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Low-Dose Propofol, Ketamine, and Their Combination for the Prevention of Post-Extubation Cough and Laryngospasm in Patients Undergoing Gynecologic Laparotomy: A Randomized Controlled Trial

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Abstract

Background

Coughing and laryngospasm during emergence from general anesthesia are common and may be particularly harmful after open abdominal surgery. Low-dose propofol and ketamine attenuate airway reflexes through different mechanisms, but their comparative and combined efficacy in a homogeneous surgical population remains incompletely defined. We compared low-dose propofol, ketamine, and their combination with control for preventing post-extubation cough and laryngospasm in women undergoing gynecologic oncologic laparotomy.

Methods

In this prospective, randomized, double-blind, placebo-controlled trial, 169 women (of 176 screened) undergoing elective gynecologic oncologic laparotomy were randomly assigned (1:1:1:1) to intravenous saline (control, n = 42), propofol 0.25 mg/kg (n = 41), ketamine 0.25 mg/kg (n = 43), or propofol–ketamine 0.25 mg/kg each (n = 43) immediately before extubation. The primary outcome was cough incidence within 2 minutes after extubation; the secondary outcome was laryngospasm. Intention-to-treat risk ratios (RRs) with 95% confidence intervals (CIs) were calculated versus control, with Holm-adjusted pairwise comparisons when the overall test was significant.

Results

Cough incidence differed significantly among groups (control, 69.0%; propofol, 43.9%; ketamine, 55.8%; propofol–ketamine, 25.6%; χ^2=17.41, P < 0.001). After adjustment, only the combination remained significantly superior to control (RR, 0.37; 95% CI, 0.21–0.64; adjusted P < 0.001) and to ketamine alone (RR, 0.46; 95% CI, 0.26–0.81; adjusted P = 0.042); reductions with propofol (RR, 0.64) and ketamine (RR, 0.81) alone were no longer significant versus control after adjustment. Laryngospasm was infrequent and similar among groups (4.7–11.9%; P = 0.688), with no reintubations and similarly infrequent peri-extubation adverse events overall.

Conclusions

Low-dose propofol–ketamine administered immediately before extubation reduced post-extubation cough more effectively than control and than ketamine alone, without a significant effect on laryngospasm, in women undergoing gynecologic oncologic laparotomy. Adequately powered, multicenter trials with factorial designs are needed to define dose–response relationships, determine whether this effect is additive or synergistic, and establish its impact on patient-centered outcomes.

Clinical trial registration:

The trial was Retrospectively registered in the Iranian Registry of Clinical Trials (IRCT) under registration number IRCT20251215068344N1 on 18/07/2026.

Introduction

Tracheal extubation represents a critical phase of general anesthesia during which restoration of spontaneous ventilation and protective airway reflexes may be accompanied by clinically relevant airway responses. Coughing and laryngospasm are among the most important complications observed during emergence from anesthesia, particularly in the period immediately before and after removal of the endotracheal tube (1, 2). Although coughing is a physiological protective response to airway stimulation, excessive coughing during emergence can produce substantial cardiovascular and respiratory perturbations, discomfort, agitation, and marked increases in intrathoracic and intra-abdominal pressures (3, 4). Laryngospasm, in contrast, involves reflex closure of the vocal cords in response to airway stimulation and can rapidly result in partial or complete upper-airway obstruction, hypoxemia, and, in severe cases, negative-pressure pulmonary edema or other life-threatening consequences (1, 5).

The clinical relevance of these responses may be particularly important in patients undergoing open abdominal surgery. Abdominal surgery is associated with postoperative pain, impaired respiratory mechanics, and reduced cough efficiency, while coughing itself can increase abdominal wall tension and exacerbate pain (3, 6). During extubation after abdominal procedures, therefore, vigorous coughing and bucking may be undesirable because of their potential effects on wound discomfort, hemodynamic stability, and the integrity of the surgical repair (6). These concerns may be especially pertinent in patients undergoing gynecologic oncologic laparotomy, in whom extensive open abdominal procedures, prolonged surgery, and the need for stable perioperative recovery can increase the clinical importance of a smooth emergence from anesthesia.

A wide range of pharmacological strategies has been investigated to attenuate airway reflexes during emergence, including intravenous lidocaine, opioids, remifentanil, dexmedetomidine, and other sedative or analgesic agents (4). Evidence from randomized trials and a network meta-analysis indicates that several pharmacological interventions can reduce moderate-to-severe emergence coughing compared with placebo or no treatment, although no single approach has consistently demonstrated superiority across all clinical settings (4). Similarly, a systematic review and meta-analysis of intravenous lidocaine reported a substantial reduction in post-extubation cough but no clear reduction in laryngospasm, highlighting the possibility that suppression of coughing and prevention of laryngeal closure are related but not necessarily equivalent therapeutic targets (7).

Propofol is an attractive agent for emergence management because, in addition to its well-established anesthetic properties, it suppresses airway reflex activity at subhypnotic doses. Its short duration of action allows administration near the time of extubation without necessarily producing prolonged

recovery. Experimental and clinical studies have demonstrated that a small intravenous bolus of propofol can reduce coughing associated with emergence, including in patients undergoing inhalational anesthesia (8). In a randomized placebo-controlled trial comparing low-dose propofol, ketamine, their combination, and saline, intravenous propofol at 0.25 mg/kg reduced the incidence of coughing compared with control, whereas the combination regimen produced a greater reduction in both cough incidence and severe coughing (9). These findings suggest that low-dose propofol may attenuate airway stimulation without requiring the deeper levels of anesthesia associated with conventional induction or maintenance doses.

