

# Effect of Controlled versus Spontaneous Ventilation on Postoperative Emergence Agitation in 2–4-Year-Old Children Undergoing Adenotonsillectomy: A Double-Blind Randomized Clinical Trial

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## Abstract

**Background:** Emergence agitation (EA), characterized by restlessness and inconsolable behavior, is a common postoperative complication in children after sevoflurane anesthesia, potentially causing secondary injuries and prolonged PACU stays. While its etiology is multifactorial, the mode of ventilation during anesthesia may be a contributing yet under-investigated factor. This study aimed to compare the effects of controlled mechanical ventilation (CMV) versus spontaneous ventilation (SV) on EA, pain, recovery time, and related outcomes in children aged 2–4 years undergoing adenotonsillectomy.

**Methods:** This randomized double-blind trial enrolled 79 children (2–4 years, ASA I) undergoing adenotonsillectomy. Patients were randomized to controlled mechanical ventilation (CMV) or spontaneous ventilation (SV) during emergence. Anesthesia was standardized with sevoflurane and reversal with neostigmine/atropine. The primary outcome was emergence agitation assessed via the Richmond Agitation-Sedation Scale (RASS). Statistical analysis involved Analysis of covariance (ANCOVA), independent t-tests, and Chi-square or Fisher's exact tests. The  $P < 0.05$  was considered a statistically significant level.

**Results:** The mean age was significantly higher in the controlled ventilation group compared to the spontaneous breathing group ( $40.75 \pm 4.73$  vs.  $37.31 \pm 5.80$  months,  $P = 0.005$ ). EA incidence and agitation scores were significantly lower in the CMV group ( $0.60 \pm 0.63$  vs.  $1.21 \pm 0.61$ ,  $P = 0.001$ ). Postoperative pain was reduced (VAS  $2.80 \pm 1.18$  vs.  $5.15 \pm 1.69$ ,  $P = 0.001$ ), recovery duration was shorter ( $38.98 \pm 6.96$  min vs.  $44.72 \pm 6.57$  min,  $P = 0.001$ ), and EtCO<sub>2</sub> levels were lower ( $34.43 \pm 2.52$  mmHg vs.  $36.82 \pm 1.83$  mmHg,  $P = 0.001$ ) in the CMV group. Oxygen saturation, neuromuscular monitoring, and postoperative nausea were comparable between groups. No delirium cases were observed.

**Conclusion:** CMV significantly reduces EA, postoperative pain, and PACU stay duration compared with SV in children undergoing adenotonsillectomy, likely by preventing hypercapnia and stabilizing physiological parameters. CMV is recommended as the preferred ventilation strategy in this population, while the absence of delirium confirms the low inherent neurological risk in children less than 5 years.

**Keywords:** Adenotonsillectomy, Emergence agitation, Controlled ventilation, Spontaneous ventilation, Pediatrics

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## Introduction

Emergence agitation (EA) is a set of disruptive behaviors occurring during early recovery from general anesthesia

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### ↑What is “already known” in this topic:

- Emergence agitation (EA) is a common postoperative complication in preschoolers undergoing sevoflurane anesthesia, particularly after ENT surgeries.
- EA is multifactorial, with contributing factors including young age, surgery type, and volatile anesthetics.
- Hypercapnia may predispose to EA, but its precise role remains unclear.

### →What this article adds:

- Direct evidence that ventilation mode at anesthesia emergence influences EA incidence and severity.
- Controlled mechanical ventilation (CMV), compared to spontaneous ventilation (SV), significantly reduces EA, postoperative pain, and PACU length of stay while maintaining normocapnia.
- Positions CMV as a simple, non-pharmacological intervention to enhance emergence quality by preventing hypercapnia.

