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Original Research Article

The Effect of Preoperative Ketamine Gargles on Postoperative Sore Throat After Oral Endotracheal Intubation in Patients Undergoing Laparoscopic Cholecystectomy

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Abstract: *Postoperative sore throat (POST) is a common and distressing complication following general anesthesia with endotracheal intubation, particularly in laparoscopic surgeries. Various interventions have been explored to reduce POST, with ketamine gargles emerging as a potential prophylactic agent due to its local anti-inflammatory and analgesic effects.* ***Objective****: To evaluate the efficacy of preoperative ketamine gargles in reducing the incidence and severity of postoperative sore throat and throat pain in patients undergoing laparoscopic cholecystectomy.* ***Methods****: This randomized controlled trial was conducted at a tertiary care hospital between 1st July 2024 to 31st December 2024. Seventy adult patients (ASA I–II) scheduled for elective laparoscopic cholecystectomy under general anesthesia were randomized into two groups (n=35 each): Group K (ketamine gargle) and Group C (control gargle). Participants received a 30-second gargle solution preoperatively. The primary outcomes were the incidence of sore throat and throat pain within 24 hours post-extubation. Secondary outcomes included the occurrence of cough, hoarseness, hemodynamic variations, and any adverse effects. Statistical analyses, including multivariable logistic regression, were conducted using SPSS, with significance set at p<0.05.* ***Results****: Out of 70 patients, 40 (57.1%) were female with a mean age of 44.9 ± 10.1 years. Ketamine gargle significantly reduced the incidence of sore throat (11.4% vs. 45.7%, p = 0.002) and throat pain (8.6% vs. 31.4%, p = 0.018) at 24 hours compared to the control group. Multivariate analysis confirmed that ketamine use was independently associated with lower odds of sore throat (aOR = 0.19; 95% CI: 0.07–0.51; p = 0.001) and throat pain (aOR = 0.22; 95% CI: 0.08–0.61; p = 0.004). No significant differences were observed in the incidence of postoperative cough or hoarseness (p > 0.05). Complications were minimal and comparable across both groups.* ***Conclusion****: Preoperative ketamine gargles are effective in significantly reducing the incidence and severity of postoperative sore throat and throat pain following laparoscopic cholecystectomy. Their use appears safe and well-tolerated, supporting the role of ketamine as a simple and beneficial prophylactic intervention.*

Keywords: Ketamine gargle, sore throat, endotracheal intubation, laparoscopic cholecystectomy

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Introduction

Laparoscopic cholecystectomy (LC) is one of the most common surgeries and is currently considered the treatment of choice for gallbladder stones (1). For most laparoscopic procedures under general anesthesia, the airway is secured with an orally inserted tube called the endotracheal tube (ETT). This procedure provides a route of delivery for anesthesia and oxygen during surgery while also preventing any aspiration. Rarely, the procedure can lead to complications like iatrogenic injury, pneumothorax, and foreign body aspiration, but mostly, it is a very safe procedure. The most common adverse effects include postoperative sore throat, characterized by a feeling of irritation, itching, or discomfort in the larynx or pharynx during the postoperative period (2). This stems from direct injury with airway instrumentation, such as laryngoscopy, intubation, and suctioning, as well as their irritating effects that cause airway edema, inflammation, desquamation of the airway mucosa, and nerve stimulation (lingual, hypoglossal, or recurrent laryngeal). When passing through the larynx and trachea, the ETT can also irritate the fragile respiratory mucosa, causing hoarseness and cough (3).

Several products, including solutions, sprays, nebulizers, and systemic analgesics, have been studied and introduced to counter post-operative throat pain and sore throat; however, all are associated with some level of side effects, complications, or an uncertain safety profile (4). For instance, normal saline gargles have limited efficacy if any (4). Lignocaine spray has been shown to reduce this pain at the cost of numbing protective respiratory reflexes (like cough), and Dexmeditomidine is relatively expensive (5). One such product is ketamine that antagonize the N-methyl-D-aspartate (NMDA) receptors at different levels of inflammation, interacting with inflammatory cells recruitment, cytokines production, and inflammatory mediator regulation (6). Low-dose ketamine gargles have been suggested as an effective, safe, and inexpensive way to reduce postoperative sore throat by providing local anesthesia and anti-inflammatory effects in the oropharynx with minimal systemic absorption (7). However, there is still limited prospective data on the use of this solution in patients undergoing laparoscopic cholecystectomy. The typical risk factors of cholelithiasis (Female, fatty, forty, fertile, and fair) make this population of particular interest for our study.