Ketamine may provide a complementary pharmacological mechanism. Primarily acting as a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, ketamine has potent analgesic and anesthetic effects and, at subanesthetic doses, can be administered without producing the degree of respiratory depression commonly associated with other sedative agents (10). NMDA receptor signaling has also been implicated in the central modulation of the cough reflex, providing a plausible mechanistic basis for investigating ketamine as an agent capable of attenuating airway responses during emergence (11). Clinical evidence supports this concept: randomized studies have demonstrated that low-dose ketamine can reduce airway responses in selected peri-extubation settings, although the magnitude of benefit appears to vary according to dose, timing, surgical population, and comparator (9, 12). More recent evidence involving ketamine/esketamine also suggests attenuation of cough-related airway responses, further supporting the potential relevance of NMDA receptor antagonism in this context (13).

The combination of propofol and ketamine is particularly interesting because the two drugs may provide complementary effects on sedation, analgesia, and airway reflex suppression. Importantly, the potential advantage of combination therapy is not simply a theoretical pharmacological interaction. In a prospective randomized clinical trial, administration of propofol 0.25 mg/kg combined with low-dose ketamine 0.15 mg/kg before extubation reduced the incidence of post-extubation cough more effectively than propofol alone or placebo (12). However, that study did not include a ketamine-alone group, limiting the ability to determine whether the benefit of the combination reflects true additive or synergistic effects. Conversely, a four-arm randomized placebo-controlled trial found that the propofol-ketamine combination produced the lowest incidence of cough, whereas the incidence of laryngospasm did not differ significantly among the treatment groups (9). These findings indicate that, despite encouraging evidence for cough suppression, the comparative efficacy of propofol, ketamine, and their combination for preventing peri-extubation laryngeal complications remains incompletely established.

Several important gaps therefore remain in the existing literature. Previous studies have included heterogeneous surgical populations, different anesthetic techniques, variable drug doses, and relatively limited sample sizes (4, 9, 12). In addition, cough and laryngospasm are often analyzed together as generalized emergence phenomena, despite their distinct pathophysiological mechanisms and different clinical implications. Evidence specifically addressing patients undergoing open gynecologic oncologic laparotomy is also limited. A direct four-arm comparison of low-dose propofol, low-dose ketamine, their

combination, and placebo/control in a clinically homogeneous surgical population could therefore provide more informative evidence regarding the relative and combined effects of these agents.

Accordingly, the present study was designed to compare the effectiveness of low-dose propofol, ketamine, and propofol-ketamine combination therapy with control in preventing post-extubation coughing and laryngospasm in patients undergoing gynecologic oncologic laparotomy under general anesthesia.

Materials and Methods

Study Design and Setting

This prospective, parallel-group, randomized, double-blind, placebo-controlled clinical trial was conducted among adult women scheduled to undergo elective gynecologic oncologic laparotomy under general anesthesia at Kowsar Hospital, Urmia, Iran, during 2025. The study was designed to compare the effects of low-dose intravenous propofol, ketamine, and their combination with placebo on post-extubation airway responses, with post-extubation cough defined as the primary outcome and laryngospasm as the secondary outcome.

Participants

Patients were included if they were adult women aged 18–65 years, had American Society of Anesthesiologists (ASA) physical status I or II, were scheduled for elective gynecologic oncologic laparotomy, required oral endotracheal intubation under general anesthesia, and were expected to undergo awake tracheal extubation at the end of surgery.

Patients were excluded if they had an active or recent upper respiratory tract infection, uncontrolled asthma, clinically significant chronic pulmonary disease, known hypersensitivity or previous adverse reaction to propofol, ketamine, or any study-related medication, unstable cardiovascular disease, including clinically significant ischemic heart disease or other unstable cardiac conditions, a body mass index (BMI) > 35 kg/m², an anticipated need for deep or otherwise non-standardized extubation, postoperative mechanical ventilation, major intraoperative complications that prevented standardized emergence or outcome assessment, or withdrawal of consent at any stage.

Sample Size Calculation

The sample size was determined a priori based on the primary outcome, namely the incidence of post-extubation cough. Because the study included four parallel treatment groups, the sample size calculation was based on a global comparison of multiple independent proportions rather than a two-group comparison.

Expected incidences of post-extubation cough of 82.5%, 57.5%, 70.0%, and 27.5% in the control, propofol, ketamine, and propofol–ketamine groups, respectively, were derived from a previous four-arm randomized placebo-controlled clinical trial that used the same study doses and evaluated coughing and laryngospasm during the first 2 min after extubation (9). Assuming an equal allocation ratio of 1:1:1:1, a two-sided α level of 0.05, and 80% statistical power, the required sample size was estimated at 156 participants (39 per group). To provide a conservative allowance for screening failures, attrition, protocol deviations, or a non-evaluable primary outcome, the target number to be screened was rounded upward to 44 participants per group (176 in total), anticipating that some would not proceed to randomization.

Randomization and Allocation Concealment

After eligibility was confirmed and written informed consent was obtained, participants were randomly assigned in a 1:1:1:1 ratio to the control, propofol, ketamine, or propofol–ketamine groups. The allocation sequence was generated using a computer-generated permuted-block randomization procedure by an investigator who was independent of participant recruitment, intervention administration, outcome assessment, and statistical analysis. Randomly varying block sizes were used to preserve approximate balance among the four groups while reducing the predictability of treatment assignments.

Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes prepared according to the randomization sequence. Each envelope contained the treatment assignment corresponding to a unique participant identification code. After eligibility had been confirmed and informed consent obtained, the next envelope in sequence was opened by a designated staff member who was not involved in participant recruitment or outcome assessment. The investigator responsible for enrollment had no access to forthcoming treatment assignments. This approach was consistent with recommended procedures for maintaining allocation concealment in randomized trials.

Blinding

The trial was conducted using a double-blind design. Study medications were prepared immediately before administration by a designated anesthesia staff member who was not involved in participant recruitment, outcome assessment, or statistical analysis. The study solutions were prepared in identical syringes and standardized to the same final volume and appearance whenever feasible and were labeled using participant-specific study codes rather than medication names.

Participants and the anesthesiologist responsible for assessing post-extubation outcomes were blinded to treatment allocation. The statistical analyst received a coded dataset in which treatment groups were identified using noninformative labels until completion of the prespecified primary analysis. Emergency unblinding was permitted only when knowledge of treatment allocation was considered necessary for patient safety.