sia, and affected patients may present with restlessness, crying, irritability, inconsolability, thrashing, and agitation (1). The term emergence delirium has been used interchangeably with EA in several studies (2, 3); however, emergence delirium is not entirely equivalent to EA, as it can manifest with hypoactive symptoms, mixed forms, or hyperactive symptoms similar to agitation (4). Patients experiencing EA may suffer secondary injuries due to displacement of surgical dressings, removal of intravenous lines, disruption of surgical closures, or the need for physical restraint by nursing staff (5). These patients often require additional interventions and may experience prolonged stays in the post-anesthesia care unit (PACU), even after short surgical procedures (6). The etiology of EA is multifactorial(7), with several contributing factors including patient characteristics, preoperative anxiety, anesthetic agents used, ventilation mode, pain, and type of surgery (8, 9). EA is more common in children than in adults, and its incidence in children has been reported to inversely correlate with age (10, 11). Moreover, studies have reported a higher prevalence of EA in pediatric patients undergoing ear, nose, and throat (ENT) and ophthalmologic surgeries (11, 12). Specifically, EA in ENT surgery patients may increase the risk of airway obstruction and hypoxemia due to the anatomical characteristics of the surgical site. Furthermore, the occurrence of EA can serve as an indicator of care quality, as it may result in longer recovery periods and delayed hospital discharge. Although agitation is typically brief, it may necessitate pharmacologic intervention, which can prolong PACU stay (11, 13, 14). Sevoflurane is an inhalational anesthetic commonly used in children because it can be administered via a face mask and induces rapid sleep in pediatric patients (15). It is administered continuously throughout surgery to maintain anesthesia and discontinued at the time upon awakening. It is very common for children, especially preschool-aged children, to emerge from sevoflurane anesthesia with restlessness, confusion, disorientation, or thrashing. This condition is referred to as emergence agitation. EA may occur even in the absence of pain and typically resolves within 15-30 minutes after awakening (16). Children experiencing sudden agitation may harm themselves, disrupt surgical wounds, or dislodge drains or intravenous lines, and agitation can be distressing for parents and caregivers (17, 18)

Given the clinical significance of agitation and the overall postoperative condition of patients, as well as the importance of improving the functional performance of the anesthesia team to prevent negative memories of surgery and anesthesia, preventing EA and restlessness after extubation and during recovery is critical. Routine pediatric anesthesia frequently involves the use of inhalational agents, particularly sevoflurane, to maintain anesthesia during surgery. While the inhalational agent sevoflurane is routinely used in pediatric anesthesia, the choice of ventilation method during extubation is often empirical, lacking evidence-based guidance.

The current study aimed to evaluate the efficacy of two end-of-anesthesia ventilation strategies, controlled versus spontaneous, on the incidence of emergence agitation in

pediatric patients (2-4 years old) undergoing adenotonsillectomy.

## Methods

### Study Design

This study was a randomized double-blind clinical trial conducted between December 2024 September 2025 on children aged 2 to 4 years undergoing adenotonsillectomy at Hazrat Rasool Akram Hospital in Tehran, Iran. The study was designed and reported in accordance with the CONSORT 2010 guidelines.

### Participants

#### Inclusion criteria

- Children aged 2–4 years scheduled for Adenotonsillectomy.
- Written informed consent was obtained from parents or legal guardians.
- Absence of underlying systemic disease.
- No history of respiratory or psychological disorders.
- American Society of Anesthesiologists (ASA) physical status I.

#### Exclusion criteria

- History of convulsive disorders (e.g., epilepsy) or any diagnosed neurological or neurodevelopmental disorder (e.g., cerebral palsy, autism spectrum disorder, intellectual disability).
- Requirement for additional reversal agents (e.g., flumazenil, naloxone) or supplemental doses of the reversal agents.

### Randomization

Randomization to the controlled ventilation or spontaneous breathing group was performed using a computer-generated, permuted block sequence (block size of four) prepared by an independent biostatistician. To ensure allocation concealment, the sequence was placed in sequentially numbered, opaque, sealed envelopes (SNOSE) by a research assistant not involved in recruitment or care. Upon eligibility confirmation and receipt of informed consent, the subsequent envelope was opened by the attending anesthesiologist in the operating room just before the induction of anesthesia, thereby disclosing the group assignment.

