins PP, Chung F, Mezei G. Postoperative sore throat after ambulatory surgery. Br J Anaesth. 2002 Apr;88(4):582-4. doi: 10.1093/bja/88.4.582. PMID: 12066737.
93. Borazan H, Kececioglu A, Okesli S, Otelcioglu S. Oral magnesium lozenge reduces postoperative sore throat: a randomized, prospective, placebo-controlled study. Anesthesiology. 2012 Sep;117(3):512-8. doi: 10.1097/ALN.0b013e3182639d5f. PMID: 22797283.
94. Forget P, Cata J. Stable anesthesia with alternative to opioids: Are ketamine and magnesium helpful in stabilizing hemodynamics during surgery? A systematic review and meta-analyses of randomized controlled trials. Best Pract Res Clin Anaesthesiol. 2017 Dec;31(4):523-531. doi: 10.1016/j.bpa.2017.07.001. Epub 2017 Jul 8. PMID: 29739541.
95. Ashton WB, James MF, Janicki P, Uys PC. Attenuation of the pressor response to tracheal intubation by magnesium sulphate with and without alfentanil in hypertensive proteinuric patients undergoing caesarean section. Br J Anaesth. 1991 Dec;67(6):741-7. doi: 10.1093/bja/67.6.741. PMID: 1768544.

96. Puri A, Ghosh SK, Singh G, Madan A. Gargling with ketamine preoperatively decreases postoperative sore throat after endotracheal intubation in middle ear surgeries: A prospective randomized control study. Indian J Otolaryngol Head Neck Surg. 2022 Dec;74(Suppl 3):5739-5743. doi: 10.1007/s12070-021-03062-1. Epub 2022 Apr 28. PMID: 36742572; PMCID: PMC9895345.