Standardized Anesthetic Management

All participants underwent a standardized general anesthetic technique to minimize between-group differences in perioperative management and potential confounding of post-extubation airway responses. Standard monitoring consisted of continuous electrocardiography, non-invasive blood pressure measurement, pulse oximetry, and capnography after tracheal intubation. Neuromuscular function was monitored quantitatively using train-of-four (TOF) stimulation at the adductor pollicis muscle whenever neuromuscular blocking agents were administered.

Before induction, patients underwent preoxygenation with 100% oxygen for approximately 3 min or until adequate oxygenation was achieved. General anesthesia was induced intravenously with fentanyl 1–2 μg/kg followed by propofol 1.5–2.5 mg/kg until loss of consciousness. Neuromuscular blockade was achieved with rocuronium 0.6 mg/kg to facilitate tracheal intubation. After adequate muscle relaxation, oral endotracheal intubation was performed by an experienced anesthesiologist.

Anesthesia was maintained with sevoflurane in an oxygen–air mixture, titrated according to clinical signs and, when available, bispectral index monitoring, with a target depth corresponding to a BIS value of approximately 40–60. Mechanical ventilation was adjusted to maintain normocapnia, with end-tidal carbon dioxide maintained at approximately 35–45 mmHg. Additional opioid analgesia and neuromuscular blocking agent doses were administered according to a standardized institutional protocol when clinically indicated. Hemodynamic variables were maintained as close as clinically feasible to baseline values.

At the end of surgery, sevoflurane was discontinued and emergence was allowed under standardized conditions. Neuromuscular recovery was quantitatively assessed at the adductor pollicis muscle. When residual neuromuscular blockade was present, sugammadex was administered for reversal of rocuronium-induced blockade according to the depth of neuromuscular block. For routine moderate blockade, sugammadex 2 mg/kg was administered intravenously; if deeper blockade was present, the dose was increased according to the manufacturer’s recommended dosing regimen. Extubation was performed only after a quantitative TOF ratio of ≥ 0.90 had been confirmed. This approach is consistent with current ASA recommendations, which favor quantitative neuromuscular monitoring and confirmation of a TOF ratio ≥ 0.9 before extubation and recommend sugammadex over neostigmine for reversal of rocuronium-induced deep, moderate, or shallow blockade.

Study Interventions

Immediately before planned tracheal extubation, participants received one of four intravenous interventions according to their randomized allocation.

The control group received 0.9% normal saline at a dose of 0.1 mL/kg intravenously. The propofol group received propofol 0.25 mg/kg intravenously. The ketamine group received ketamine 0.25 mg/kg

intravenously. The combination group received propofol 0.25 mg/kg plus ketamine 0.25 mg/kg intravenously. These doses and the control regimen were based on the previous four-arm randomized placebo-controlled trial by Safavi et al. (9), which used the same treatment groups and reported a reduction in post-extubation coughing with propofol and, particularly, with the propofol–ketamine combination.

Study medications were administered during the emergence phase according to the predefined protocol. The timing of study-drug administration relative to tracheal extubation was standardized across all groups. The final volume of the syringes was standardized to preserve masking.

Tracheal Extubation and Post-extubation Observation

Tracheal extubation was performed in the operating room after completion of surgery and confirmation of predefined extubation criteria, including adequate spontaneous ventilation, satisfactory oxygenation, hemodynamic stability, recovery of airway protective reflexes, and quantitative recovery from neuromuscular blockade with a TOF ratio ≥ 0.90. Awake extubation was used for all participants. Awake extubation is generally recommended for most patients when a standard extubation strategy is appropriate.

Before extubation, oral and pharyngeal secretions were gently suctioned according to a standardized technique while avoiding unnecessary airway stimulation. Following cuff deflation and removal of the endotracheal tube, supplemental oxygen was immediately administered through a facemask. Patients were continuously observed for 2 min after extubation for the occurrence of coughing and laryngospasm. The use of standardized suctioning and minimizing unnecessary airway stimulation was consistent with established extubation guidance.

Assessment of Post-extubation Cough

The primary outcome was the incidence of post-extubation cough during the first 2 min after tracheal extubation. Coughing was assessed continuously from the moment of extubation until completion of the 2-min observation period.

Cough severity was graded using a four-point ordinal scale based on the grading system used in the directly comparable randomized trial of propofol, ketamine, and their combination: grade 0, no cough; grade 1, a single cough; grade 2, two coughs to mild coughing; and grade 3, severe or repetitive coughing. A cough grade ≥ 1 was considered indicative of post-extubation cough.

Assessment of Laryngospasm

The secondary outcome was the incidence of laryngospasm during the same 2-min period following tracheal extubation. Laryngospasm was defined as reflex glottic closure resulting in clinically evident upper-airway obstruction.

Any episode of laryngospasm was immediately managed according to a predefined rescue protocol. Initial management consisted of airway repositioning and oxygen administration, with positive-pressure ventilation using 100% oxygen when obstruction persisted or oxygenation was inadequate. If laryngospasm persisted or oxygen saturation decreased substantially, additional pharmacological treatment was administered according to clinical severity. The rescue protocol included intravenous propofol when appropriate and succinylcholine in refractory cases requiring rapid neuromuscular relaxation, followed by tracheal reintubation and controlled ventilation when clinically necessary.

Peri-extubation safety outcomes were monitored during emergence and the immediate 2-min post-extubation observation period. Clinically relevant adverse events recorded for analysis included hypotension, bradycardia, oxygen desaturation defined as SpO_2 <94%, nausea or vomiting, agitation or emergence reactions, and any airway rescue intervention. Peri-extubation recovery characteristics, including quantitative train-of-four (TOF) ratio before extubation, sugammadex use and dose, and the interval from study-drug administration to extubation, were also recorded.

