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Bougie-First Versus Stylet-First Technique for Tracheal Intubation in Adults: A Systematic Review and Meta-analysis

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Abstract

Introduction: Bougie-first and stylet-first techniques are widely used to facilitate adult tracheal intubation, but randomized evidence remains inconsistent across emergency, intensive care, and operating room settings. This systematic review and meta-analysis aimed to compare bougie-first versus stylet-first intubation in adults, focusing on first-attempt intubation success and key procedural and airway-related safety outcomes.

Material and Methods: We conducted a PRISMA 2020–compliant systematic review registered in PROSPERO (CRD420261298317). PubMed, Scopus, Web of Science, and Cochrane CENTRAL were searched from database inception to 31 January 2026. Records were screened in duplicate, and randomized controlled trials enrolling adults (≥18 years) undergoing oral tracheal intubation comparing a planned bougie-first strategy versus a planned stylet-first strategy were included. Random-effects meta-analyses pooled dichotomous outcomes as odds ratios (ORs) and continuous outcomes as mean differences (MDs).

Results: From 1,158 records, eight randomized controlled trials involving 2,578 participants were included. Trials spanned emergency department, emergency department/intensive care unit, intensive care unit, and operating room settings. First-attempt intubation success did not differ significantly between bougie-first and stylet-first techniques (OR 0.99, 95% CI 0.37–2.65; p = 0.980), with substantial heterogeneity (I^2 = 89.05%; p < 0.001). Bougie-first was associated with longer time to successful intubation (MD 21.84 seconds, 95% CI 5.55–38.14; p = 0.010), although heterogeneity was very high (I^2 = 97.37%; p < 0.001). There were no significant differences in more than one attempt (OR 0.91, 95% CI 0.21–3.91; p = 0.900), esophageal intubation (OR 0.48, 95% CI 0.17–1.40; p = 0.180), pulmonary aspiration (OR 1.47, 95% CI 0.57–3.75; p = 0.420), or postoperative sore throat (OR 1.10, 95% CI 0.48–2.52; p = 0.830).

Conclusion: Current randomized evidence did not demonstrate a consistent difference in first-attempt intubation success between bougie-first and stylet-first tracheal intubation in adults. Bougie-first was associated with longer intubation time, but this finding should be interpreted cautiously because of very high heterogeneity and variable timing definitions. Major airway-related complications and postoperative sore throat did not differ significantly between groups.

Keywords: Airway management; Bougie; Randomized controlled trial; Stylet; Tracheal intubation

Introduction

Securing the airway is central to anesthesia, emergency medicine, and intensive care, where delays or failed tracheal

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intubation can rapidly lead to hypoxemia and preventable morbidity. Contemporary difficult-airway guidance therefore emphasizes structured preparation and the use of adjuncts that improve first-attempt success while minimizing harm.[1] This focus is clinically important because multiple intubation attempts are consistently associated with higher rates of peri-intubation adverse events, including severe complications in emergency airway management.[2] In everyday practice, two common and relatively low-cost adjunct strategies are the use of a tracheal tube introducer ("bougie-first") and an endotracheal tube preloaded with a stylet ("stylet-first"). However, practice patterns vary widely across operators, devices, laryngoscopy modalities, and clinical environments.

Randomized evidence comparing these techniques remains mixed. In a single-center emergency department trial, bougie-first intubation increased first-attempt success compared with stylet-first intubation,[3] whereas a large multicenter trial in critically ill adults did not demonstrate a significant difference between the two strategies.[4] More recent randomized trials in settings such as hyperangulated videolaryngoscopy, anticipated difficult airway, and intensive care suggest that device- and context-specific effects may influence comparative performance.[5] A recent systematic review and meta-analysis concluded that bougie use may improve first-attempt success overall, but it also highlighted substantial heterogeneity and included both randomized and observational studies with variable outcome definitions.[6] Consequently, uncertainty persists regarding the comparative effectiveness, procedural efficiency, and safety of bougie-first versus stylet-first techniques when evidence is restricted to randomized trials.

Accordingly, this systematic review and meta-analysis aimed to compare bougie-first versus stylet-first tracheal intubation in adults. The primary outcome was first-attempt intubation success. Secondary outcomes included more than one intubation attempt, intubation time, and airway-related complications, including esophageal intubation, pulmonary aspiration, postoperative sore throat, and narratively summarized hypoxemia-related outcomes.

Material and Methods

Protocol and Registration

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline. The protocol was developed a priori and registered in PROSPERO (CRD420261298317). As this study synthesized data from previously published reports and did not involve the collection of individual identifiable data, institutional ethical approval and informed consent were not required.

Search Strategy

A comprehensive literature search was conducted in PubMed/MEDLINE, Scopus, Web of Science, and Cochrane CENTRAL from database inception to 31 January 2026. The search strategy combined controlled vocabulary, including MeSH terms where applicable, and free-text terms related to tracheal intubation and airway adjuncts. Core concepts included tracheal or endotracheal intubation, bougie or tracheal tube introducer, stylet, and randomized

trials. Reference lists of eligible trials and relevant review articles were manually screened to identify additional studies. The complete database-specific search strategies are provided in Supplementary Table S1.

Eligibility Criteria

Eligibility was defined using the PICO framework. We included randomized controlled trials enrolling adult patients (≥18 years) undergoing oral tracheal intubation in any clinical setting, including the emergency department, intensive care unit, or operating room. The intervention was a bougie-first strategy, defined as planned use of a bougie or tracheal tube introducer as the primary adjunct on the first intubation attempt. The comparator was a stylet-first strategy, defined as planned use of an endotracheal tube preloaded with a stylet on the first attempt. The primary outcome was first-attempt tracheal intubation success. Secondary outcomes included more than one intubation attempt, intubation time, and airway-related complications, including esophageal intubation, pulmonary aspiration, postoperative sore throat, and hypoxemia-related outcomes. Studies were excluded if they enrolled pediatric populations, were conducted only in simulation/manikin or animal models, did not directly compare bougie-first versus stylet-first techniques, or did not provide extractable outcome data.

Screening Process

All retrieved records were imported into a reference manager, and duplicates were removed. Two reviewers independently screened titles and abstracts, followed by full-text assessment of potentially eligible articles. Disagreements were resolved through discussion and, when required, adjudication by a third reviewer. The selection process and reasons for full-text exclusion were documented in a PRISMA flow diagram.

Data Extraction

Two reviewers independently extracted data using a piloted standardized extraction form. Extracted information included study characteristics (author, year, country, and clinical setting), participant characteristics (sample size, age, and sex), airway context, intervention and comparator details, bougie type, stylet details, and laryngoscopy method. Airway context included anticipated or predefined difficult airway criteria when reported, and laryngoscopy modality was categorized as direct laryngoscopy, non-hyperangulated videolaryngoscopy, or hyperangulated videolaryngoscopy where applicable. For dichotomous outcomes, event and non-event counts were extracted for each treatment group. For continuous outcomes, means and standard deviations were extracted when available.