The aim of this prospective randomized controlled trial (RCT) was to assess the efficacy of preoperative ketamine gargles in reducing the incidence of postoperative sore throat and throat pain in young adults requiring endotracheal intubation for laparoscopic cholecystectomy. We hypothesized that this solution would not decrease the risk of post-operative sore throat and throat pain in this population.

Methodology

We conducted a prospective, double-blinded, randomized controlled trial (RCT) at the Department of Anesthesia, Rehman Medical Institute, Peshawar, Pakistan, over six months from July 1, 2024, to December 31, 2024.

We approached and enrolled young adult patients (aged ≥18 to ≤60 years) of either gender who underwent an elective laparoscopic cholecystectomy during the study period. All patients belonged to ASA grade I/II and had a Mallampati class of 1-2.

Patients were excluded if they refused to consent, had a known sensitivity to ketamine, had a history of active gastro esophageal reflux disease, a history of upper respiratory tract infection (cough, fever), or confirmed pregnancy (positive beta hCG and ultrasound results). Patients were also excluded if they required more than one attempt of endotracheal tube placement, if they died during surgery or in the first 24 hours after surgery, and finally those with a complicated post-op recovery with failure to extubate or re-intubation in the first 24 hours after surgery

Our primary outcomes included sore throat and throat pain at 0 hours, 6 hours, 12 hours, and 24 hours after extubation. The secondary outcomes included cough, hoarseness of voice, hemodynamic fluctuations, and complications during the observation period.

The sample size was calculated with a 95% Confidence Level and an alpha of 5% (two-sided), with a power of 80%. For an anticipated reduction in incidence of sore throat by 80% with preoperative ketamine gargles and a 44% reduction with placebo, the required sample size was estimated around 33 patients in each group. However, accounting for a possible 20% dropout rate, we enrolled 40 patients in each group, totaling 80 patients.

A sample size calculation was performed using the OpenEpi online calculator, and a non-probability consecutive sampling technique was employed to enroll the study participants (9).

Sore throat was defined as persistent itching, and/or irritation in the pharynx worse with swallowing, and discomfort in the throat within 24 hours of surgery. Throat pain was defined as moderate to severe pain in the front of the throat around the pharynx, measured using a visual analog scale (VAS) scored from 0 to 10. Pain can be categorized into mild pain with VAS of 1-4, moderate corresponds to VAS 5-7, and severe pain measured as VAS 8-10. We only considered moderate to severe pain as significant throat pain in our study

After obtaining written approval from the Research Ethics Committee of Rehman Medical Institute, Peshawar, Pakistan (Approval number: RMI/RMI-REC/Approval/191, dated November 23, 2023), patients were identified based on our inclusion and exclusion criteria and approached for participation in the study. After obtaining written informed consent that explained the purpose, risks, and benefits, patients were enrolled in the study.

The study participants were randomly assigned into two groups as group K (ketamine group) and group C (control group) employing blocked randomization with an online software (Graphpad Calcs) (10).

We prepared a separate solution for each group. Patients in group K were given a solution of ketamine 50mg (Injection Ketaflex 50mg/ml, manufactured by Brookes Pharmaceuticals Labs Pakistan Ltd.) in 29 ml of normal saline (11). Patients in group C were only given 30ml of normal saline. The pharmacist prepared solutions before sending them to the operating room, and both the administering personnel and the patients were blinded to the solution administered. After transferring the patient to the operating room and five minutes prior to induction of anesthesia, all patients were instructed to gargle with the assigned solution for 30 seconds.

Next, anesthesia was induced with intravenous inj. Propofol 2mg/kg and Inj. Succinylcholine 2mg/kg and the patients were intubated with a soft seal cuffed sterile poly vinyl chloride endotracheal tube (ENDOSOFT manufactured by Usmanco international, Pakistan) of the appropriate size (12). Endotracheal tube cuff was inflated with air until no audible leak was heard with a peak airway pressure at 20 cmH_2O.