### Interventions

General anesthesia was induced by the intravenous administration of thiopental sodium at a dose of 3 mg/kg and maintained with inhaled sevoflurane in a mixture of oxygen and air. Anesthesia in both groups was maintained using sevoflurane, with the end-tidal concentration titrated between 0.8 and 1.0 MAC based on hemodynamic status and age. Standard monitoring was applied. Approximately 15 minutes before the conclusion of surgery, neuromuscular blockade was pharmacologically reversed if the train-of-four (TOF) count was  $\geq 3$ . Reversal was achieved with intravenous neostigmine (0.04 mg/kg) and atropine (0.02 mg/kg).

**Extubation Criteria:** To ensure a standardized and comparable emergence phase, extubation in both groups was performed only when the patient fulfilled all the following objective criteria:

**Neurological Criteria:** Patient was awake, defined as eye-opening spontaneously or in response to a verbal command.

**Respiratory Criteria A** regular, spontaneous breathing pattern was established. In the SV group, this was inherent to the mode. In the CMV group, this was assessed by temporarily switching the ventilator mode to pressure support (PSV) with 5 cmH<sub>2</sub>O support and observing adequate, spontaneous respiratory effort and tidal volume (> 5 mL/kg) for at least one minute.

**Muscular Criteria:** Train-of-four (TOF) ratio > 0.9.

**Hemodynamic Criteria:** Stable heart rate and blood pressure (within 20% of preoperative baseline values).

**Gas Exchange Criteria:** Maintenance of adequate oxygenation (SpO<sub>2</sub> > 95% on FiO<sub>2</sub> 0.4) and normocapnia (EtCO<sub>2</sub> between 35-45 mmHg) for at least three minutes before extubation.

*At the completion of surgery:*

**Controlled Mechanical Ventilation (CMV) Group:** Patients were ventilated using volume-controlled ventilation (VCV). The ventilator was set to deliver a tidal volume of 6–8 mL/kg (based on ideal body weight), with a fixed inspiratory flow rate. The respiratory rate was actively titrated by the attending anesthesiologist to maintain an end-tidal carbon dioxide (EtCO<sub>2</sub>) level between 35–40 mmHg. Positive end-expiratory pressure (PEEP) was set at 5 cmH<sub>2</sub>O. This mode was continued until standard extubation criteria were met.

**Spontaneous Breathing Group (Control):** Patients were switched to pressure support ventilation (PSV) mode with 5 cmH<sub>2</sub>O of support to allow spontaneous breathing without mandatory mechanical breaths. Extubation was performed in both groups when the patients met the standard phase II emergence criteria. Postoperatively, all patients were transferred to the recovery unit, where they were monitored for the study outcomes, including agitation, nausea, oxygen saturation, and pain levels.

The anesthesia protocol was identical for both groups to ensure comparability:

- Thiopental sodium: 3 mg/kg
- Midazolam: 0.02 mg/kg (administered at induction)
- Apotel: 15 mg/kg (administered at the end of surgery for postoperative analgesia)
- Fentanyl: 3 µg/kg
- Atracurium: 0.5 mg/kg

All drugs were administered in the same doses for both groups, and analgesia was standardized to maintain comparable postoperative conditions.

### Outcome Measures

Agitation and overall patient condition were assessed using the Richmond Agitation-Sedation Scale (RASS), which includes three stages:

1. **Observation:** Patient is observed; scores of 0 to +4 are assigned if responsive.

2. **Verbal stimulation:** Scores of -3 to +1 assigned based on verbal response.

3. **Physical stimulation:** Scores of -5 to +4 assigned if the patient responds only to physical stimulus.

Additionally, a researcher-designed checklist was used to record variables such as end-tidal CO<sub>2</sub>, TOF ratio, age, sex, and oxygen saturation. Postoperative pain was assessed using the Visual Analog Scale (VAS).

### Protocol Administration and Adherence Verification

The assigned ventilation mode was administered by the attending anesthesiologist who was part of the surgical-anesthesia team. Adherence to the protocol was continuously verified by a dedicated research nurse who monitored and documented the ventilator settings, EtCO<sub>2</sub> values, and any deviations from the assigned mode in real-time. No major protocol deviations occurred during the trial. All patients received the intervention as randomized.