For studies reporting continuous outcomes as median and interquartile range, the mean and standard deviation were estimated using the method described by Wan et al.[7] Specifically, when the median, first quartile (Q1), and third quartile (Q3) were available, the mean was approximated as (Q1 + median + Q3) / 3, and the standard deviation was approximated as (Q3 − Q1) / 1.35. These converted estimates were used only for quantitative synthesis and were considered in sensitivity interpretation.

For outcomes reported using multiple categories of attempts, data were harmonized by dichotomizing the outcome as more than one attempt versus one attempt. When first-attempt success was not explicitly labelled but could be derived from reported attempt categories, the corresponding one-attempt success count

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was extracted. For example, first-attempt success in Thevar Manoharan et al. was derived from the reported distribution of intubation attempts.

For multi-arm trials involving more than one bougie arm and one stylet arm, relevant bougie arms were combined into a single bougie-first group to avoid selective arm inclusion and double-counting of the shared stylet comparator. In Kumar et al., the preloaded bougie and standard bougie groups were combined into one bougie-first group for the main analysis, while the stylet-guided group was retained as the comparator. For continuous outcomes from combined bougie arms, pooled means and standard deviations were calculated using standard formulas based on group sample size, mean, and standard deviation.

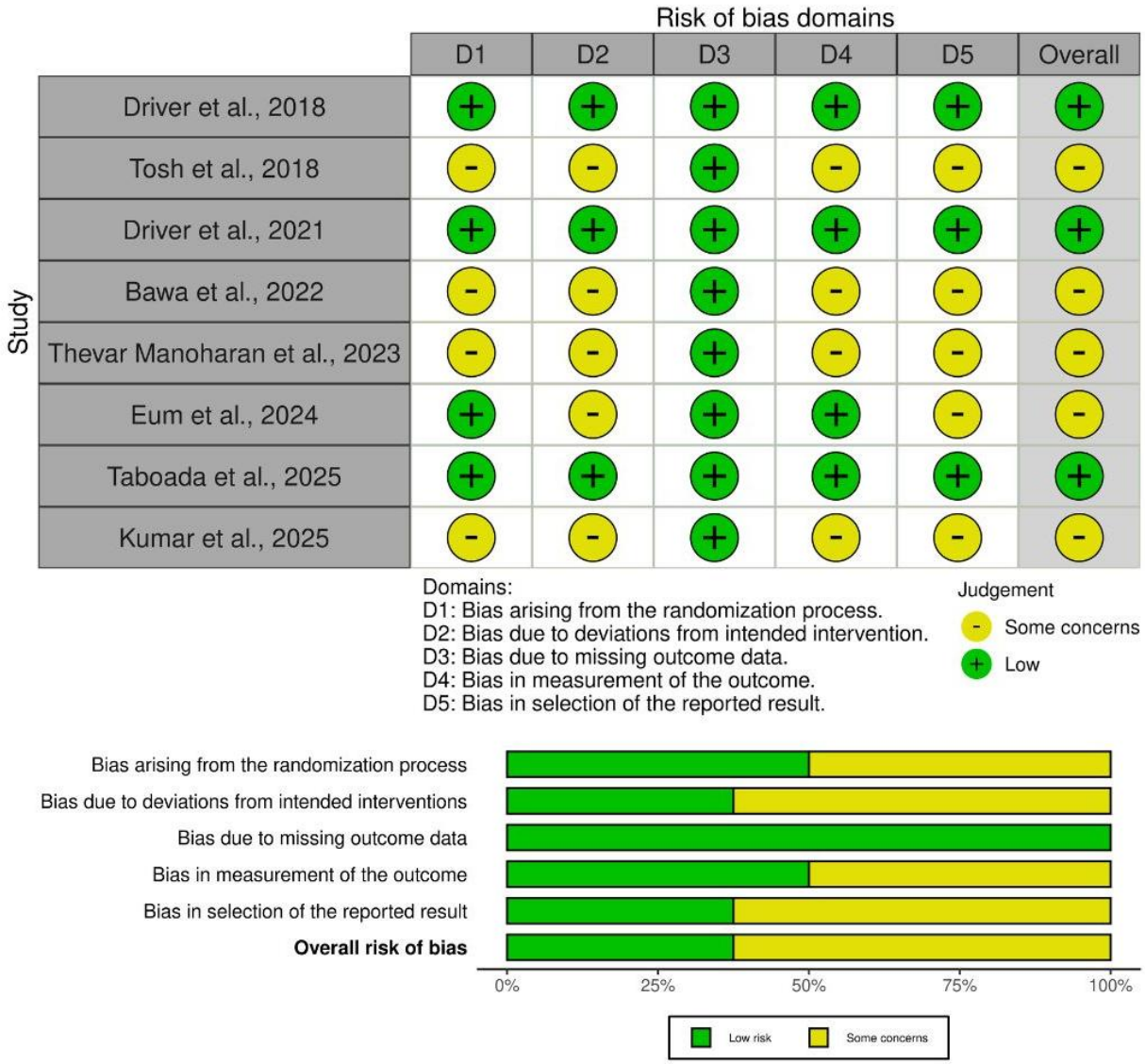

Figure 1. Outcome-level risk of bias assessment of the included studies using the Cochrane Risk of Bias 2 (RoB 2.0) tool, with primary emphasis on first-attempt intubation success and additional consideration of key secondary outcomes.

Definitions of intubation time were extracted as reported by each study, including the start and end points used for timing. Because intubation time was not fully harmonized across trials, with some studies measuring time from induction and others measuring time from laryngoscope insertion or device insertion to successful intubation, this outcome was analyzed as an exploratory secondary procedural outcome and interpreted cautiously. Residual methodological heterogeneity in timing definitions was addressed in the interpretation of findings.

Hypoxemia-related outcomes were extracted when reported. Because definitions and measurement windows varied across trials, including study-defined hypoxemia, desaturation, oxygen saturation <90%, and severe hypoxemia <80%, these outcomes were not pooled quantitatively. Instead, they were summarized narratively as clinically important airway-related safety outcomes.

Risk of Bias Assessment

Risk of bias was assessed using the Cochrane Risk of Bias 2 (RoB 2.0) tool by two independent reviewers. Assessment was performed at the outcome level, with primary emphasis on first-attempt intubation success and additional consideration of key secondary outcomes, including intubation time and airway-related complications. The following domains were evaluated: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Each domain was judged as low risk, some concerns, or high risk, and an overall judgment was assigned according to RoB 2 guidance. Disagreements were resolved by consensus.

Synthesis of Results

Meta-analysis was conducted when at least two studies reported an outcome with sufficiently comparable definitions. Dichotomous outcomes were pooled as odds ratios (ORs) with 95% confidence intervals (CIs). To improve clinical interpretability, crude event rates were also reported for the primary outcome alongside the pooled OR. Risk ratios or absolute risk differences were considered descriptively where appropriate, but ORs were retained as the primary pooled effect measure for consistency across dichotomous outcomes. Continuous outcomes were pooled as mean differences (MDs) with 95% CIs when measured in the same unit. Random-effects models were used because clinical and methodological heterogeneity was anticipated across settings, devices, airway contexts, and operator factors. Analyses were performed in Stata (StataCorp, College Station, TX, USA) using a random-effects model with restricted maximum likelihood (REML) estimation for between-study variance (τ^2). Statistical heterogeneity was assessed using Cochran's Q and the I^2 statistic, with τ^2 reported where applicable. An I^2 value ≥50% was considered indicative of substantial heterogeneity.

