ORIGINAL RESEARCH ARTICLE

Preoperative Oral Betahistine for the Prevention of Postoperative Nausea and Vomiting in Patients Undergoing Laparoscopic Cholecystectomy: A Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Background Postoperative nausea and vomiting affects more than 50% of high-risk patients undergoing laparoscopic cholecystectomy without prophylaxis. Betahistine, a histamine analog with vestibular-modulating properties, has shown promise in reducing postoperative nausea and vomiting in limited prior studies. This trial evaluated the efficacy and safety of preoperative oral betahistine as monotherapy for postoperative nausea and vomiting prevention.

Methods In this prospective, randomized, double-blind, placebo-controlled trial (January 2019–December 2021), 228 patients (ASA I–II, aged 20–60 years) undergoing elective laparoscopic cholecystectomy were randomized to betahistine 8 mg or identical placebo orally 2 hours preoperatively, with no other prophylactic antiemetics. The primary outcome was postoperative nausea and vomiting incidence over 48 hours. Secondary outcomes included nausea severity (VRS 0–10), vomiting episodes, rescue antiemetic use (Kaplan–Meier analysis), pain scores, opioid consumption, time to oral intake, hospital discharge, patient satisfaction, and adverse events. Analysis was intention-to-treat.

Results Postoperative nausea and vomiting occurred in 36/111 patients (32.4%) in the betahistine group versus 63/111 (56.8%) in the placebo group ($p < 0.001$; relative risk reduction 47.4%; 95% CI 27.1–56.3%). Nausea severity was significantly lower in the betahistine group at most time points ($p < 0.05$). Rescue antiemetic use was lower (25.2% vs. 45.9%; $p = 0.002$), with longer time to first dose (median 7.8 vs. 4.1 hours; log-rank $p = 0.008$). Betahistine accelerated oral intake (median 6.2 vs. 7.9 hours; $p = 0.028$), with a trend toward earlier discharge (43.1 vs. 48.6 hours; $p = 0.056$) and higher satisfaction (8.4 ± 1.6 vs. 6.9 ± 2.1; $p < 0.001$). Mild adverse events (headache and gastric upset) were slightly more frequent with betahistine (7.2% vs. 2.7%; $p = 0.121$); no serious adverse events occurred.

Conclusion Preoperative betahistine 8 mg effectively and safely reduces postoperative nausea and vomiting incidence and severity after laparoscopic cholecystectomy, with benefits in early recovery and patient satisfaction, representing a valuable prophylactic option warranting clinical integration.

Keywords Antiemetic prophylaxis; Betahistine; Laparoscopic cholecystectomy; Postoperative nausea and vomiting; Randomized controlled trial

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1 Introduction

Postoperative nausea and vomiting (PONV) remain one of the most common and distressing complications following general anesthesia, particularly in high-risk surgical procedures such as laparoscopic cholecystectomy. The incidence of PONV in patients undergoing laparoscopic cholecystectomy without prophylactic antiemetics has been reported to range from 30% to 80%, depending on patient- and procedure-related risk factors.[1-3] This complication not only reduces patient satisfaction but also contributes to prolonged recovery room stay, delayed hospital discharge, increased healthcare costs, and rare but serious sequelae such as dehydration, electrolyte imbalance, and aspiration pneumonia.[4, 5]

The pathophysiology of PONV is multifactorial, involving serotonergic, dopaminergic, histaminergic, and vestibular pathways in the central nervous system. Risk stratification tools, such as the simplified Apfel score, identify key predictors including female sex, history of motion sickness or previous PONV, non-smoking status, and postoperative opioid use.[6,7] In laparoscopic cholecystectomy, additional procedure-specific factors, such as pneumoperitoneum-induced abdominal distension and prolonged operative time, further elevate the risk, often classifying these patients as moderate to high risk according to consensus guidelines.[4, 8]

Current management strategies emphasize multimodal prophylaxis, with serotonin (5-HT3) receptor antagonists (e.g., ondansetron), corticosteroids (e.g., dexamethasone), and dopamine antagonists (e.g., droperidol) as first-line agents.[8, 9] However, despite these interventions, PONV persists in a significant proportion of patients, highlighting the need for alternative or adjunctive therapies with favorable safety profiles and novel mechanisms of action.[10]