Data Collection

Baseline demographic and perioperative data were collected using a standardized case report form. Variables included age, body weight, body mass index, ASA physical status, duration of surgery, duration of anesthesia, number of tracheal intubation attempts, difficult intubation, additional opioid administration, additional neuromuscular blocker administration, treatment allocation, study-drug dose, timing of administration, occurrence and severity of post-extubation cough, occurrence of laryngospasm, oxygen saturation, quantitative TOF ratio before extubation, and any airway rescue intervention or adverse event.

Each participant was assigned a unique study identification code, and personal identifiers were excluded from the analytical dataset. Data were entered into a secure database and checked for completeness and consistency before statistical analysis.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 27 (IBM Corp., Armonk, NY, USA). The primary analysis followed the intention-to-treat principle, and participants were analyzed according to their randomized allocation.

Continuous variables were assessed for normality using the Shapiro–Wilk test and graphical methods. Normally distributed variables were summarized as mean ± standard deviation, whereas non-normally distributed variables were presented as median and interquartile range. Categorical variables were summarized as frequencies and percentages.

Baseline characteristics were summarized descriptively by treatment group. Continuous variables were summarized as mean ± standard deviation or median (interquartile range), as appropriate, and

categorical variables as frequencies and percentages; no hypothesis tests were used to assess baseline balance.

The primary outcome, incidence of post-extubation cough, was compared across the four groups using the Pearson chi-square test. For the binary primary outcome, risk ratios (RRs) and risk differences (RDs), each with 95% confidence intervals, were calculated for each active intervention relative to the control group. When the overall comparison was statistically significant, prespecified pairwise comparisons were performed using the Holm method to control the family-wise error associated with multiple comparisons. The incidence of laryngospasm was analyzed using the same approach, with Fisher's exact test used when expected cell counts were too small for the chi-square approximation.

Cough severity was treated as an ordinal outcome. Between-group differences in severity distribution were evaluated using ordinal (proportional-odds) logistic regression with group as the predictor and control as the reference category. The proportional-odds assumption was assessed using a likelihood-ratio test comparing this model with an unconstrained model allowing group-specific category probabilities. Odds ratios with 95% confidence intervals are reported for each active group versus control.

Missing data were summarized by treatment group and reason. The number of participants contributing to each analysis was reported explicitly. Sensitivity analyses were considered when missing outcome data were sufficiently frequent to potentially influence the interpretation of the primary outcome.

All statistical tests were two-sided. A P value < 0.05 was considered statistically significant. For pairwise comparisons, the prespecified Holm multiplicity adjustment was applied.

Ethical Considerations and Trial Registration

The study was approved by the Ethics Committee of Urmia University of Medical Sciences under approval code IR.UMSU.HIMAM.REC.1404.036. Written informed consent was obtained from all participants before enrollment. Participants were informed about the study procedures, potential risks and benefits, the voluntary nature of participation, and their right to withdraw at any time without affecting their medical care. Participant confidentiality was maintained throughout data collection, storage, analysis, and reporting. The trial was Retrospectively registered in the Iranian Registry of Clinical Trials (IRCT) under registration number IRCT20251215068344N1 on 18/07/2026. The final report was prepared in accordance with the CONSORT 2025 statement for randomized trials (14).

Results

Participant flow and baseline characteristics

A total of 176 women entered the recruitment/assessment process. This corresponds to the pre-specified screening target described above. Seven women did not enter the randomized study phase and were excluded before randomization. The temporary classification of these exclusions was as follows: n

= 2 withdrew consent before randomization, n = 2 did not meet all eligibility criteria after final assessment, and n = 3 were unable to proceed to the planned surgical intervention. The remaining 169 participants were randomly allocated to the four study groups: 42 to the control group, 41 to the propofol group, 43 to the ketamine group, and 43 to the propofol–ketamine combination group. All 169 randomized participants contributed data to the primary outcome analysis, and no participant required reintubation. The flow of participants through eligibility assessment, randomization, allocation, follow-up, and analysis is presented in the CONSORT 2025 flow diagram (Fig. 1).

Baseline demographic and perioperative characteristics are summarized in Table 1. The groups showed similar descriptive distributions of age, body weight, body mass index, ASA physical status, duration of surgery, duration of anesthesia, tracheal intubation attempts, difficult intubation, additional opioid administration, and additional neuromuscular blocker administration. Mean age was approximately 52 years across the four groups, and mean BMI ranged from 27.2 to 27.6 kg/m². Approximately 69–71% of participants in each group were classified as ASA II.

Table 1
Baseline and perioperative characteristics of the study participants

Characteristic	**Control (n = 42)**	**Propofol (n = 41)**	**Ketamine (n = 43)**	**Propofol–Ketamine (n = 43)**
Age, years	52.3 ± 7.1	51.7 ± 7.3	52.0 ± 7.0	52.2 ± 7.0
Weight, kg	73.7 ± 6.2	73.1 ± 6.0	73.6 ± 6.3	73.5 ± 6.1
BMI, kg/m²	27.5 ± 3.2	27.2 ± 3.3	27.6 ± 3.1	27.4 ± 3.2
ASA physical status I, n (%)	13 (31.0)	12 (29.3)	13 (30.2)	13 (30.2)
ASA physical status II, n (%)	29 (69.0)	29 (70.7)	30 (69.8)	30 (69.8)
Duration of surgery, min	188 ± 39	192 ± 42	186 ± 40	190 ± 41
Duration of anesthesia, min	226 ± 43	231 ± 46	224 ± 44	229 ± 45
Tracheal intubation > 1 attempt, n (%)	2 (4.8)	2 (4.9)	1 (2.3)	2 (4.7)
Difficult intubation, n (%)	1 (2.4)	1 (2.4)	1 (2.3)	1 (2.3)
Additional opioid administration, n (%)	8 (19.0)	7 (17.1)	8 (18.6)	8 (18.6)
Additional neuromuscular blocker, n (%)	16 (38.1)	15 (36.6)	17 (39.5)	16 (37.2)

Values are presented as mean ± SD or n (%). BMI, body mass index; ASA, American Society of Anesthesiologists. Baseline variables are presented descriptively; no formal between-group significance testing was performed.