For rare binary outcomes, studies with zero events in one arm were retained using a continuity correction of 0.5. Studies with zero events in both arms, if present, were not included in odds-ratio pooling but were considered in narrative interpretation. Because rare-event analyses may be sensitive to sparse data and model assumptions, pooled estimates for complications were interpreted cautiously alongside absolute event counts.

Although more than one attempt is conceptually related to first-attempt success, it was retained as a secondary procedural outcome because repeated laryngoscopy attempts represent a clinically relevant escalation endpoint and were reported as attempt categories in several trials. For postoperative sore throat, when multiple postoperative time points were reported, the earliest routinely reported postoperative assessment was extracted for quantitative synthesis.

To further explore clinical and methodological heterogeneity, exploratory subgroup assessment was planned according to clinical setting (ED/ICU vs operating room), laryngoscopy modality (direct or non-hyperangulated laryngoscopy vs hyperangulated videolaryngoscopy), airway difficulty profile (anticipated or predefined difficult airway vs general or unselected population), and bougie type (standard bougie, preloaded bougie, or flexible-tip bougie). Because the number of included studies was limited and the distribution across subgroup categories was uneven, formal subgroup-specific pooled estimates were not generated. These assessments were therefore interpreted qualitatively and considered hypothesis-generating.

For the primary outcome, robustness and heterogeneity were further explored using leave-one-out influence analysis and visual diagnostics, including Galbraith and L'Abbé plots. Potential small-study effects were assessed visually using funnel plots for the primary outcome and interpreted cautiously because fewer than ten studies were included. No formal certainty-of-evidence assessment using GRADE was performed; therefore, findings were described in terms of imprecision, heterogeneity, and limited evidence rather than formal certainty ratings. A two-sided p value <0.05 was considered statistically significant.

Results

Literature Search Result

A total of 1,158 records were identified through database searching (PubMed, n = 412; Scopus, n = 356; Web of Science, n = 296; Cochrane CENTRAL, n = 94). After removal of 318 duplicates, 840 unique records were screened by title and abstract, of which 771 were excluded. Sixty-nine reports were sought for full-text retrieval; three reports could not be retrieved, leaving 66 reports assessed for eligibility. Of these, 58 were excluded for the following reasons: non-randomized design (n = 21), no direct bougie versus stylet comparison (n = 14), ineligible population (pediatric/simulation/animal; n = 9), outcomes not extractable (n = 8), and duplicate or overlapping data (n = 6). Ultimately, eight randomized controlled trials met the inclusion criteria and were included in the qualitative synthesis and quantitative meta-analysis (Figure 2).

Study Characteristics

Across eight randomized controlled trials, a total of 2,578 participants were included to compare bougie-first versus stylet-first tracheal intubation. The included studies were published between 2018 and 2025 and were conducted across diverse clinical settings, including the emergency department, mixed emergency department/intensive care unit environments, intensive care units, and operating rooms. Overall, the included trials were multinational, involving studies from the United States, India, South Korea, and Spain. Sample sizes ranged from small single-center studies to large pragmatic trials. Mean participant age was broadly

comparable between treatment arms within individual trials, with mean ages spanning approximately the late 30s to late 60s across studies. Outcomes reported across trials commonly captured procedural performance, including first-attempt intubation success, number of attempts, and intubation time, as well as safety endpoints such as hypoxemia, esophageal intubation, pulmonary aspiration, postoperative sore throat, dysphagia, and hoarseness (Table 1).

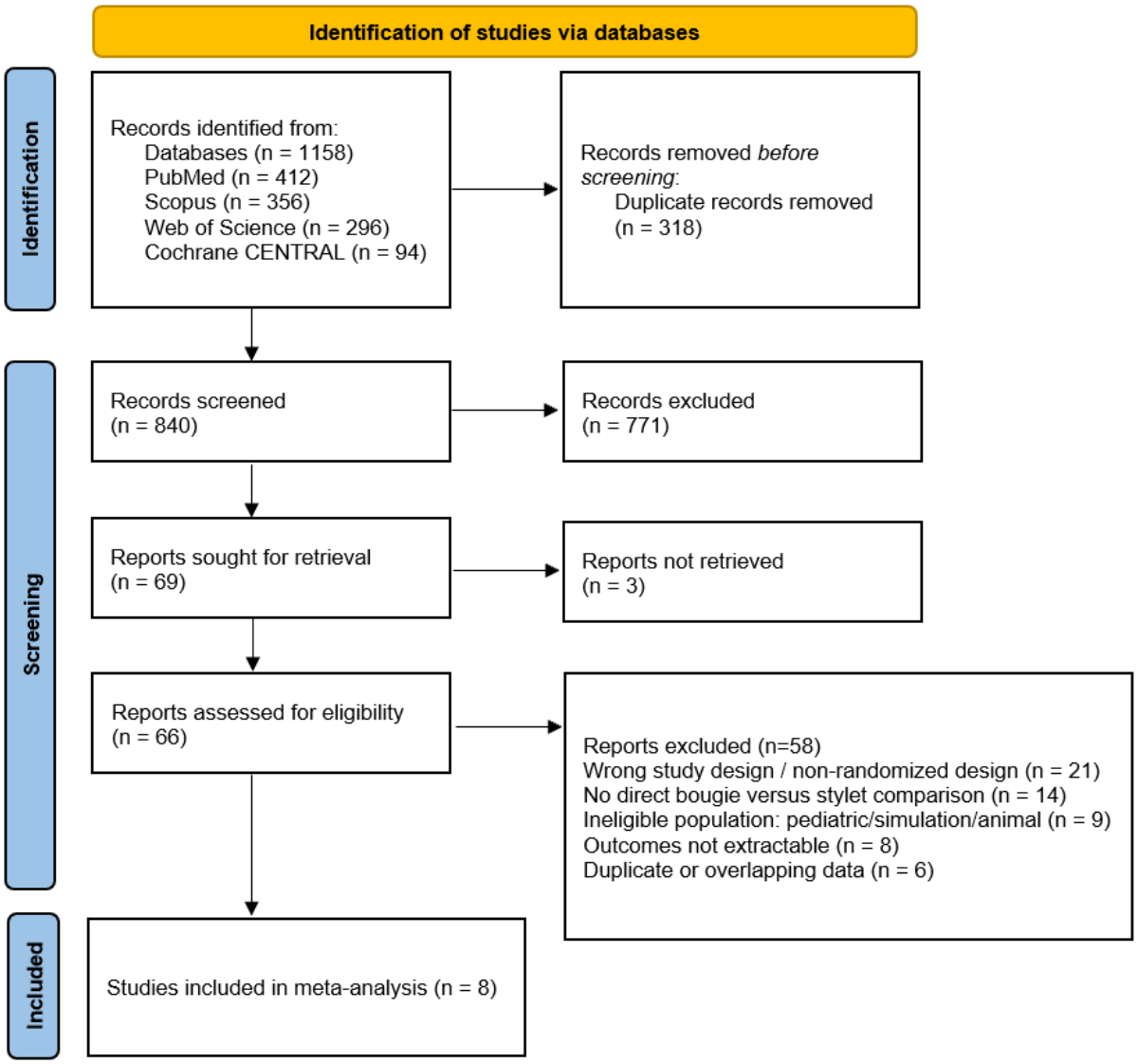

Figure 2. PRISMA Flow Diagram Showing the Results of The Database Search

For Kumar et al., which included two bougie arms and one stylet arm, the preloaded bougie and standard bougie groups were combined into a single bougie-first group for the meta-analysis. For Thevar Manoharan et al., first-attempt intubation success was derived from the reported distribution of intubation attempts.