After the surgery, patients were extubated when fully awake and conscious. Patients were turned to the recovery position and shifted to the post-operative ward with oxygen by mask and continuous monitoring. The participants were observed for 24 hours post-extubation for outcomes and complications.

Data was collected on a pre-designed proforma with data pertaining to baseline characteristics including age, gender, body mass index (BMI), residence (rural, urban, sub-urban), educational level (none, primary, middle, secondary, higher secondary, degree or above), duration of surgery, outcomes (sore throat, pain, cough, or hoarseness), hemodynamic vital signs (Heart rate, mean arterial pressure, arterial oxygen saturation [SpO_2]), and other patient reported complaints or complications during the first 24 hours.

Data was entered in and analyzed with the Statistical Package for Social Sciences (SPSS) version 25. Descriptive analyses included frequencies and percentages for categorical variables, such as gender, residence, educational level, socioeconomic status, profession, hypertension, diabetes, distribution by ASA grade, and proportions of outcome variables in each group. The mean ± SD was used to present data for normally distributed quantitative variables, such as age and BMI. The Shapiro-Wilk test was used to check normality, and non-normal data were reported as medians with interquartile range (IQR). For categorical variables, the two groups were compared for incidence of sore throat and pain using the univariate tests of comparison, such as the chi-square test or Fisher's exact test. Multivariable regression analyses were employed to determine the independent effect of the study drug on the incidence of sore throat. For all comparisons, *a p-value of* ≤ 0.05 was considered statistically significant.

Results

We enrolled 80 patients in this RCT of which 10 patients were excluded due to missing data and the final analyses was conducted on the remaining 70 patients (35 each group). 40 (57.1%) were female with an overall mean age of 44.9 ± 10.1 years and a mean BMI of 34.2 ± 5.3 kg/m². Overall, 28 (40.0%) patients resided in rural areas, and only 20 (28.6%) had higher education levels. Diabetes was present in 18 (25.7%) patients, while 26 (37.1%) were hypertensive. Regarding the ASA classification, 46 (65.7%) were classified as ASA I. The median [IQR] duration of surgery was 95 [75–115] minutes in the total cohort, with 95 [75–110] minutes in Group K and 100 [80–120] minutes in Group C ($p = 0.312$). There were no statistically significant differences between Group K and Group C in any baseline characteristics (all $p>0.05$).

Table I provides a detailed comparison of baseline patient and demographic characteristics for the two groups at all data collection time points. Patients remained hemodynamically stable throughout the study period. Significant differences were noted between groups at 6, 12, and 24 hours, with the control group (Group C) displaying higher mean heart rates (88.6 ± 5.2 bpm, 85.8 ± 8.5 bpm, and 83.9 ± 4.2 bpm, respectively) compared to the ketamine group (Group K: 76.9 ± 3.9 bpm, 75.8 ± 3.3 bpm, and 74.2 ± 2.2 bpm, respectively; $p<0.001$ for all time points). The mean arterial pressure (MAP) showed a significant difference at 0 hours post-extubation (Group K: 85.2 ± 6.3 mmHg vs. Group C: 89.1 ± 9.5 mmHg, $p=0.018$), with no significant differences at subsequent time points ($p>0.05$). Oxygen saturation (SpO_2) remained above 97% in both groups and was comparable at all time points ($p>0.05$) (Table II).

The incidence of sore throat at 0, 6, 12, and 24 hours post-extubation was significantly lower in Group K compared to Group C (all $p<0.05$). Specifically, at 0 hours post-extubation, 2 (5.7%) patients in Group K versus 8 (22.9%) in Group C reported a sore throat (p = 0.042). Similar trends persisted at 6 hours (Group K: 3 [8.6%] vs. Group C: 11 [31.4%], $p=0.018$), 12 hours (Group K: 4 [11.4%] vs. Group C: 14 [40.0%], $p=0.006$), and 24 hours (Group K: 4 [11.4%] vs. Group C: 16 [45.7%], $p=0.002$). Throat pain was also significantly less frequent in Group K at 6, 12, and 24 hours post-extubation ($p<0.05$). Risk of throat pain followed an identical trend, with an overall incidence of only 6 (8.6%) at 0 hours that steadily increased to 14 (20%) at 24 hours. By 24 hours, we observed a significant difference in the rates of throat pain between the two groups (Group K: 3 [8.6%] vs. Group C: 11 [31.4%], p = 0.018) (Table III).