Primary outcome: post-extubation cough

The incidence of post-extubation cough during the first 2 min after tracheal extubation differed significantly across the four treatment groups (χ^2=17.41, P < 0.001) (Table 2). Cough occurred in 29 of 42 participants (69.0%) in the control group, compared with 18 of 41 (43.9%) in the propofol group, 24 of 43 (55.8%) in the ketamine group, and 11 of 43 (25.6%) in the propofol–ketamine group.

Table 2
Primary outcome and effect estimates for post-extubation cough

Outcome	Control (n = 42)	Propofol (n = 41)	Ketamine (n = 43)	Propofol–Ketamine (n = 43)	Overall P value
Post-extubation cough, n (%)	29 (69.0)	18 (43.9)	24 (55.8)	11 (25.6)	< 0.001
Cough severity: overall distribution					
Grade 0	13 (31.0)	23 (56.1)	19 (44.2)	32 (74.4)	0.002
Grade 1	14 (33.3)	9 (22.0)	11 (25.6)	4 (9.3)	
Grade 2	10 (23.8)	5 (12.2)	8 (18.6)	4 (9.3)	
Grade 3	5 (11.9)	4 (9.8)	5 (11.6)	3 (7.0)	
RR vs control, any cough (95% CI)	1.00 (reference)	0.636 (0.426–0.949)	0.808 (0.579–1.129)	0.370 (0.214–0.641)	
RD vs control, any cough, percentage points (95% CI)	0.0 (reference)	−25.1 (− 45.8 to − 4.5)	−13.2 (− 33.6 to 7.2)	−43.5 (− 62.6 to − 24.3)	
OR vs control, severity (95%, CI)	1.00 (reference)	0.45 (0.20 to 0.99)	0.7 (0.33 to 1.49)	0.21 (0.09 to 0.50)	
Laryngospasm, n (%)	5 (11.9)	4 (9.8)	4 (9.3)	2 (4.7)	0.688
RR vs control (95% CI)	1.00 (reference)	0.820 (0.237–2.839)	0.781 (0.225–2.711)	0.391 (0.080–1.904)	
RD vs control, percentage points (95% CI)	0.0 (reference)	−2.1 (− 15.5 to 11.2)	−2.6 (− 15.7 to 10.5)	−7.3 (− 18.9 to 4.4)	

RR, risk ratio; RD, risk difference; OR, odds ratio. RR and RD were calculated for each active intervention relative to the control group; the RR for post-extubation cough incidence is based on the risk of any cough (grade ≥ 1), and the corresponding Overall P value is from the Pearson chi-square test. Cough-severity grade was analyzed using ordinal (proportional-odds) logistic regression with group as the sole predictor and control as the reference category; the OR reflects the odds of a higher (worse) severity grade for each active intervention relative to control, and the corresponding Overall P value is from the model's likelihood-ratio test. Additional pairwise comparisons for post-extubation cough incidence: propofol vs ketamine, RR 0.79 (95% CI 0.51–1.22); propofol vs propofol–ketamine, RR 0.58 (95% CI 0.32–1.08; raw P = 0.078, not significant even before multiplicity adjustment)."

Relative to the control group, the incidence of cough was lower in the propofol group (risk ratio [RR], 0.64; 95% confidence interval [CI], 0.43–0.95; risk difference [RD], − 25.1 percentage points; 95% CI, − 45.8 to − 4.5), although the Holm-adjusted pairwise comparison did not remain statistically significant (adjusted P

= 0.147). The ketamine group also showed a lower cough incidence than the control group (RR, 0.81; 95% CI, 0.58–1.13; RD, − 13.2 percentage points; 95% CI, − 33.6 to 7.2), with no statistically significant adjusted difference (adjusted P = 0.601).

The greatest reduction in cough incidence was observed in the propofol–ketamine group, in which cough occurred in 25.6% of participants. Compared with control, combination therapy was associated with a substantially lower risk of post-extubation cough (RR, 0.37; 95% CI, 0.21–0.64; RD, − 43.5 percentage points; 95% CI, − 62.6 to − 24.3; Holm-adjusted P < 0.001). In the pairwise comparison between the ketamine and propofol–ketamine groups, cough was also less frequent with combination therapy (RR, 0.46; 95% CI, 0.26–0.81; RD, − 30.2 percentage points; 95% CI, − 50.0 to − 10.5; Holm-adjusted P = 0.042). No significant difference was observed between propofol and ketamine (RR, 0.79; 95% CI, 0.51–1.22) or between propofol and the propofol–ketamine combination (RR, 0.58; 95% CI, 0.32–1.08; raw P = 0.078, not significant even before multiplicity adjustment).

Cough severity

The distribution of cough severity grades is presented in Table 2. The proportion of participants with no cough (grade 0) was highest in the propofol–ketamine group (74.4%), followed by the propofol group (56.1%), ketamine group (44.2%), and control group (31.0%). Grades 2 and 3 coughing were observed less frequently in the combination group than in the control group. Ordinal logistic regression indicated a significant overall difference in cough-severity distribution among groups (likelihood-ratio χ^2_3=14.65, P = 0.002); the proportional-odds assumption was assessed and held (goodness-of-fit likelihood-ratio test comparing the proportional-odds model with an unconstrained model: χ^2_6=4.31, P = 0.635). Relative to control, the odds of a higher (worse) severity grade were significantly lower with the propofol–ketamine combination (OR 0.21, 95% CI 0.09–0.50, P < 0.001) and with propofol alone (OR 0.45, 95% CI 0.20–0.99, P = 0.047), but not with ketamine alone (OR 0.70, 95% CI 0.33–1.49, P = 0.35).