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Table 1. Characteristics of included randomized controlled trials comparing bougie-first versus stylet-first tracheal intubation.

No	Study	Country	Type of Study	Sample Size		Mean Age (SD)		Outcomes
				Bougie	Stylet	Bougie	Stylet	
1	Driver et al., 2018 [3]	United States	Single-center randomized clinical trial (ED)	381	376	46 (18)	46 (18)	First-attempt intubation success; first-attempt duration; and hypoxemia.
2	Tosh et al.,2018 [8]	India	Randomized controlled trial (OR, RSI)	35	35	40.1 (14.4)	42.2 (14.8)	Ease/difficulty of intubation; loss of airway; hemodynamic responses; intubation time; and number of attempts.
3	Driver et al.,2021 [4]	United States	Multicenter randomized clinical trial (ED/ICU)	556	546	56.3 (20)	56.3 (17)	First-attempt intubation success; and incidence of severe hypoxemia.
4	Bawa et al.,2022 [9]	India	Randomized controlled trial (OR, RSI)	50	50	37.34 (NR)	41.12 (NR)	Time to intubation; number of attempts; hemodynamic responses; airway trauma; and other complications.
5	Thevar Manoharan et al.,2023 [10]	India	Prospective randomized controlled trial (OR, simulated difficult airway)	24	24	40.33 (13.83)	41.96 (11.34)	Ease/difficulty of intubation; time to intubation; number of attempts; and hemodynamic responses.
6	Eum et al.,2024 [5]	South Korea	Randomized controlled trial (OR, elective, videolaryngoscopy)	83	83	52 (16.1)	53 (15.4)	First-attempt intubation success; second- and third-attempt success; intubation time; and postoperative airway symptoms (sore throat, dysphagia, hoarseness).
7	Taboada et al.,2025 [11]	Spain	Prospective randomized controlled trial (ICU)	70	70	68 (13)	68 (13)	First-attempt intubation success; number of attempts; intubation difficulty; and complications.
8	Kumar et al.,2025 [12]	India	Randomized controlled trial (OR, elective) Three-arm RCT; preloaded and standard bougie arms combined for meta-analysis.	130	65	37.91 (13.11)	34.63 (13.82)	Time to successful intubation; number of attempts; need for adjunct airway maneuvers; hemodynamic responses; and incidence/severity of postoperative sore throat (POST).

Primary Outcome – First-Attempt Intubation Success

Eight randomized trials contributed data to the primary analysis of first-attempt intubation success (Figure 3a). Individual trial effects were highly variable, with some trials favoring bougie-first and others favoring stylet-first. The pooled random-effects analysis showed no significant difference between bougie-first and stylet-first techniques for first-attempt intubation success (OR 0.99, 95% CI 0.37–2.65; p = 0.980). Statistical heterogeneity was substantial (I^2 = 89.05%; Q = 63.94; p < 0.001), indicating considerable between-study variability.

The funnel plot for the primary outcome (Figure 3b) was interpreted cautiously because fewer than ten studies were included. Visual inspection suggested variability around the pooled estimate, but the small number of studies precluded reliable assessment of publication bias or small-study effects. Leave-one-out sensitivity analysis (Figure 3c) did not identify a single study that fully explained the heterogeneity or materially changed the overall non-significant conclusion. In absolute terms, first-attempt intubation success occurred in 1,139 of 1,329 patients in the bougie-first group and 1,062 of 1,249 patients in the stylet-first group, corresponding to crude event rates of 85.7% and 85.0%, respectively.

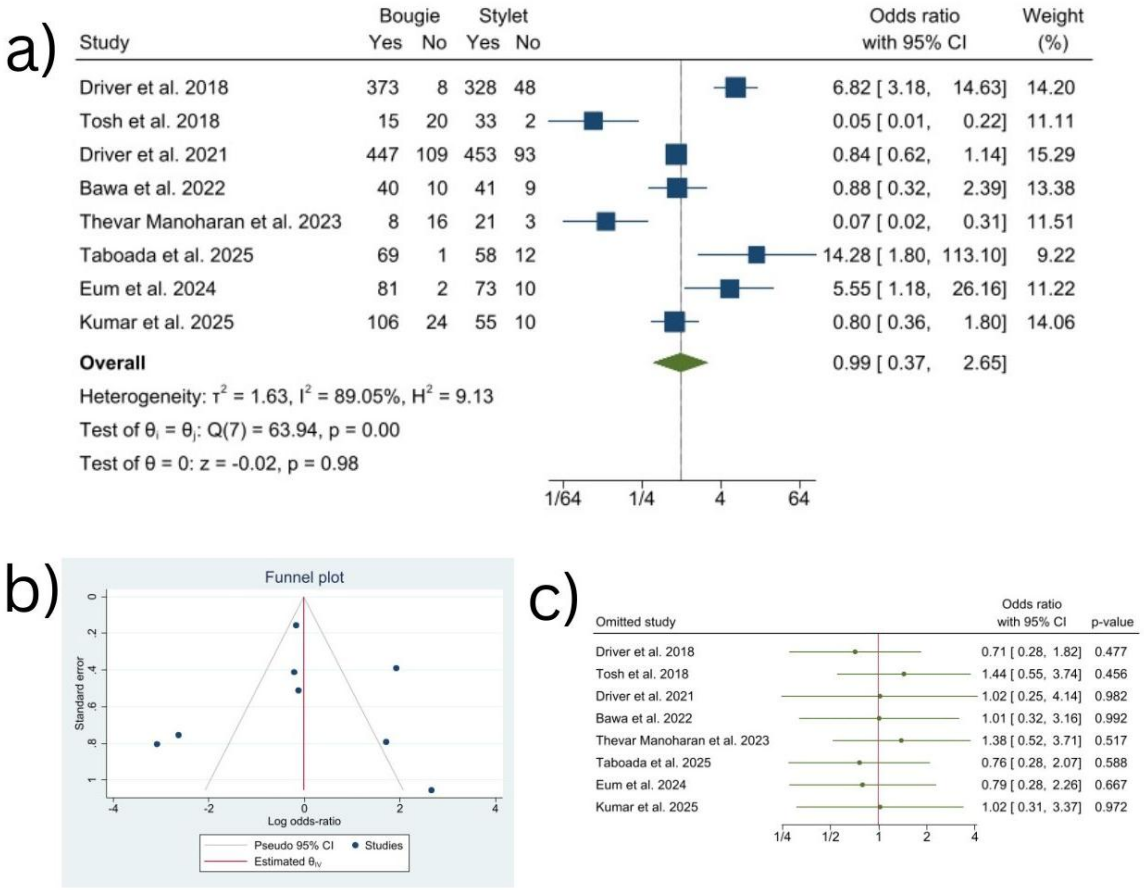

Figure 3. First-attempt intubation success comparing bougie-first versus stylet-first techniques: (a) random-effects forest plot (odds ratios); (b) funnel plot for small-study effects; and (c) leave-one-out sensitivity analysis.