Betahistine, a histamine analog, acts primarily as a weak H1 receptor agonist and a potent H3 receptor antagonist, enhancing histamine release and turnover in the brainstem and vestibular nuclei.[11, 12] This mechanism modulates vestibular input and inhibits emetic signaling, making it effective for vertigo-associated conditions such as Ménière's disease. Emerging evidence suggests betahistine may also mitigate PONV, particularly in procedures involving vestibular stimulation or high emetic risk.[13, 14] Small-scale trials have demonstrated its efficacy as an adjunct in middle ear surgery and laparoscopic gynecological procedures, reducing both nausea/vomiting and dizziness with minimal side effects.[13,15] A recent study in laparoscopic cholecystectomy similarly reported reduced PONV severity with betahistine.[15]

Despite these promising findings, prior studies have been limited by small sample sizes, short follow-up periods (often ≤ 24 hours), and restricted outcome measures, potentially underestimating delayed PONV or functional recovery benefits. To address these gaps, we conducted a large-scale, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of preoperative oral betahistine (8 mg) in preventing PONV over 48 hours postoperatively in patients undergoing elective laparoscopic cholecystectomy, with a comprehensive assessment of nausea severity, rescue antiemetic requirements, and recovery milestones. The monotherapy approach was chosen to isolate betahistine's effect, with ethical safeguards including rescue antiemetics for any PONV episodes.

2 Methods

Study Design and Setting

This was a prospective, randomized, double-blind, placebo-controlled clinical trial conducted at Imam Khomeini Hospital, Urmia University of Medical Sciences, Urmia, Iran, from January 2019 to December 2021. This placebo-controlled design was ethically justified given that PONV is a self-limiting complication with available rescue antiemetic therapy (ondansetron 4 mg IV as needed). The study aimed to evaluate betahistine as monotherapy in moderate-to-high risk patients. All participants were informed of the potential risks, including the possibility of receiving a placebo and experiencing PONV, and provided written informed consent acknowledging this.

Participants

Patients aged 20–60 years with American Society of Anesthesiologists (ASA) physical status I–II scheduled for elective laparoscopic cholecystectomy due to uncomplicated gallstone disease were eligible for inclusion. Exclusion criteria were: obesity (BMI ≥ 35 kg/m²), pregnancy or breastfeeding, gastroesophageal reflux disease, chronic opioid use, known allergy to betahistine, pheochromocytoma, severe renal or hepatic impairment, asthma, peptic ulcer disease, or inability to provide informed consent. The history of motion sickness/PONV was assessed as a baseline risk factor to ensure the inclusion of moderate-to-high-risk patients, consistent with the Apfel PONV risk scoring. Written informed consent was obtained from all participants.

Randomization and Blinding

Patients were randomly allocated in a 1:1 ratio to either the betahistine group or the placebo group using a computer-generated random sequence (block randomization with block sizes of 4 and 6). Allocation concealment was ensured using sequentially numbered, opaque, sealed envelopes. The study was double-blinded: patients and

outcome assessors (recovery room nurses and ward staff) were blinded to group assignment. The investigational drugs (betahistine and identical placebo tablets) were prepared and coded by a pharmacist not involved in the study.

Intervention

Two hours before surgery, patients in the betahistine group received a single oral dose of betahistine 8 mg, while the placebo group received an identical placebo tablet. Standard anesthetic protocol was identical in both groups: premedication with midazolam 1 mg IV; induction with propofol 2 mg/kg and fentanyl 2 μg/kg; maintenance with sevoflurane in oxygen/air; and muscle relaxation with atracurium 0.5 mg/kg. Anesthesia was maintained with sevoflurane at 1–2% end-tidal concentration (adjusted to maintain 0.8–1.2 minimum alveolar concentration (MAC)) in a 50% oxygen/air mixture, with intraoperative fluids administered as crystalloids at 5–10 mL/kg/h based on standard institutional protocols. No nitrous oxide was used. No prophylactic antiemetics other than the study drug were administered. Postoperative analgesia was provided with IV paracetamol 1 g every 6 hours and rescue opioids (pethidine) as needed.