### Intraoperative Monitoring and Complications

Standard intraoperative monitoring comprised electrocardiography (ECG), non-invasive blood pressure measurement, pulse oximetry (SpO<sub>2</sub>), capnography (EtCO<sub>2</sub>), and quantitative neuromuscular monitoring. No intraoperative complications such as laryngospasm, bronchospasm, significant desaturation (SpO<sub>2</sub> < 90%), hemodynamic instability requiring vasopressor support, or unexpected surgical events occurred in any participant.

### Sample Size

The sample size was calculated a priori to detect a difference between two independent proportions. Based on expert clinical expectation, the incidence of emergence agitation (EA) was estimated at 38% in the control group (spontaneous ventilation, P<sub>1</sub>) and targeted at 8% in the intervention group (controlled ventilation, P<sub>2</sub>). Using a two-sided test with  $\alpha=0.05$  ( $Z_{1-\alpha/2} = 1.96$ ) and 80% power ( $Z_{1-\beta} = 0.84$ ), 27 participants per group were required. Accounting for a 20% dropout rate, the target was increased to 33 per group (66 total). The final analysis included 79 participants, exceeding the minimum requirement. The following formula was used:

$$n = \frac{(Z_{(1-\alpha/2)} + Z_{(1-\beta)})^2 (p_1(1-p_1) + p_2(1-p_2))}{d^2}$$

### Blinding

Blinding was applied at two levels. The outcome assessor, who evaluated postoperative agitation, pain, and recovery parameters, was blinded to group allocation and not involved in intraoperative management. In addition, the statistician conducting the data analysis was blinded to group assignments, with the intervention groups coded as A and B until the completion of statistical procedures.

### Statistical Analysis

Continuous variables are presented as mean  $\pm$  standard deviation, while categorical variables are expressed as frequency (percentage). Between-group comparisons were performed as follows: normally distributed continuous

variables were analyzed using the independent samples t-test; categorical variables were assessed using the Chi-square test or Fisher's exact test, as appropriate. For continuous outcome measures, an Analysis of Covariance (ANCOVA) was conducted to compare the two groups, with age included as a covariate. Statistical significance was set at  $P < 0.05$ . All analyses were performed using SPSS software version 22.0 (IBM Corp., Armonk, NY, USA).

## Results

### Baseline Characteristics

A total of 79 children were included in the final analysis, with 40 patients allocated to the controlled ventilation group and 39 patients to the spontaneous breathing group. The CONSORT flow diagram illustrating patient selection and enrollment is presented in Figure 1. The baseline characteristics of the participants are summarized in Table 1. The mean age was significantly higher in the controlled ventilation group compared to the spontaneous breathing group ( $40.75 \pm 4.73$  vs.  $37.31 \pm 5.80$  months,  $P=0.005$ ). There were no significant differences in sex distribution between groups ( $P=0.583$ ), with males representing 35% and 41% of the controlled ventilation and spontaneous

breathing groups, respectively.

### Recovery and Postoperative Outcomes

Recovery and postoperative outcomes by adjusting for the age effect are presented in Table 2. The mean time to full awakening was slightly shorter in the controlled ventilation group ( $10.98 \pm 3.29$  min) than in the spontaneous breathing group ( $12.38 \pm 3.73$  min). However, this difference did not reach statistical significance ( $P=0.240$ ). Postoperative pain, assessed by the Visual Analog Scale (VAS), was significantly lower in the controlled ventilation group compared to the spontaneous breathing group ( $2.80 \pm 1.18$  vs.  $5.15 \pm 1.69$ ,  $P=0.001$ ). No significant differences were observed in oxygen saturation ( $SpO_2$ ) between groups ( $0.97 \pm 0.01$  vs.  $0.97 \pm 0.01$ ,  $P=0.115$ ). End-tidal  $CO_2$  ( $EtCO_2$ ) levels were significantly higher in the spontaneous breathing group compared to the controlled ventilation group ( $36.82 \pm 1.83$  vs.  $34.43 \pm 2.52$  mmHg,  $P=0.001$ ).