Exploratory Heterogeneity Analyses

Exploratory subgroup assessment was conducted qualitatively according to clinical setting, laryngoscopy modality, airway difficulty profile, and bougie type where data were available. Because of the small number of trials and the uneven distribution of studies across subgroup categories, formal subgroup-specific pooled estimates were not generated. The observed variability suggested that between-study heterogeneity was likely multifactorial and context-dependent, while leave-one-out analysis did not identify any single study as the main driver of heterogeneity.

Secondary Outcomes - Procedural

Five randomized trials reported the need for more than one intubation attempt (Figure 4a). The pooled analysis showed no significant difference between bougie-first and stylet-first techniques in the likelihood of requiring more than one attempt (OR 0.91, 95% CI 0.21–3.91; p = 0.900). Between-study heterogeneity was substantial (I^2 = 84.61%; Q = 25.99; p < 0.001), suggesting that trial-level effects varied considerably across clinical settings, airway difficulty profiles, and procedural approaches.

Five trials contributed data to the analysis of intubation time (Figure 4b). Bougie-first was associated with a longer time to successful intubation compared with stylet-first (MD 21.84 seconds, 95% CI 5.55–38.14; p = 0.010). However, heterogeneity was very high (I^2 = 97.37%; Q = 151.91; p < 0.001). Because timing definitions differed across trials, including differences in whether timing started from induction, laryngoscope insertion, or device insertion, this finding was interpreted as an exploratory procedural result rather than a fully harmonized endpoint.

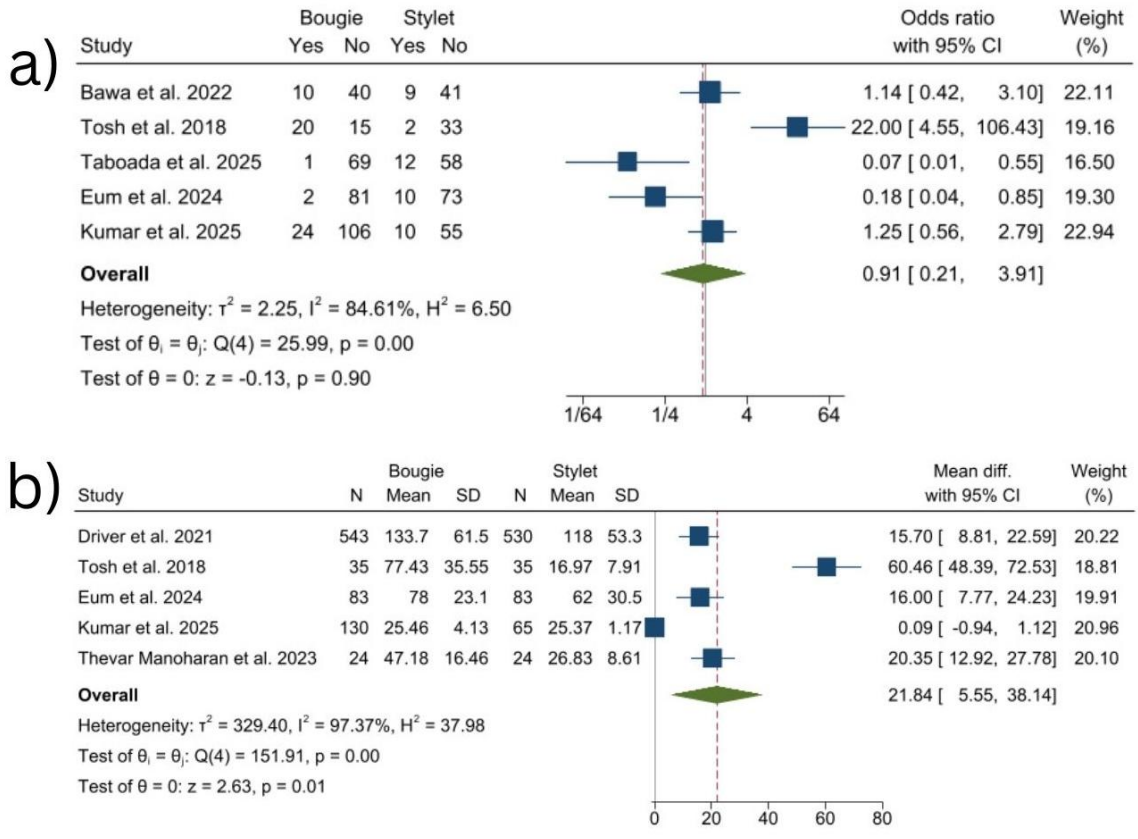

Figure 4. Secondary procedural outcomes comparing bougie-first versus stylet-first techniques: (a) more than one intubation attempt and (b) intubation time.

Secondary Outcomes - Complications

Four randomized trials reported esophageal intubation as an adverse event (Figure 5a). The pooled analysis showed no significant difference between bougie-first and stylet-first techniques (OR 0.48, 95% CI 0.17–1.40; p = 0.180). Statistical heterogeneity was negligible (I^2 = 0.00%; Q = 1.59; p = 0.660), although the estimate remained imprecise because of the low number of events.

Three trials reported pulmonary aspiration (Figure 5b). There was no significant difference between bougie-first and stylet-first techniques (OR 1.47, 95% CI 0.57–3.75; p = 0.420), with no observed heterogeneity (I^2 = 0.00%; Q = 1.32; p = 0.520). Given the low event rates, this estimate should be interpreted cautiously.

Three operating room–based trials reported postoperative sore throat (Figure 5c). The pooled analysis showed no significant difference between bougie-first and stylet-first techniques (OR 1.10, 95% CI 0.48–2.52; p = 0.830). Heterogeneity was substantial (I^2 = 71.92%; Q = 7.12; p = 0.030), likely reflecting differences in bougie design, postoperative assessment timing, and outcome ascertainment.