Secondary outcome: laryngospasm

Laryngospasm was relatively uncommon and did not differ significantly among the treatment groups (P = 0.688) (Table 2). Laryngospasm occurred in 5 participants (11.9%) in the control group, 4 (9.8%) in the propofol group, 4 (9.3%) in the ketamine group, and 2 (4.7%) in the propofol–ketamine group. Relative to control, the corresponding risk ratios were 0.82 (95% CI, 0.24–2.84) for propofol, 0.78 (95% CI, 0.23–2.71) for ketamine, and 0.39 (95% CI, 0.08–1.90) for combination therapy; the corresponding risk differences were − 2.1, − 2.6, and − 7.3 percentage points, respectively, with confidence intervals spanning the null value for all comparisons.

Peri-extubation safety and rescue interventions

Peri-extubation safety characteristics and rescue interventions are summarized in Table 3. Quantitative neuromuscular recovery before extubation was comparable across groups, with mean TOF ratios of 0.97–0.98. Sugammadex was administered to all participants, with a mean dose of approximately 2.0

mg/kg across groups. The interval between study-drug administration and extubation was approximately 1 min in all groups.

Table 3
Peri-extubation safety, rescue interventions, and recovery characteristics

Variable	Control (n = 42)	Propofol (n = 41)	Ketamine (n = 43)	Propofol–Ketamine (n = 43)
TOF ratio before extubation	0.97 ± 0.02	0.97 ± 0.02	0.97 ± 0.02	0.98 ± 0.01
Sugammadex use, n (%)	42 (100)	41 (100)	43 (100)	43 (100)
Sugammadex dose, mg/kg	2.01 ± 0.18	2.04 ± 0.19	2.02 ± 0.17	2.03 ± 0.18
Time from study drug to extubation, min	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1
Laryngospasm requiring rescue intervention, n (%)	2 (4.8)	1 (2.4)	1 (2.3)	1 (2.3)
Positive-pressure ventilation, n (%)	2 (4.8)	1 (2.4)	1 (2.3)	1 (2.3)
Rescue propofol, n (%)	1 (2.4)	0	0	0
Succinylcholine, n (%)	1 (2.4)	0	0	0
Reintubation, n (%)	0	0	0	0
Hypotension, n (%)	3 (7.1)	4 (9.8)	2 (4.7)	3 (7.0)
Bradycardia, n (%)	1 (2.4)	1 (2.4)	1 (2.3)	1 (2.3)
SpO_2 <94%, n (%)	2 (4.8)	1 (2.4)	2 (4.7)	1 (2.3)
Nausea/vomiting, n (%)	3 (7.1)	2 (4.9)	3 (7.0)	2 (4.7)
Agitation/emergence reaction, n (%)	1 (2.4)	1 (2.4)	3 (7.0)	2 (4.7)

TOF, train-of-four. Peri-extubation recovery characteristics, safety outcomes, and rescue interventions are presented descriptively; no hypothesis tests were performed for these variables because the safety analyses were not intended as confirmatory comparisons.

Rescue interventions for laryngospasm were infrequent. Positive-pressure ventilation was required in 2 participants (4.8%) in the control group and in 1 participant in each active-treatment group (2.3–2.4%). Rescue propofol and succinylcholine were required only in the control group, each in 1 participant (2.4%). No participant required tracheal reintubation.

The frequencies of hypotension, bradycardia, oxygen desaturation, nausea or vomiting, and agitation or emergence reactions were low across groups. Overall, no major peri-extubation safety signal or clinically

important difference in immediate recovery characteristics was identified among the four treatment groups.

Discussion

This randomized controlled trial compared low-dose propofol, ketamine, and their combination with control for preventing post-extubation cough and laryngospasm in women undergoing gynecologic oncologic laparotomy. The principal finding was a significant between-group difference in cough incidence (69.0% control, 43.9% propofol, 55.8% ketamine, 25.6% propofol–ketamine). Relative to control, the absolute risk reduction was 25.1 percentage points with propofol, 13.2 with ketamine, and 43.5 with the combination. After Holm correction for multiple comparisons, only the combination remained significantly superior to both control and ketamine alone; the propofol-versus-control comparison no longer met the adjusted threshold. The most robust and consistent treatment effect was therefore observed with the propofol–ketamine combination, which was superior to both control and ketamine alone; a direct comparison with propofol alone showed a numerically lower cough incidence with the combination (25.6% vs. 43.9%) that did not reach statistical significance (P = 0.078).

These findings closely reproduce the four-arm trial by Safavi et al., which used identical doses of propofol, ketamine, their combination, and saline and reported cough incidences of 82.5%, 57.5%, 70.0%, and 27.5%, respectively (9). The near-identical combination-group incidence across the two studies (27.5% vs. 25.6%), despite differing surgical populations and baseline risk, strengthens confidence that this is a genuine and reproducible antitussive effect rather than a chance finding. A concordant pattern was reported by Chungsamarnyart et al., who compared saline, propofol 0.25 mg/kg, and propofol combined with a lower ketamine dose (0.15 mg/kg) and likewise found the greatest reduction in cough with combination therapy (12). Because that trial lacked a ketamine-only arm, the present four-arm design provides a more informative estimate of ketamine’s incremental contribution beyond propofol alone.

The effect of propofol monotherapy is biologically plausible: propofol suppresses airway reflex activity at subhypnotic doses, and its rapid redistribution and short duration of action make it well suited to administration close to extubation (4, 10). A 2023 randomized trial similarly found that a propofol bolus reduced coughing at emergence from desflurane anesthesia, albeit using a higher dose and a different anesthetic technique (8). The loss of statistical significance for propofol-versus-control after Holm adjustment should therefore be interpreted as weaker evidence relative to the combination under a multiplicity-adjusted analysis, not as an absence of pharmacological activity. Ketamine’s more modest monotherapy effect is likewise consistent with its proposed mechanism: as a noncompetitive NMDA-receptor antagonist, ketamine may modulate central processing of the cough reflex (10, 11), but clinical studies of ketamine for emergence airway responses have produced heterogeneous results depending on dose, timing, anesthetic technique, and patient population (11, 15). The confidence interval for the relative risk of cough with ketamine crossed unity in the present study, suggesting that its effect alone may be modest or variable, while becoming more clinically apparent when combined with propofol.