Agitation scores were significantly lower in the controlled ventilation group ( $0.60 \pm 0.63$ ) than in the spontaneous breathing group ( $1.21 \pm 0.61$ ,  $P=0.001$ ). Likewise, the duration of stay in the recovery unit was shorter in the controlled ventilation group ( $38.98 \pm 6.96$  min) compared

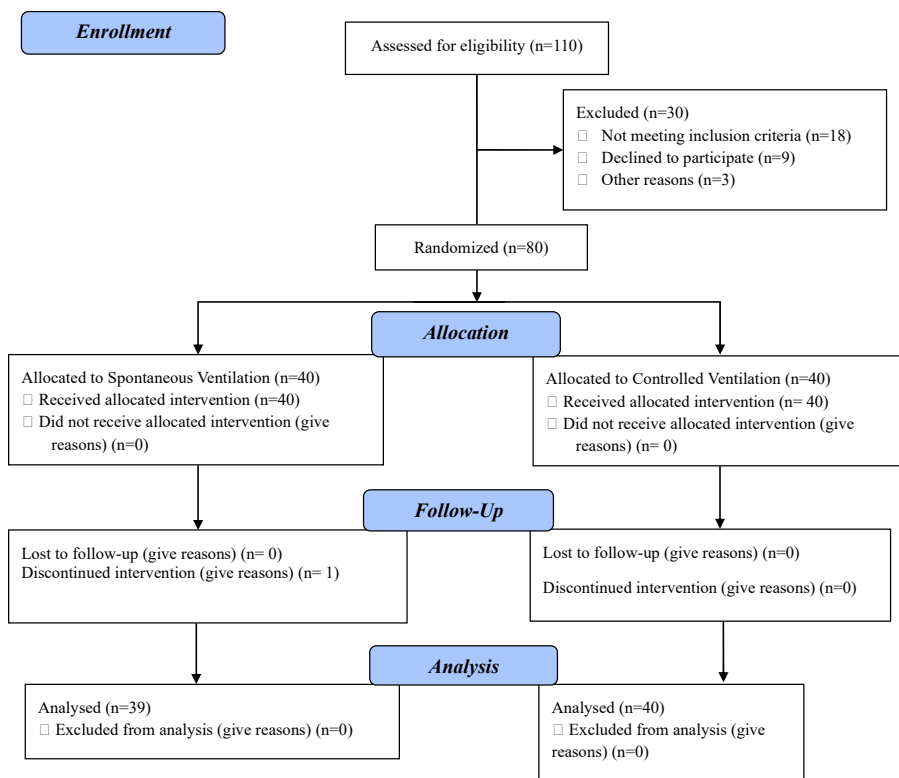


Figure 1. Consort diagram related to the sample selection process

Table 1. Baseline Characteristics of participants

Variable	Controlled Ventilation (n=40)	Spontaneous Ventilation (n=39)	P
Age (Month)	40.75 ± 4.73	37.31 ± 5.80	0.005
Sex, n (%)			
Female	26 (65.0%)	23 (59.0%)	0.583
Male	14 (35.0%)	16 (41.0%)	

**Table 2.** Recovery and Postoperative Outcomes in understudied groups

Variable	Controlled Ventilation (n=40)	Spontaneous Breathing (n=39)	F	p	Partial $\eta^2$ (group)
Agitation Score	0.60 ± 0.63	1.21 ± 0.61	14.826	0.001	0.163
Time to Full Awakening (min)	10.98 ± 3.29	12.38 ± 3.73	1.401	0.240	0.018
Pain Score (VAS)	2.80 ± 1.18	5.15 ± 1.69	38.747	0.001	0.338
SpO <sub>2</sub> in Recovery (%)	97.35 ± 1.29	96.92 ± 1.13	2.536	0.115	0.032
End-Tidal CO <sub>2</sub> (mmHg)	34.43 ± 2.52	36.82 ± 1.83	19.897	0.001	0.207
Recovery duration (min)	38.98 ± 6.96	44.72 ± 6.57	11.178	0.001	0.128

Notes: Data presented as Mean ± Standard Deviation.