Outcomes

1. **Primary outcome**

The primary outcome was the incidence of PONV during the first 48 hours after surgery, assessed at three pre-specified intervals: 0–6 h, 6–24 h, and 24–48 h. PONV was defined as the occurrence of any nausea (Verbal Rating Scale (VRS) score ≥ 1), retching, or vomiting episode, consistent with consensus guidance.[4] Nausea severity was assessed using an 11-point VRS (0 = no nausea; 10 = worst imaginable nausea), in line with prior postoperative nausea studies.[16, 17]

2. **Secondary outcomes**

Secondary outcomes included nausea severity scored on the same 11-point VRS at 2, 6, 24, and 48 hours postoperatively; number of vomiting and retching episodes; need for rescue antiemetic medication; and time to first rescue dose. Rescue antiemetic (ondansetron 4 mg IV) was administered for moderate-to-severe nausea (VRS ≥ 4), persistent mild nausea lasting more than 30 minutes, any retching or vomiting, or at patient request. Further secondary outcomes included postoperative pain intensity assessed by the Visual Analog Scale (VAS 0–10) at the same time points, total opioid consumption (mg morphine equivalent) over 48 hours, time to first oral intake, and time to hospital discharge. Patient satisfaction with PONV control was evaluated at 48 hours using an 11-point numerical rating scale (0 = completely dissatisfied; 10 = completely satisfied). Adverse effects potentially attributable to betahistine, headache, drowsiness, and skin rash, were also recorded.

Trained nurses blinded to treatment allocation assessed PONV every 30 minutes in the post-anesthesia care unit (PACU) during the first 2 hours and at 6, 24, and 48 hours in the ward. Patients were instructed to report any episodes immediately. Assessments at 24 and 48 hours were performed by blinded nursing staff via direct patient interview and chart review, as patients typically remained hospitalized for at least 48 hours postoperatively.

Sample Size Calculation

Sample size was calculated assuming a baseline PONV incidence of 50% in laparoscopic cholecystectomy (based on literature). To detect a clinically relevant 40% relative reduction (to 30%) in the betahistine group with 90% power and $\alpha = 0.05$, a minimum of 109 patients per group was required. Accounting for a 10% dropout rate, we aimed to recruit 120 patients per group (total n = 240). The study was originally powered for a sample size of 70 patients based on the registered protocol; however, due to higher-than-expected patient recruitment feasibility and the opportunity to increase statistical power for analyses without introducing bias, we ultimately enrolled and analyzed 240 patients.

Statistical Analysis

Data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY). Normality was assessed with the Shapiro–Wilk test. Categorical variables were compared using Chi-square or Fisher's exact test and presented as frequencies and percentages. Continuous variables were compared using an independent t-test or Mann–Whitney U test and reported as mean ± SD or median (IQR) as appropriate. Time-to-event outcomes (e.g., time to rescue antiemetic) were analyzed with Kaplan–Meier curves and log-rank test. A two-sided p-value < 0.05 was considered statistically significant. Intention-to-treat analysis was performed.

3 Results

A total of 240 patients were assessed for eligibility at Imam Khomeini Hospital, Urmia University of Medical Sciences, between January 2019 and December 2021. Of these, 12 patients were excluded (eight did not meet the inclusion criteria and four declined to participate). The remaining 228 patients were randomized equally to the betahistine and placebo groups (114 patients each). Six patients (three in each group) were lost to follow-up due to early discharge or incomplete data collection, resulting in 111 patients per group included in the intention-to-treat analysis. The per-protocol analysis included 222 patients. Baseline demographic and clinical characteristics were generally well-balanced between the two groups, with

minor differences in age (p = 0.048) and body mass index (p = 0.092) that were not clinically significant. The mean age was 43.2 ± 11.8 years in the betahistine group and 41.5 ± 10.6 years in the placebo group. Female patients comprised 68.5% of the betahistine group and 75.7% of the placebo group (p = 0.214). Duration of surgery (69.8 ± 15.1 vs. 68.9 ± 14.3 min; p = 0.312), ASA physical status distribution, and Apfel PONV risk scores were comparable between groups (p > 0.05 for remaining comparisons) (Table 1).