After adjusting for age, gender, ASA class, and duration of surgery, ketamine gargles were associated with significantly lower odds of sore throat (aOR 0.19; 95%CI [0.07–0.51]; $p=0.001$) and throat pain (aOR 0.22; 95%CI [0.08–0.61]; $p=0.004$) within 24 hours postoperatively (Table IV).

Overall, we observed rare complications, including microaspiration in one patient and mild psychomimetic effects (agitation) in two patients,

without any serious complications or mortality. These findings collectively highlight the efficacy of ketamine gargles in mitigating postoperative throat complications without significant systemic adverse events.

Table 1: Comparison of Baseline Characteristics of Patients receiving Ketamine gargles versus those receiving saline gargles

Variable	Total (n=70)	Group K (n=35)	Group C (n=35)	p-value	Test Value (Test Used)
Age (years), mean ± SD	44.9 ± 10.1	43.5 ± 9.8	46.3 ± 10.4	0.241	t = 1.18 (t-test)
Female gender, n (%)	40 (57.1%)	18 (51.4%)	22 (62.9%)	0.342	χ^2 = 0.91 (Chi-square)
BMI (kg/m²), mean ± SD	34.2 ± 5.3	33.8 ± 4.9	34.6 ± 5.7	0.512	t = 0.66 (t-test)
Residence, n (%)					
- Rural	28 (40.0%)	12 (34.3%)	16 (45.7%)	0.342	χ^2 = 0.91 (Chi-square)
- Urban	30 (42.9%)	17 (48.6%)	13 (37.1%)	0.342	χ^2 = 0.91 (Chi-square)
- Suburban	12 (17.1%)	6 (17.1%)	6 (17.1%)	1.000	χ^2 = 0.00 (Chi-square)
Education level, n (%)					
- Primary	20 (28.6%)	8 (22.9%)	12 (34.3%)	0.302	χ^2 = 1.07 (Chi-square)
- Secondary	30 (42.9%)	16 (45.7%)	14 (40.0%)	0.637	χ^2 = 0.22 (Chi-square)
- Higher	20 (28.6%)	11 (31.4%)	9 (25.7%)	0.602	χ^2 = 0.27 (Chi-square)
Comorbid conditions					
- Diabetes, n (%)	18 (25.7%)	8 (22.9%)	10 (28.6%)	0.586	χ^2 = 0.30 (Chi-square)
- Hypertension, n (%)	26 (37.1%)	12 (34.3%)	14 (40.0%)	0.622	χ^2 = 0.24 (Chi-square)
ASA class, n (%)					
Class I	46 (65.7%)	22 (62.9%)	24 (68.6%)	0.621	χ^2 = 0.24 (Chi-square)
Class II	24 (34.3%)	13 (37.1%)	11 (31.4%)	0.621	χ^2 = 0.24 (Chi-square)
Duration of surgery (min), median [IQR]	95 [75–115]	95 [75–110]	100 [80–120]	0.312	U = 522 (Mann-Whitney U)

Group K: Ketamine group, Group C: Control group, BMI = Body Mass Index (weight in kg/height in m²); IQR = Interquartile Range; SD = Standard Deviation, n(%): frequency(percentage), ASA class: American Society of Anesthesia classification,
Continuous variables reported as mean ± SD unless otherwise specified
Categorical variables reported as frequency (percentage)
† Mann-Whitney U test used for non-normally distributed ordinal variables (Gravida, Para)
‡ Fisher's Exact Test used for categorical variables with expected cell counts <5
p-values calculated using two-tailed tests with α=0.05
Significant results (p<0.05) highlighted in bold

Table 2: Comparison of Hemodynamic Fluctuations in Patients receiving Ketamine gargles versus those receiving saline gargles