ANCOVA was conducted with age as a covariate.

Bold p-values indicate statistical significance ( $P < 0.05$ ).

VAS = visual analog scale; SpO<sub>2</sub> = peripheral oxygen saturation

to the spontaneous breathing group ( $44.72 \pm 6.57$  min,  $P=0.001$ ).

### Neuromuscular Monitoring

Neuromuscular function, evaluated using the train-of-four (TOF) index and TOF ratio, did not differ significantly between the groups (TOF index:  $3.0 \pm 0.0$  vs.  $3.0 \pm 0.0$ ,  $P=1.00$ ; TOF ratio:  $0.9 \pm 0.0$  vs.  $0.9 \pm 0.0$ ,  $P=1.00$ ) (Table 3).

### Postoperative Nausea and Delirium

The incidence and frequency of postoperative nausea are summarized in Table 4. Nausea was reported in 25.0% of the controlled ventilation group and 28.2% of the spontaneous breathing group, with no statistically significant difference ( $P=0.812$ ). The distribution of nausea episodes (0, 1, or 2 episodes) was also comparable between groups ( $P=0.781$ ). No cases of postoperative delirium were observed in either group.

### Adverse Events and Protocol Compliance

As documented during protocol adherence monitoring, no major protocol deviations or intraoperative complications occurred. Specifically, there were no cases of airway complications (laryngospasm, bronchospasm), significant oxygen desaturation (SpO<sub>2</sub> < 90%), or hemodynamic instability requiring intervention. All 79 randomized participants completed the study and received the intervention as allocated, with 100% protocol compliance.

### Discussion

In this randomized clinical trial, the effects of controlled

mechanical ventilation (CMV) and spontaneous ventilation (SV) on postoperative emergence agitation (EA) were compared in children aged 2–4 years undergoing adenotonsillectomy. The findings indicate that optimizing ventilation strategy during general anesthesia significantly influences the incidence of EA, a condition characterized by severe restlessness, inconsolable crying, and inappropriate behavior following anesthesia (14).

EA was significantly more frequent in the SV group, likely due to hypercapnia associated with inadequate ventilation. Elevated end-tidal CO<sub>2</sub> (EtCO<sub>2</sub>) can trigger neurochemical alterations in neurotransmitters such as glutamate and GABA, promoting agitation after awakening (19-21). These findings emphasize that CMV can reduce hypercapnia, thereby mitigating EA, postoperative pain, prolonged PACU stay, and the need for pharmacologic interventions (22).

Postoperative pain scores were higher in the SV group, likely related to non-physiological respiratory muscle activity during spontaneous ventilation, leading to mechanical stress, oxidative stress, and mast cell-mediated inflammatory responses that sensitize nociceptors and exacerbate hyperalgesia (23). Additionally, hypercapnia induces central sensitization in spinal-thalamic pathways and stimulates the hypothalamic-pituitary-adrenal axis, increasing cortisol release and enhancing pain perception (24, 25). These observations align with prior studies showing that controlled ventilation reduces opioid consumption and improves postoperative pain control (26-28).

Recovery duration in the SV group was longer, primarily due to respiratory acidosis secondary to hypercapnia, which impairs metabolism of lipophilic anesthetics via

**Table 3.** Neuromuscular Monitoring in understudied groups

Variable	Controlled Ventilation (n=40)	Spontaneous Ventilation (n=39)	P
TOF index	3.0 ± 0.0	3.0 ± 0.0	1.00
TOF ratio	0.9 ± 0.0	0.9 ± 0.0	1.00

Note: TOF = train-of-four.