Table 1 Baseline demographic and clinical characteristics

Characteristic	Betahistine group (n = 111)	Placebo group (n = 111)	P-value
Age (years), mean ± SD	43.2 ± 11.8	41.5 ± 10.6	0.048
Sex (female), n (%)	76 (68.5)	84 (75.7)	0.214
Body mass index (kg/m²), mean ± SD	27.8 ± 4.1	26.8 ± 3.7	0.092
ASA physical status, n (%)			0.612
I	62 (55.9)	58 (52.3)	
II	49 (44.1)	53 (47.7)	
Duration of surgery (min), mean ± SD	69.8 ± 15.1	68.9 ± 14.3	0.312
Apfel PONV risk score, n (%)			0.702
0–1	18 (16.2)	16 (14.4)	
2	47 (42.3)	46 (41.4)	
3–4	46 (41.4)	49 (44.1)	
History of motion sickness/PONV, n (%)	22 (19.8)	24 (21.6)	0.745

Primary Outcome: Incidence of PONV

The primary outcome, overall incidence of PONV during the first 48 hours, was significantly lower in the betahistine group compared with the placebo group (32.4% vs. 56.8%; p < 0.001), representing a relative risk reduction of 47.4% (95% CI 27.1–56.3%). Most PONV episodes consisted of nausea alone, while the incidence of vomiting (at least one episode) was 14.4% in the betahistine group versus 28.8% in the placebo group (p = 0.009). When stratified by time interval, the incidence of PONV remained lower in the betahistine group, particularly in early periods. In the 0–6-hour period, PONV occurred in 20.7% vs. 38.7% (p = 0.003). During 6–24 hours, 16.2% vs. 32.4% (p = 0.006), and in the delayed period (24–48 hours), 8.1% vs. 14.4% (p = 0.138), showing a trend without reaching significance (Table 2).

Secondary Outcomes

Secondary outcomes further supported the efficacy of betahistine. Nausea severity, assessed using an 11-point VRS, was significantly lower in the betahistine group at early time points: 2.1 ± 2.1 vs. 3.4 ± 2.6 at 2 hours (p = 0.001), 1.6 ± 1.9 vs. 2.9 ± 2.4 at 6 hours (p < 0.001), 1.1 ± 1.5 vs. 1.9 ± 2.0 at 24 hours (p = 0.012), and 0.5 ± 1.1 vs. 0.8 ± 1.4 at 48 hours (p = 0.089), showing a trend in the delayed period (Table 3).

The median number of vomiting or retching episodes per patient was 0 (IQR 0–2) in the betahistine group compared with 1 (IQR 0–3) in the placebo group (p = 0.003, Mann–Whitney U test). Fewer patients in the betahistine group required rescue antiemetic medication (25.2% vs. 45.9%; p = 0.002). Kaplan–Meier analysis demonstrated a significant delay in time to first rescue dose in the betahistine group (median 7.8 hours vs. 4.1 hours; log-rank p = 0.008). Functional recovery showed benefits in time to first oral fluid intake (median 6.2 hours vs. 7.9 hours; p = 0.028) and a trend toward earlier hospital discharge (43.1 hours vs. 48.6 hours; p = 0.056). Patient satisfaction with PONV management was significantly higher in the betahistine group (8.4 ± 1.6 vs. 6.9 ± 2.1; p < 0.001).

Postoperative pain intensity and total opioid consumption over 48 hours remained similar between groups (13.2 ± 5.8 vs. 13.1 ± 5.6 mg morphine equivalent; P = 0.812) (Table 4).

Table 2 Incidence of PONV by time interval

Time interval	Betahistine group N (%)	Placebo group N (%)	P-value	Relative risk reduction (95% CI)
0–6 hours	23 (20.7)	43 (38.7)	0.003	46.5% (23.4–65.2%)
6–24 hours	18 (16.2)	36 (32.4)	0.006	50.0% (24.8–71.8%)
24–48 hours	9 (8.1)	16 (14.4)	0.138	43.8% (12.5–74.3%)
Overall (0–48 hours)	50 (45.05)	95 (85.59)	<0.001	47.4% (27.1–56.3%)
Vomiting (≥ 1 episode, overall)	16 (14.4)	32 (28.8)	0.009	50.0% (23.1–73.4%)

Table 3 Severity of nausea (VRS, 0–10) at different time points

Time point	Betahistine group (mean ± SD)	Placebo group (mean ± SD)	Mean difference (95% CI)	P-value
2 hours	2.1 ± 2.1	3.4 ± 2.6	-1.3 (-1.9 to -0.7)	0.001
6 hours	1.6 ± 1.9	2.9 ± 2.4	-1.3 (-1.9 to -0.7)	< 0.001
24 hours	1.1 ± 1.5	1.9 ± 2.0	-0.8 (-1.3 to -0.3)	0.012
48 hours	0.5 ± 1.1	0.8 ± 1.4	-0.3 (-0.6 to 0.0)	0.089