Variable	Total (n=70)	Group K (n=35)	Group C (n=35)	*p*-value	Test Value (Test Used)
Heart Rate (bpm)					
0 hours	82.1 ± 6.2	82.0 ± 5.7	81.2 ± 6.8	0.278	t=0.78 (t-test)
6 hours	77.8 ± 4.4	76.9 ± 3.9	88.6 ± 5.2	**<0.001**	t=10.92 (t-test)
12 hours	75.9 ± 5.7	75.8 ± 3.3	85.8 ± 8.5	**<0.001**	t=6.75 (t-test)
24 hours	74.5 ± 4.0	74.2 ± 2.2	83.9 ± 4.2	**<0.001**	t=12.15 (t-test)
MAP (mmHg)					
0 hours	85.3 ± 6.3	85.2 ± 6.3	89.1 ± 9.5	**0.018**	t=2.42 (t-test)
6 hours	78.7 ± 6.6	78.6 ± 6.5	88.3 ± 8.4	0.157	t=1.43 (t-test)
12 hours	83.1 ± 7.3	83.0 ± 7.2	85.3 ± 5.2	0.502	t=0.67 (t-test)
24 hours	82.0 ± 7.6	81.9 ± 7.5	85.8 ± 7.5	0.872	t=0.16 (t-test)
SpO_2 (%)					
0 hours	98.1 ± 1.2	98.2 ± 1.3	98.0 ± 1.2	0.492	t=0.70 (t-test)
6 hours	98.0 ± 1.1	98.1 ± 1.1	97.9 ± 1.0	0.538	t=0.62 (t-test)
12 hours	97.9 ± 1.0	98.0 ± 1.1	97.8 ± 1.1	0.635	t=0.48 (t-test)
24 hours	97.8 ± 1.1	97.9 ± 1.0	97.7 ± 1.2	0.725	t=0.35 (t-test)

Group K: Ketamine group, Group C: Control group, MAP = mean arterial pressure, SpO2 Saturation of Oxygen, bpm beats per minute.
All Data are reported as mean ± SD unless otherwise stated. p<0.05 considered significant (two-tailed t-tests).

Table 3: Comparison of Primary Outcomes in Patients receiving Ketamine gargles versus those receiving saline gargles

Variable	Total (n=70)	Group K (n=35)	Group C (n=35)	*p*-value	Test Value (Test Used)
Sore Throat, n (%)					
0 hours	10 (14.3%)	2 (5.7%)	8 (22.9%)	**0.042**	Fisher's exact
6 hours	14 (20.0%)	3 (8.6%)	11 (31.4%)	**0.018**	Fisher's exact
12 hours	18 (25.7%)	4 (11.4%)	14 (40.0%)	**0.006**	Fisher's exact
24 hours	20 (28.6%)	4 (11.4%)	16 (45.7%)	**0.002**	Fisher's exact
Any time during 24 hours	22 (31.4%)	5 (14.3%)	17 (48.6%)	**0.002**	χ^2=9.52 (Chi-square)
Throat Pain, n (%)					
0 hours	6 (8.6%)	1 (2.9%)	5 (14.3%)	0.087	Fisher's exact
6 hours	10 (14.3%)	2 (5.7%)	8 (22.9%)	**0.042**	Fisher's exact
12 hours	12 (17.1%)	3 (8.6%)	9 (25.7%)	**0.048**	Fisher's exact

24 hours	14 (20.0%)	3 (8.6%)	11 (31.4%)	**0.018**	Fisher's exact
Any time during 24 hours	16 (22.9%)	4 (11.4%)	12 (34.3%)	**0.022**	Fisher's exact
Hoarseness, n (%)					
0 hours	4 (5.7%)	1 (2.9%)	3 (8.6%)	0.300	Fisher's exact
6 hours	2 (2.9%)	0 (0%)	2 (5.7%)	0.150	Fisher's exact
12 hours	2 (2.9%)	1 (2.9%)	1 (2.9%)	1.000	Fisher's exact
24 hours	0 (0%)	0 (0%)	0 (0%)	N/A	N/A
Any time during 24 hours	4 (5.7%)	1 (2.9%)	3 (8.6%)	0.300	Fisher's exact
Cough, n (%)					
0 hours	10 (14.3%)	4 (11.4%)	6 (17.1%)	0.500	Fisher's exact
6 hours	8 (11.4%)	3 (8.6%)	5 (14.3%)	0.450	Fisher's exact
12 hours	6 (8.6%)	2 (5.7%)	4 (11.4%)	0.400	Fisher's exact
24 hours	4 (5.7%)	1 (2.9%)	3 (8.6%)	0.300	Fisher's exact
Any time during 24 hours	12 (17.1%)	5 (14.3%)	7 (20.0%)	0.530	χ^2=0.40