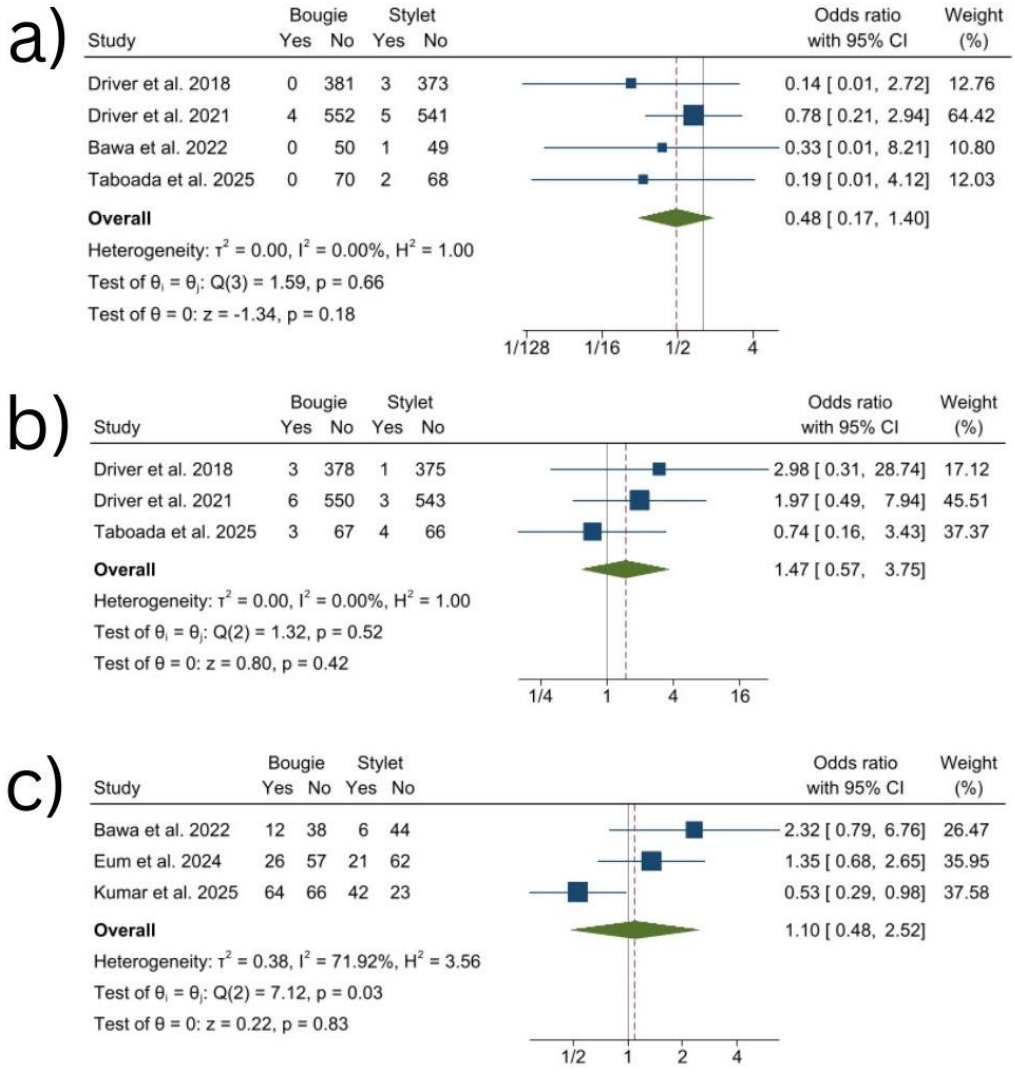

Figure 5. Airway-related complications comparing bougie-first versus stylet-first techniques: (a) esophageal intubation, (b) pulmonary aspiration, and (c) postoperative sore throat.

Discussion

Primary Outcome – First-Attempt Intubation Success

This systematic review and meta-analysis synthesized randomized evidence comparing bougie-first versus stylet-first tracheal intubation in adults. First-attempt intubation success was selected as the primary outcome because it is a clinically meaningful endpoint in airway management, where repeated laryngoscopy attempts are associated with higher rates of peri-intubation adverse events.[1,2] In the pooled analysis, bougie-first did not significantly improve first-attempt intubation success compared with stylet-first intubation. However, the substantial heterogeneity indicates that the pooled estimate should not be interpreted as evidence of a uniform effect across all clinical settings.

The heterogeneity observed in the primary outcome likely reflects clinically meaningful differences among included trials. The included studies varied by clinical setting, airway difficulty profile, laryngoscopy modality, bougie design, and operator workflow. This is illustrated by the contrast between the BEAM trial, which showed improved first-attempt success with bougie-first intubation in emergency department patients with at least one difficult airway characteristic, and the BOUGIE trial, which did not demonstrate a significant difference among critically ill adults undergoing emergency tracheal intubation.[3,4] More recent trials in hyperangulated videolaryngoscopy and difficult airway settings further suggest that the comparative effect of bougie-first versus stylet-first techniques may depend on the device used and the airway context.[5,11,12] These findings suggest that bougie-first intubation should be viewed as a context-dependent strategy rather than a universal default approach. A bougie may be advantageous when the glottic view is limited, the tube trajectory is difficult, or a hyperangulated blade creates a mismatch between glottic visualization and tube passage. Conversely, stylet-first intubation may perform similarly in settings where operators are highly familiar with stylet-guided tube shaping or where laryngoscopy conditions are optimized. This interpretation is consistent with previous meta-analytic evidence showing variable effects of bougie use across clinical contexts. [6,13,14]

Secondary Outcomes - Procedural

The need for more than one intubation attempt did not differ significantly between bougie-first and stylet-first techniques. Although this outcome is closely related to first-attempt success, it remains clinically relevant because repeated attempts represent escalation of airway manipulation and may increase the risk of complications.[2] The absence of a significant difference in this outcome supports the interpretation that neither strategy consistently reduces the need for additional attempts across heterogeneous adult intubation settings.

Bougie-first intubation was associated with a longer intubation time compared with stylet-first intubation. However, this finding should be interpreted cautiously because heterogeneity was very high and timing definitions differed across trials. Some studies measured intubation time from induction, whereas others measured time from laryngoscope insertion, device insertion, or confirmation of successful intubation.[4,5,8,10,12] These differences in timing anchors limit direct comparability

across studies and suggest that intubation time should be interpreted as an exploratory procedural endpoint rather than a fully harmonized outcome.

The clinical significance of longer intubation time is context-dependent. In critically ill patients with limited apnea tolerance, even modest delays may be important. In contrast, in elective operating room settings with adequate preoxygenation and controlled conditions, a short increase in procedural time may be less clinically consequential if intubation remains successful and safe. These findings highlight that both bougie-first and stylet-first techniques require adequate operator training, and institutional airway algorithms should incorporate competency in both adjuncts rather than relying on a single universal strategy.[1]

Secondary Outcomes - Complications

Major airway-related complications were uncommon across included trials. The pooled analyses did not show significant differences between bougie-first and stylet-first techniques for esophageal intubation or pulmonary aspiration. However, because event rates were low, these estimates were imprecise and should be interpreted cautiously. The absence of a statistically significant difference should not be interpreted as definitive equivalence, particularly because the included trials were not primarily powered to detect rare but clinically important airway complications.