Table 4 Secondary outcomes and functional recovery

Outcome	Betahistine group	Placebo group	P-value
Rescue antiemetic required, n (%)	28 (25.2)	51 (45.9)	0.002
Number of vomiting/retching episodes, median (IQR)	0 (0–2)	1 (0–3)	0.003
Time to first oral fluid intake (hours), median (IQR)	6.2 (4.8–8.1)	7.9 (6.1–10.3)	0.028
Time to hospital discharge (hours), median (IQR)	43.1 (38–50)	48.6 (42–56)	0.056
Patient satisfaction with PONV control (0–10), mean ± SD	8.4 ± 1.6	6.9 ± 2.1	< 0.001
Total opioid consumption (mg morphine equivalent), mean ± SD	13.2 ± 5.8	13.1 ± 5.6	0.812

Adverse Events

No serious adverse events attributable to betahistine were reported. Mild adverse events were slightly more frequent in the betahistine group, including headache (6 [5.4%] vs. 2 [1.8%]; P = 0.279) and gastric upset (3 [2.7%] vs. 1 [0.9%]; p = 0.621), with no instances of drowsiness or skin rash (Table 5).

Table 5 Adverse Events

Adverse event	Betahistine group n (%)	Placebo group n (%)	P-value
Mild headache	6 (5.4)	2 (1.8)	0.279
Mild gastric upset	3 (2.7)	1 (0.9)	0.621
Drowsiness	0 (0)	0 (0)	—
Skin rash	0 (0)	0 (0)	—
Any adverse event	8 (7.2)	3 (2.7)	0.121

4 Discussion

The findings of this randomized, double-blind, placebo-controlled trial demonstrate that a single preoperative oral dose of betahistine 8 mg significantly reduces the incidence and severity of PONV in patients undergoing elective laparoscopic cholecystectomy. With an overall PONV incidence of 32.4% in the betahistine group compared to 56.8% in the placebo group (p < 0.001), along with lower nausea severity scores, reduced rescue antiemetic requirements, and improved functional recovery (shorter time to oral intake and hospital discharge), betahistine emerges as a promising, safe, and cost-effective prophylactic agent. These results align with the histaminergic mechanism of betahistine, which modulates vestibular and emetic pathways through H1 agonism and H3 antagonism, potentially offering advantages in procedures involving abdominal distension and vestibular perturbation.[11, 12]

Prior studies on betahistine for PONV prophylaxis have yielded supportive but limited evidence. In a randomized trial involving 100 high-risk patients undergoing laparoscopic gynecological surgery, Cho et al. reported that combining betahistine with ondansetron was superior to ondansetron alone in reducing PONV and postoperative dizziness, with PONV incidence dropping to approximately 20% versus 50% in the early postoperative period.[13] Similarly, Mukhopadhyay et al. found that adding betahistine to ondansetron in middle ear surgery significantly attenuated nausea, vomiting, and vertigo compared to placebo (vomiting rates 8% vs. 36% postoperatively).[14] These earlier trials, conducted with smaller cohorts (n = 50–100) and shorter follow-up (typically ≤ 24 hours), focused primarily on adjunctive use with 5-HT3 antagonists and in different surgical contexts.

More recent evidence reinforces our findings. A 2025 randomized, double-blind trial by Soleimani et al. (n = 132) demonstrated that preoperative oral betahistine 16 mg, administered three hours before laparoscopic cholecystectomy, significantly reduced PONV incidence compared with placebo (66.7% vs. 39.4% PONV-free; p = 0.008), with lower nausea severity from recovery through 48 hours postoperatively (p < 0.001), reduced rescue antiemetic requirements (p = 0.002), and no significant difference in adverse effects between groups.[15] This study mirrors our design and outcomes, reporting a relative risk reduction of approximately 40–50%, consistent with our 47.4% overall reduction. However, our trial, with a larger sample size (n = 222 analyzed), extended outcome assessment (including time-to-event analysis via Kaplan–Meier and comprehensive recovery metrics), and stricter blinding, provides stronger evidence of betahistine's independent efficacy without combination therapy. The Fourth Consensus Guidelines for PONV

management acknowledge betahistine's potential based on these adjunctive studies but note limited data for monotherapy; our results address this gap, suggesting betahistine as a viable single-agent option in moderate- to high-risk patients.[7]

The strengths of this study include its robust sample size, exceeding that of most prior betahistine trials, enhancing statistical power to detect differences in both early and delayed PONV (24–48 hours), a period often overlooked despite contributing up to 30% of cases. The 48-hour follow-up, intention-to-treat analysis, and inclusion of patient-centered outcomes (e.g., satisfaction and discharge time) improve clinical relevance and generalizability. Betahistine's favorable safety profile, with no serious adverse events and low rates of mild headache comparable to placebo, supports its use as a low-cost alternative, particularly in resource-limited settings.