Contemporary evidence on the NMDA-antagonist esketamine reinforces the biological plausibility of this pathway, although these formulations and routes are not directly interchangeable with intravenous racemic ketamine. A 2026 double-blind randomized trial found that preoperative nebulized esketamine reduced extubation cough incidence from 71.4% to 31.0% and also reduced cough intensity (16), and a 2026 meta-analysis of randomized trials similarly reported that prophylactic esketamine reduced cough or bucking during extubation (RR 0.55, 95% CI 0.37–0.82) (13). Regarding the propofol–ketamine combination itself, the present trial was not designed as a formal pharmacological interaction study and therefore cannot establish true synergism; the observed advantage may instead reflect complementary effects of two agents acting through different pathways, with propofol suppressing airway reflex excitability and ketamine contributing NMDA antagonism and analgesia that influence central processing of airway stimulation (10, 11). A prespecified factorial design across multiple doses would be required to formally test additivity or synergy.

These results also fit within the broader pharmacological literature on prevention of emergence cough. A systematic review and network meta-analysis of 70 randomized trials and 5,286 patients found that several agents, including lidocaine, dexmedetomidine, remifentanil, and fentanyl, reduce moderate-to-severe emergence cough compared with placebo or no treatment, without consistent superiority of any single agent (4). Similarly, a systematic review and meta-analysis of 16 trials (n = 1,516) found that intravenous lidocaine reduced post-extubation cough (RR 0.64, 95% CI 0.48–0.86) without significantly reducing laryngospasm (7). This confirms that cough is a pharmacologically modifiable endpoint that does not necessarily translate into prevention of laryngeal closure, a pattern that the present findings extend to low-dose propofol–ketamine therapy.

Cough severity distributions also favored active treatment, particularly the combination regimen (74.4% grade 0 vs. 31.0% in control). Ordinal logistic regression confirmed a significant overall difference in severity distribution among groups (likelihood-ratio χ^2_3=14.65, P = 0.002), with significantly lower odds of a more severe cough grade for the propofol–ketamine combination (OR 0.21, 95% CI 0.09–0.50, P < 0.001) and for propofol alone (OR 0.45, 95% CI 0.20–0.99, P = 0.047) relative to control, but not for ketamine alone (OR 0.70, 95% CI 0.33–1.49, P = 0.35). This pattern is consistent with Safavi et al.'s finding of fewer grade-3 events with combination therapy (9) and indicates that the benefit of propofol and, particularly, the combination extends beyond the binary presence of cough to its severity — reinforcing, rather than merely supplementing, the primary incidence findings (17). Because this severity analysis was a secondary outcome not included in the Holm multiplicity adjustment, it should be interpreted as supportive rather than confirmatory, and future trials should prespecify severity as an independently powered ordinal endpoint with formal adjustment for multiple comparisons.

In contrast, none of the interventions produced a statistically significant reduction in laryngospasm (11.9% control vs. 4.7% combination, with confidence intervals spanning the null), a result broadly consistent with both Safavi et al. and Chungsamarnyart et al. (9, 12). This divergence between cough and laryngospasm likely reflects differing underlying physiology: cough is a protective reflex involving afferent sensory activation and coordinated respiratory muscle activity, whereas laryngospasm

represents a more abrupt, potentially all-or-none glottic closure that is also influenced by depth of anesthesia, airway secretions, and direct airway stimulation (1). With only 15 laryngospasm events overall, the study was substantially underpowered to detect a moderate between-group difference; the null result should therefore be regarded as inconclusive rather than as evidence of equivalence between interventions.

Rescue interventions, including positive-pressure ventilation, rescue propofol, and succinylcholine, were required infrequently, and no participant required reintubation, consistent with current extubation guidance emphasizing structured planning, continuous observation, and prompt escalation when obstruction occurs (1). Quantitative neuromuscular recovery before extubation was high in all groups (TOF ratio 0.97–0.98), and all participants received sugammadex, consistent with 2023 ASA guidelines recommending confirmation of a TOF ratio of at least 0.90 before extubation (18); this standardization reduces the likelihood that differences in residual neuromuscular blockade confounded the comparison of airway outcomes. Hypotension, bradycardia, desaturation, nausea or vomiting, and emergence reactions were all infrequent and similar across groups, although the study was not powered to establish comparative safety for uncommon adverse events.

Several methodological features strengthen these findings: the four-arm design permits simultaneous comparison of monotherapy, combination, and control rather than a simple two-group comparison; allocation was concealed and outcome assessment was blinded; anesthetic technique, drug timing, and extubation criteria were standardized; and the directional pattern closely reproduces that reported by Safavi et al. using the same doses (9), providing valuable external consistency. Limitations include the single-center design restricted to women undergoing gynecologic oncologic laparotomy, which limits generalizability to other populations; a 2-minute observation window chosen for methodological consistency with the comparator trial (9) that did not capture events occurring later in the post-anesthesia care unit; a small number of laryngospasm events that limits the precision of the secondary outcome; the absence of a factorial design to formally test pharmacological interaction; and the pre-randomization exclusion of 7 of 176 women screened, although the randomized sample of 169 still exceeded the prespecified minimum of 156 participants and all randomized participants were retained in the intention-to-treat analysis.

Clinically, the propofol–ketamine combination reduced the absolute probability of post-extubation cough by 43.5 percentage points compared with control, corresponding to an approximately 63% relative reduction, a difference that remained significant after multiplicity adjustment and was also superior to ketamine alone. These findings suggest that, in comparable surgical populations, this low-dose combination may be a useful strategy when attenuating emergence cough is a clinical priority, although the present study does not establish superiority over other pharmacological approaches to emergence management, since several agents have shown efficacy in network meta-analytic evidence (4). Future dose-ranging trials are needed to determine whether a lower ketamine dose preserves the observed benefit or whether higher doses add further benefit at the cost of sedation or other effects, and factorial designs are needed to formally test additivity or synergy with propofol. Larger multicenter trials should

also examine less frequent but clinically important outcomes, including laryngospasm requiring pharmacological treatment, delayed emergence, and patient-centered recovery measures, while further clarifying how newer NMDA-modulating strategies such as esketamine relate to the intravenous racemic ketamine regimen evaluated here (13, 16).