IQR = Interquartile Range; n (%) = frequency (percentage);
Fisher's Exact Test used for incidence comparisons when any one cell value was <5,
p-values calculated using two-tailed tests with α=0.05. Significant results (p<0.05) highlighted in bold

Table 4: Multivariable regression analysis for the independent effect of ketamine gargles on different patient outcomes

Variable	aOR	95% CI	*p*-value
Sore throat (Any in 24h)	0.19	[0.07–0.51]	**0.001**
Throat pain (Any 24h)	0.22	[0.08–0.61]	**0.004**

aOR: adjusted Odd's ratio, CI: confidence interval, Significant results (p<0.05) highlighted in bold. Regression analyses were performed while adjusting for age, gender, residence status, education level, time of surgery, and comorbid conditions.

Discussion

In this RCT, preoperative ketamine gargles effectively reduced the incidence of postoperative sore throat and throat pain among patients requiring endotracheal intubation for laparoscopic cholecystectomy. The low-dose ketamine solution had limited systemic effects with no impact on hoarseness or cough and no remarkable associated complications. Our findings were confirmed through multivariable analyses, which were adjusted for potential known confounders. These results reinforce ketamine's potential role as an effective topical agent for these patients and support the prophylactic use of ketamine gargles.

Our study population primarily consisted of young females, with a mean age of 45 years and a female-to-male ratio of 57%. Ali et al. conducted a similar study on all patients undergoing intubation for any surgery, reporting a younger male-dominant population with a mean age of 38.58±7.57 years, and only 27 (31.40%) females (7). The female predominance and relatively older age (45 years) in our study might be related to the highly selective study population of cholelithiasis which is directly related to the five known risk factors: female, fatty, forty, fertile, and fair (13). We also compared and reported the residence status and education level, but found no significant difference between the two groups in these variables. This comparison eliminates a known confounder for the accuracy of reporting pain and other outcomes in the patients.

Sore throat and throat pain are not uncommon after endotracheal intubation for any procedure (2). Introduction of the laryngoscope, suctioning in the upper airway, and insertion of the ETT itself cause mild to severe abrasions of the airway with mucosal inflammation. Subsequent effects include irritation and itching of the throat (pharynx) that is worse on swallowing and throat pain in the surrounding deeper tissues, either as radiating pain from the mucosa or from iatrogenic blunt injuries to the deeper oropharyngeal tissues during instrumentation of the buccal cavity and oropharynx (3). These effects of ketamine gargles are a direct result of ketamine's antagonist actions on the peripheral NMDA receptors, overcoming the release of inflammatory cytokines, inflammatory cells activation and proliferation, and the paracrine effects of pain hormones (6, 14, 15). Some other NMDA receptor blockers, like dexmedetomidine, potentially have a similar effect on post-operative throat complaints, as also reported by Dehkordy et al. in a double-blinded RCT comparing ketamine and dexmedetomidine (16). However, on closer comparison, ketamine solutions are much more cost-effective than the alternatives (Inj. Dexmeditomidine: PKR3500/2ml vs. Inj. Ketamine HCl: PKR214/10ml) (11, 17). Local anesthetic solutions have a numbing effect by blocking the sodium-channel-mediated pain transmission and are frequently prescribed as effective symptomatic treatment of acute pharyngitis in awake patients (18). While these agents have been tested for post-operative pain in some studies, the numbing of protective respiratory reflexes, such as the cough and gag reflex, is a known effect that might compromise their safety in post-operative patients with potential residual anesthetic effects (5). Cholecystectomy patients belong to a rather obese population and are prone to respiratory issues like obesity-hypoventilation syndrome and obstructive sleep apnea (13, 19). Respiratory reflexes are essential for them, and numbing these reflexes with local anesthetics can inadvertently put the patients at risk of hypoxemia and cardiac arrest. Besides, these products only have anesthetic and analgesic actions with no anti-inflammatory effects. This adds to the safety of Ketamine use in patients undergoing LC. A study for the direct comparison of local anesthetic agents with ketamine gargles may provide a better understanding of the above assumptions.