Postoperative sore throat also did not differ significantly between techniques in the updated pooled analysis. Nevertheless, heterogeneity was substantial, likely reflecting differences in bougie type, stylet technique, cuff pressure control, postoperative assessment timing, and outcome ascertainment. Postoperative sore throat is clinically relevant for patient comfort, but its interpretation may differ between elective operating room studies and emergency or intensive care intubation settings.[5,9,12]

Hypoxemia was considered an important safety outcome, but it was not pooled quantitatively because definitions varied across trials. Reported thresholds included study-defined hypoxemia, desaturation, oxygen saturation <90%, and severe hypoxemia <80%, with different measurement windows across studies.[3,4,11] Therefore, hypoxemia-related outcomes were summarized narratively rather than combined as a single pooled endpoint.

Overall, the complication findings suggest no clear signal of increased major airway-related harm with either bougie-first or stylet-first intubation, but the evidence remains limited by sparse events, variable definitions, and heterogeneous clinical contexts. Large airway audits and systematic reviews of introducer-associated airway trauma emphasize that airway-related harm is uncommon but clinically important, and that standardized adverse-event reporting is needed to better interpret safety outcomes.[15,16]

Future Directions

Future research should prioritize adequately powered, pragmatic randomized trials with standardized outcome definitions across emergency department, intensive care unit, and operating room settings. Studies should report first-attempt success, number of attempts, intubation time using clearly defined timing anchors, hypoxemia thresholds, and airway-related complications in a consistent manner. Further investigation is also needed to

evaluate effect modification by laryngoscopy modality, bougie design, stylet configuration, operator experience, and airway difficulty. These factors are likely to determine which adjunct provides the greatest benefit in specific clinical scenarios.

Conclusion

Current randomized evidence did not demonstrate a consistent overall difference in first-attempt intubation success between bougie-first and stylet-first tracheal intubation in adults. The likelihood of requiring more than one intubation attempt was also similar between techniques. Bougie-first intubation was associated with longer intubation time, but this finding should be interpreted cautiously because timing definitions varied across trials and heterogeneity was very high. Major airway-related complications, including esophageal intubation and pulmonary aspiration, did not differ significantly between groups, and postoperative sore throat was also not significantly different in the updated analysis. Overall, these findings suggest that bougie-first and stylet-first techniques should be considered context-dependent adjunct strategies rather than one universally superior approach.

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None reported.

Conflict of Interest

The author(s) report no conflict of interest.

Data Availability Statement

All data analyzed in this study were extracted from previously published articles. The extracted dataset used for the meta-analysis is available from the corresponding author upon reasonable request.

Author's Contributions

Conceptualisation: O.J.K.J., I.P.F.N. Methodology: O.J.K.J., G.B.S.P.N.O., R.F.N. Investigation: G.B.S.P.N.O., J.F.L., T.F.A., E.S.C. Data Curation: J.F.L., T.F.A. Formal Analysis: O.J.K.J. Writing – original draft: R.F.N. Writing – review & editing: O.J.K.J., I.P.F.N., G.B.S.P.N.O., R.F.N., J.F.L., T.F.A., E.S.C. Supervision: I.P.F.N. All authors have read and approved the final manuscript.

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SYSTEMATIC REVIEW

Phenylephrine Infusion for Preventing Hypotension in Obese Parturients Undergoing Caesarean Delivery: A Systematic Review

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Abstract

Introduction: Spinal anaesthesia-induced hypotension is common during caesarean delivery, and the optimal phenylephrine dosing strategy for obese parturients remains uncertain. This systematic review evaluated the efficacy and dosing regimens of prophylactic phenylephrine infusion in this population.

Material and Methods: PubMed, ScienceDirect, the Cochrane Library, and Scopus were searched for randomised controlled trials published from 2010 through 2025. Eligible studies included parturients with singleton pregnancies at ≥36 weeks of gestation, a body mass index ≥30 kg/m², and no major comorbidities. Phenylephrine infusion was compared with bolus regimens or alternative infusion doses. The primary outcome was maternal hypotension; secondary outcomes included reactive hypertension, maternal adverse effects, and neonatal outcomes. Risk of bias was assessed using Cochrane RoB 2, and findings were synthesised narratively because of clinical and methodological heterogeneity.

Results: Three randomised controlled trials involving 334 parturients were included. Phenylephrine infusion was associated with fewer hypotensive episodes than bolus administration, although the certainty of evidence was low. One dose-response trial reported preliminary ED_{50} and ED_{90} estimates of 0.42 and 0.68 μg/kg/min, respectively. Higher infusion doses were associated with more reactive hypertension, whereas bradycardia did not differ significantly across groups. Nausea, vomiting, and neonatal outcomes showed no consistent between-group differences.

Conclusion: The certainty of evidence was low for most outcomes, precluding firm conclusions about the efficacy and optimal dosing of phenylephrine infusion in obese parturients without major comorbidities. Reactive hypertension increased with higher infusion doses, whereas evidence for bradycardia and neonatal safety remained limited. Larger, standardised trials are needed, particularly in parturients with severe obesity or comorbidities.

Keywords: Anesthesia, Spinal; Cesarean Section; Hypotension; Obesity; Phenylephrine

Introduction

Spinal anaesthesia is frequently used for caesarean section in obese parturients. However, spinal anaesthesia-induced hypotension remains the most common complication, posing a risk of impaired placental perfusion, which might affect the fetal outcome. This occurs due to sympathetic blockage leading to venous dilatation, decreased venous return and reduced cardiac output, which further exacerbate aortocaval compression by the uterus.[1]

Obesity is a growing global health issue. As of 2022, obesity affected approximately 16% of adults worldwide.[2] Maternal obesity complicates up to 39 million pregnancies globally each year, with prevalence during pregnancy exceeding 60% in several countries.[3] Phenylephrine, an α-1 receptor agonist, is well established as a preventive treatment of intraoperative hypotension in caesarean surgery.[1] It is considered the first-line vasopressor used for obstetric anaesthesia.[4]

Although prophylactic phenylephrine infusion reduces hypotension, it may cause adverse effects such as reactive hypertension and reflex bradycardia.[5] International consensus guidance recommends prophylactic vasopressor administration during caesarean delivery but does not provide obesity-specific dosing recommendations.[6] A recent trial compared a fixed-rate phenylephrine infusion with rescue boluses in obese parturients but did not establish an optimal dosing strategy.[7] Existing reviews of obesity in pregnancy focus mainly on broad maternal and neonatal outcomes rather than vasopressor dosing.[3] Therefore, this systematic review evaluated the efficacy and dosing regimens of prophylactic phenylephrine infusion for preventing spinal anaesthesia-induced hypotension in obese parturients undergoing caesarean delivery.

Material and Methods

Study Design

This systematic review evaluated phenylephrine infusion for preventing hypotension and was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD420251139013). The completed PRISMA 2020 checklist is provided as Supplementary Material.

Literature Search

Three reviewers independently searched PubMed, ScienceDirect, the Cochrane Library, and Scopus for studies published from January 1, 2010, through the final search date. PubMed, ScienceDirect, and the Cochrane Library were last searched on July 14, 2025; Scopus was updated on September 2, 2025. The strategy combined Medical Subject Headings and free-text terms related to obesity, phenylephrine, hypotension, and caesarean delivery. Complete database-specific strategies, Boolean operators, publication-year limits, and search dates are provided in Supplementary Table 1.