Conclusion

In conclusion, low-dose propofol–ketamine administered immediately before extubation was associated with the lowest incidence of post-extubation cough among the four treatment groups and produced a substantial reduction in cough compared with control. This effect remained statistically significant after adjustment for multiple comparisons and was also evident when compared with ketamine alone. Propofol monotherapy showed a favorable numerical effect, but its comparison with control did not remain statistically significant after Holm adjustment, while ketamine monotherapy did not demonstrate a statistically significant adjusted benefit. None of the interventions significantly reduced laryngospasm, although combination therapy showed a numerically favorable direction. Taken together, these findings support further adequately powered trials of propofol–ketamine combinations, particularly studies designed to define dose-response relationships, formally test interaction effects, and determine whether reducing peri-extubation cough translates into improvements in clinically meaningful postoperative outcomes.

Declarations

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Author’s Contribution

Nasim Shamsa contributed to the conception and design of the study, data acquisition, analysis, interpretation, and critically revising the manuscript for important intellectual content. Nazli karami contributed to the concept and design of the study, data acquisition, analysis, interpretation, and drafting and critically revising the manuscript for important intellectual content. Danial Hashemi contributed to the data acquisition and formal analysis. All authors take full responsibility for the content of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Urmia University of Medical Sciences (IR.UMSU.HIMAM.REC.1404.036) and registered in the Iranian Clinical Trials Registry (IRCT20251215068344N1; registered on 18/07/2026- Retrospectively registered). All participants provided written informed consent following the principles outlined in the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The dataset generated and analyzed during the current study are available from corresponding author on reasonable request.

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Figures

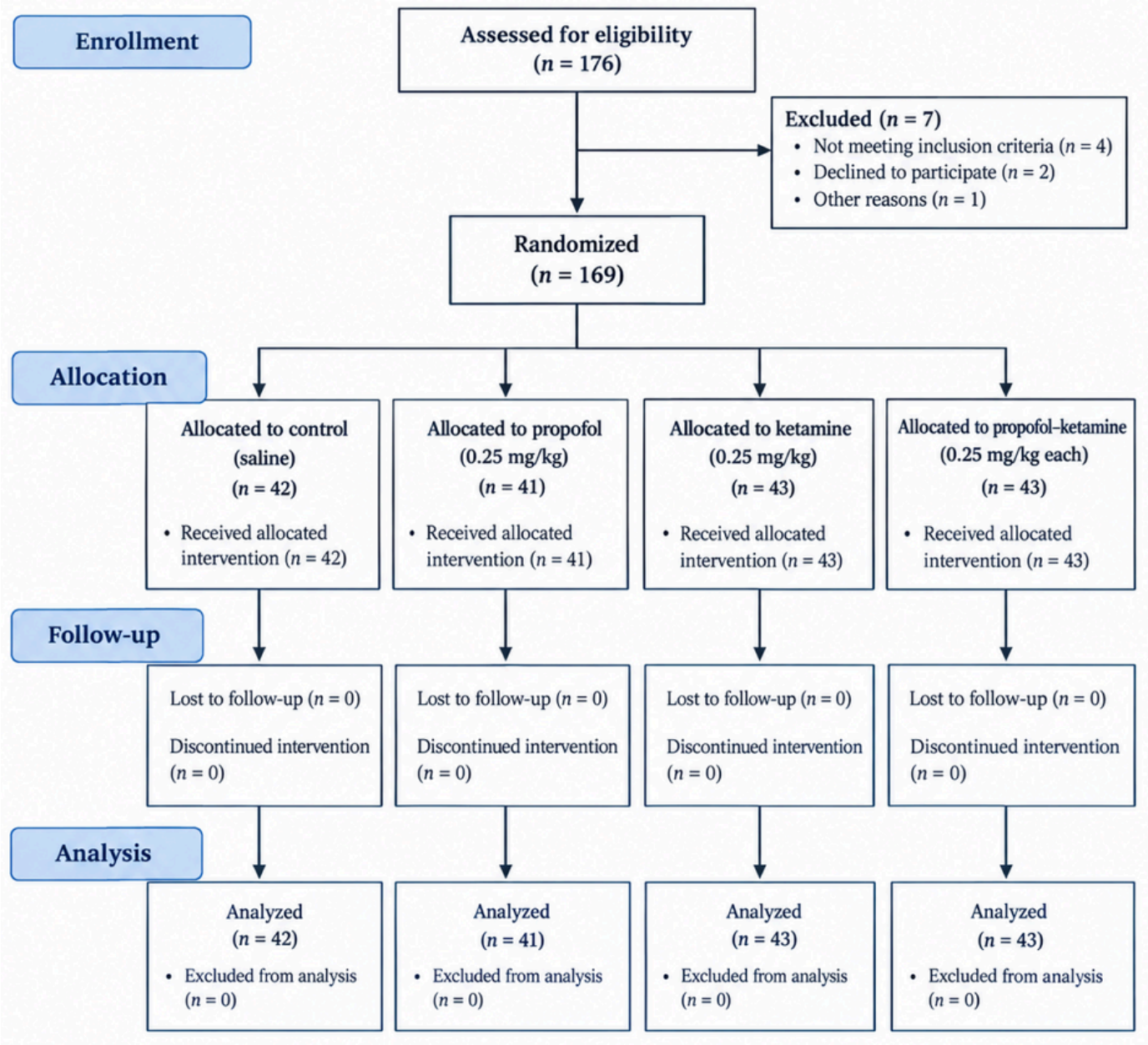


Figure 1

CONSORT 2025 flow diagram of participant enrollment, allocation, follow-up, and analysis.