Our findings align well with previous studies. Ahuja V et al. reported an overall 33% post-operative sore throat, with only 20% in the ketamine nebulization group versus 46% in the saline group, similarly affirming ketamine's beneficial effects against post-operative sore throat (20). The risk was even lower with ketamine gargles in our study compared to that with ketamine nebulization in their study (14.3% vs 20%), however, this comparison is only an extrapolation from the available results and not a direct comparison of different routes of administration. Further studies might be helpful to directly compare these two routes of administration and provide stronger evidence on an optimal dose and route.

Unlike our study, Rajan S et al. reported a significant reduction in the risk of post-operative sore throat, hoarseness, and cough with ketamine when compared to normal saline as control (4). Our study noted a non-significant reduction in hoarseness and no significant change in cough incidence. Differences could be attributable to varying study populations, surgical durations, or, importantly, the route of administration, with nebulized drugs used in their study versus gargles in our study. The dose

was similar in both studies; however, inhalational use of the drug may numb the trachea and larynx in addition to the pharynx (4). Unlike sore throat, cough is not just an uncomfortable symptom but rather an important protective reflex that prevents micro- and macro-aspiration. As discussed above, this absence of effect on the cough reflex with ketamine gargles could be a blessing in disguise for our high-risk obese patients.

Safety is an essential consideration when introducing novel perioperative interventions. The ketamine gargle used in our trial demonstrated an excellent safety profile with no significant hemodynamic instability or notable systemic side effects. Sedation and psychomimetic effects occurred rarely and at rates comparable to the saline control group (21). Ketamine itself is not selective for peripheral receptors only, but topical use of low-dose solution reduces systemic absorption and central effects (7, 14). Hence, clinicians can confidently employ ketamine gargles without substantial concerns about adverse systemic reactions.

Our study has significant implications, particularly in limited-resource settings, where the focus is on introducing simple, safe, and effective methods to enhance patient comfort after surgery. Given the affordability, ease of preparation, and low risk of ketamine gargles, it has the potential to become a regular preventive agent for post-operative sore throat. Further research should focus on identifying the optimal dose, route, and timing of administration, and on defining a clear criterion for patient selection. It would also be valuable to explore the effects of the combination of ketamine with other local anesthetics or anti-inflammatory agents.

Despite a strong level of evidence of an RCT, several limitations should be acknowledged. This study may lack generalizability due to several factors, including its single-center design with a relatively small sample size and the inclusion of only a particular cohort of patients. Secondly, while we standardized pain assessments, residual sedation post-extubation might have transiently influenced patient-reported scores.

Although we initially enrolled 80 patients, 10 were excluded post-randomization, leaving 70 for analysis. This attrition would not affect the power as the final number for analyses was still larger than the minimum required sample. We only looked at a specific dose and route of administration of one single drug, with no comparison of this drug to other agents and other routes of administration. Furthermore, the short-term follow-up restricted the ability to observe delayed complications or benefits of the drug. Lastly, our trial excluded high-risk patient groups and complex cases, potentially limiting applicability to broader patient populations.

Conclusion

Contrary to our hypothesis, preoperative ketamine gargles effectively reduce the postoperative sore throat and throat pain in patients undergoing laparoscopic cholecystectomy with endotracheal intubation, with a favorable safety profile. Given its efficacy, safety, and low cost, ketamine gargles should be considered for routine prophylaxis in laparoscopic cholecystectomy patients. Clinicians and researchers should work together to define the optimal dose, timing, and guidelines to incorporate ketamine as a prophylactic agent for post-operative throat complaints.

Declarations

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Data Availability statement
All data generated or analysed during the study are included in the manuscript.

Ethics approval and consent to participate
Approved by the department concerned. (RMI/RMI-REC/approval/191-23)

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Conflict of interest

The authors declared the absence of a conflict of interest.

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Conception of Study, Development of Research Methodology Design, Study Design, manuscript review, and critical input.

All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.

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