**Table 4.** Postoperative Nausea and Delirium in understudied groups

Variable	Controlled Ventilation (n=40)	Spontaneous Ventilation (n=39)	P
Nausea, n (%)			0.812
No	30 (75.0%)	28 (71.8%)	
Yes	10 (25.0%)	11 (28.2%)	
Number of nausea episodes, n (%)			0.781
0	31 (77.5%)	28 (71.8%)	
1	7 (17.5%)	8 (20.5%)	
2	2 (5.0%)	3 (7.7%)	

altered protein binding and decreased cytochrome P450 activity, creating a cycle of prolonged recovery and increased need for interventions (29). EtCO<sub>2</sub> levels were significantly higher in the SV group, reflecting impaired alveolar ventilation and increased physiological dead space, which can lead to cerebral vasodilation and elevated cerebral blood flow, contributing to EA (30-32). In contrast, CMV maintained stable blood gas homeostasis, prevented sudden fluctuations in cerebral perfusion, and modulated GABAergic neuronal activity, facilitating coordination between thalamocortical regions and the default mode network during recovery, thereby reducing EA (33).

No cases of delirium were observed in either group, consistent with the low risk in children under 5 years undergoing minimally invasive procedures such as adenotonsillectomy (34, 35). Despite the absence of statistical differences in some parameters, the cumulative benefits observed in EA, pain, and recovery duration support CMV as a safer and more effective ventilation strategy in this population.

The findings of this study should be interpreted in the context of certain limitations. First, the single-center design may restrict the generalizability of the results to other institutions with differing patient populations and healthcare resources. Secondly, the study focused on a narrow, specific age group (2-4 years old), and therefore, the results may not be applicable to older children or infants. A notable limitation was the absence of any cases of postoperative delirium, which prevented a comparative analysis of this outcome between the two ventilation strategies; this is likely due to the inherently low risk in this young age group undergoing brief procedures, but it remains a gap in the findings. Furthermore, while the trial was double-blind, the significantly different EtCO<sub>2</sub> levels between groups could have potentially unblinded the attending clinicians to the intervention, introducing a possible source of bias. The use of fixed, standardized ventilator settings for the controlled ventilation group, rather than a protocol titrated to individual patient physiology, may also affect the external validity and optimization of the intervention. Also, the duration of surgery was not recorded or compared between groups. Although randomization should theoretically distribute this variable evenly, we cannot definitively rule out unequal surgical times as a potential, unmeasured confounding factor. Future studies should systematically record and account for surgical duration to strengthen the causal inference between ventilation mode and emergence outcomes. Finally, the follow-up was limited to the immediate postoperative period in the PACU; thus, the study provides no data on longer-term outcomes such as patient satisfaction, post-discharge complications, or the potential for long-term neurocognitive effects.

### Conclusion

This clinical trial demonstrates that employing CMV at the end of anesthesia, as opposed to SV, confers significant benefits for pediatric patients undergoing adenotonsillectomy. The findings robustly indicate that CMV ef-

fectively reduces the incidence and severity of emergence agitation, alleviates postoperative pain, shortens PACU recovery time, and maintains better physiological stability by preventing hypercapnia. These advantages are likely mediated through the prevention of respiratory acidosis and its subsequent neurochemical effects, which promote a smoother and more controlled emergence from sevoflurane anesthesia. Therefore, CMV is recommended as the superior and preferred ventilation strategy during the emergence phase for this specific pediatric population. The absence of delirium in both groups further underscores the safety profile of both techniques while highlighting the particular efficacy of CMV in enhancing the quality of recovery.

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### Conflict of Interests

The authors declare that they have no competing interests.

### Authors' Contributions

Authors' Contribution: All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by T A., S SK. The first draft of the manuscript was written by T A S SK M Gh, T S., and M S. All authors commented on previous versions of the manuscript, read, and approved the final manuscript.

### Ethical Considerations

The trial protocol was registered with the Iranian Registry of Clinical Trials (IRCT20240519061842N1) and approved by the Ethics Committee of Iran University of Medical Sciences (IR.IUMS.FMD.REC.1403.258).

### Funding Support

N/A.

### Data Availability

The dataset presented in the study is available on request from the corresponding author during submission or after publication.

### AI Use Statement

During the preparation of this work, the authors used artificial intelligence solely to improve the writing quality and language clarity of the manuscript. No AI was employed for data analysis, statistical inference, clinical decision-making, or interpretation of results. The authors assume full responsibility for the content.

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