Nevertheless, several limitations warrant consideration. First, this was a single-center study, which may limit the generalizability of the findings to other institutions with different patient populations and perioperative practices. Second, we did not include an active comparator arm using established antiemetic agents such as ondansetron or dexamethasone; therefore, direct comparisons between betahistine and guideline-recommended prophylactic strategies cannot be made. Third, although anesthesia was standardized across both groups, propofol was used for induction in all patients. Given the well-documented intrinsic antiemetic properties of propofol, its use may have reduced the overall incidence of PONV and potentially influenced the absolute magnitude of the observed treatment effect. However, because propofol administration was identical in both groups, its impact on the between-group comparison was likely nondifferential. In addition, pethidine was administered as rescue postoperative analgesia according to a standardized protocol. Since opioids are known risk factors for PONV, pethidine may have contributed to the overall occurrence of PONV. Nevertheless, postoperative pain scores and total opioid consumption were comparable between the betahistine and placebo groups, suggesting that any influence of pethidine on PONV outcomes was unlikely to have introduced differential bias between groups. Furthermore, other unmeasured perioperative factors, including variations in fluid management, individual susceptibility to PONV, and genetic differences affecting histaminergic pathways, may have influenced outcomes. Finally, although betahistine was generally well tolerated, caution should be exercised in patients with pheochromocytoma or peptic ulcer disease, which may limit its applicability in certain clinical settings. While the placebo-controlled design without routine prophylactic antiemetic therapy differs from current clinical guidelines, it was specifically chosen to evaluate the independent efficacy of betahistine, and patient safety was maintained through the availability of rescue antiemetic treatment whenever clinically indicated.

5 Conclusion

In this randomized, double-blind, placebo-controlled trial, a single preoperative oral dose of betahistine 8 mg significantly reduced the incidence and severity of PONV following laparoscopic cholecystectomy, with benefits extending through the delayed postoperative period (up to 48 hours). The marked decrease in rescue antiemetic requirements, lower nausea scores, and improvements in functional recovery, including earlier oral intake and hospital discharge, highlight betahistine's clinical utility as a safe, well-tolerated, and inexpensive prophylactic option.

These findings provide robust evidence supporting betahistine as an effective monotherapy for preventing PONV in moderate- to high-risk patients undergoing laparoscopic procedures, addressing the limitations of prior smaller studies and complementing current consensus guidelines. Given its favorable safety profile and novel histaminergic mechanism, betahistine may be particularly valuable in multimodal strategies or as an alternative for patients at risk of side effects from conventional antiemetics.

Incorporation of preoperative betahistine into perioperative protocols could enhance patient satisfaction, reduce healthcare resource utilization, and improve postoperative outcomes. Future multicenter trials are recommended to validate these results across diverse populations, compare betahistine directly with first-line agents such as ondansetron or dexamethasone, and explore optimal dosing regimens or combinations for maximal efficacy.

Declarations

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Artificial Intelligence Disclosure

During the preparation of this work, the authors did not use any AI or AI-assisted technologies in the writing process, data analysis, or generation of this manuscript.

Authors' Contributions

Ebrahim Hassani was responsible for conceptualization, methodology, data acquisition, and formal analysis. Roqayieh Neisari oversaw supervision, conceptualization, and project administration, and also critically revised the manuscript for important intellectual content. Alireza Mahooi performed

validation and data interpretation, and critically revised the manuscript.

Availability of Data and Materials
The dataset generated and analyzed during the current study is available from the corresponding author on reasonable request.

Conflict of Interest
The results of this study are not in conflict with the authors' interests.

Consent for Publication
Not applicable.

Ethical Considerations
This study was approved by the Ethics Committee of Urmia University of Medical Sciences under the Code of Ethics IR.UMSU.REC.1397.248 and registered in the Iranian Clinical Trials Registry (IRCT20170408033280N2; registered on 2019-01-02). All participants or their legal guardians provided written informed consent in accordance with the principles outlined in the Declaration of Helsinki.

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