No automated study-design or language filters were applied during the database searches. Eligibility was restricted to randomised controlled trials published in English during screening. Records were imported into Rayyan, and duplicates were removed. Two reviewers independently screened titles and abstracts, followed by full-text assessment of potentially eligible reports. Disagreements were resolved by discussion or consultation with a third reviewer. Reasons for full-text exclusion were recorded and are presented in the PRISMA 2020 flow diagram.

Eligibility Criteria

Eligible studies enrolled parturients undergoing caesarean delivery under spinal anaesthesia, restricted to singleton pregnancies at ≥36 weeks of gestation, a BMI ≥30 kg/m², and no hypertension,

preeclampsia, diabetes mellitus, or other specified comorbidities. The intervention was intravenous phenylephrine administered as a weight-based or fixed-rate infusion. The primary outcome was maternal hypotension. Additional haemodynamic outcomes included blood pressure trends and rescue vasopressor requirements. Only randomised controlled trials published in English were included. Studies were excluded if phenylephrine dosing was not clearly reported, the population included participants both below and above the BMI threshold without separate data, BMI was not reported, or participants had pre-existing comorbidities.

Data extraction and outcome measures

Three reviewers independently extracted data using a standardised form. Disagreements were resolved by consensus. When multiple publications reported the same trial, the most complete and recent report was retained. Extracted data included author, year, country, study design, sample size, baseline BMI, and phenylephrine dosing regimen.

The primary outcome was the incidence of maternal hypotension. Additional haemodynamic outcomes included blood pressure trends and rescue vasopressor use. Secondary outcomes, when reported, included bradycardia, reactive

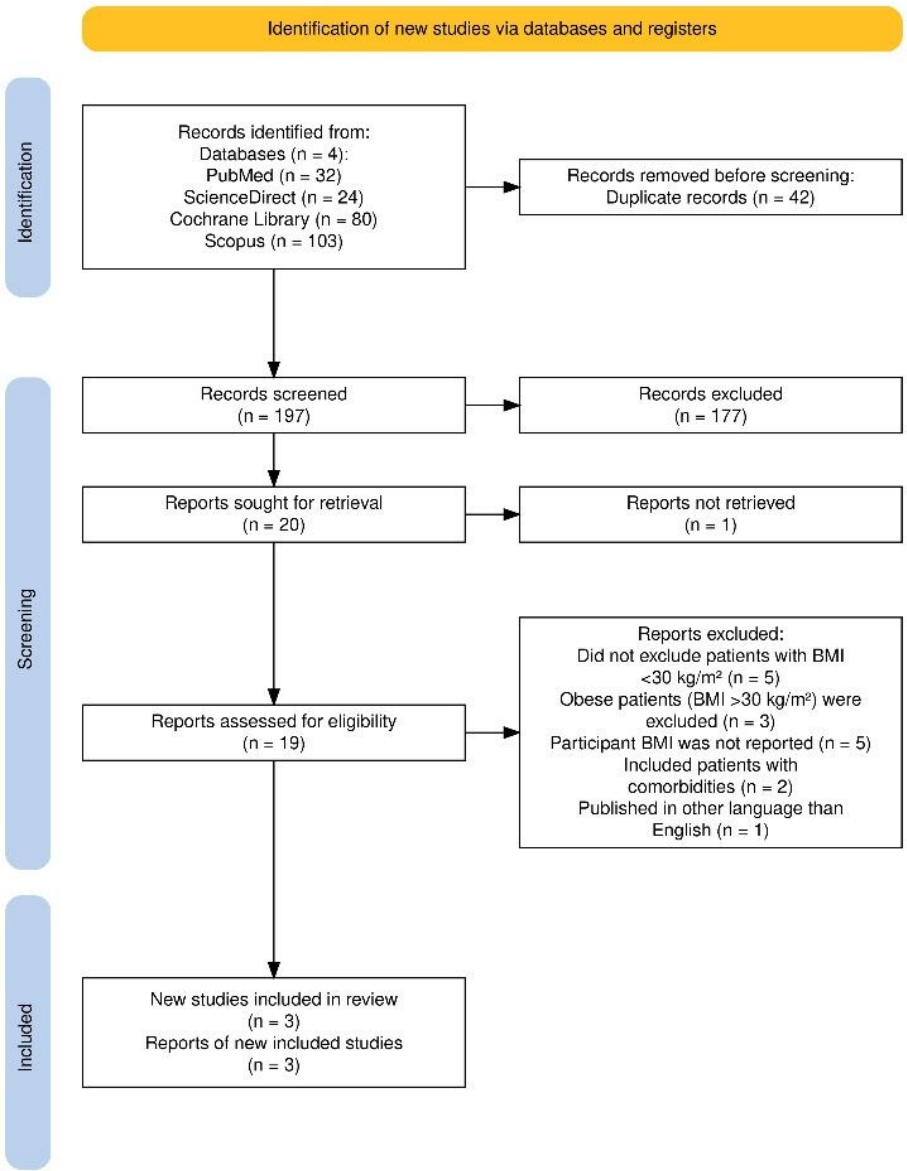

Figure 1. PRISMA Flowchart

hypertension, intraoperative nausea and vomiting, Apgar scores, and umbilical arterial pH.

Risk-of-bias assessment and data synthesis

Three reviewers independently assessed risk of bias using version 2 of the Cochrane Risk of Bias tool for randomised trials (RoB 2)[8]. The domains were bias arising from the randomisation process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of the reported result. Each study was rated as having a low risk of bias, some concerns, or a high risk of bias. A quantitative meta-analysis was considered but was not performed because only three studies were eligible and substantial clinical and methodological heterogeneity was present. Mean baseline BMI ranged from approximately 32 kg/m² in Xing et al. to 34 kg/m² in Hassan et al. and 41 kg/m² in George et al. The trials also differed in hypotension definitions, blood pressure monitoring intervals, fluid co-loading, spinal anaesthetic regimens, rescue vasopressor protocols, and outcome reporting (Table 1). Findings were therefore synthesised narratively.

Table 1. Methodological Heterogeneity Across Included Studies

Domain	Xing et al. 2024	Hassan et al. 2024	George et al. 2018
Mean BMI	~32 kg/m²	~34 kg/m²	~41 kg/m²
Hypotension definition	SBP <90 mmHg or <80% of baseline	Algorithm-based: SBP within 20% of baseline and >90 mmHg	SBP <90 mmHg or <80% of baseline
BP monitoring timing	Every 1 minute	Every 2 minutes	Every 1 minute (first 15 min), then every 2.5 minutes until delivery
Fluid co-loading	Crystalloid 5 mL/kg over ≥20 min	Not reported	Crystalloid bolus targeting 2 L before delivery
Spinal anaesthetic dose	Hyperbaric bupivacaine 10 mg + sufentanil 5 μg	Height-based hyperbaric bupivacaine + fentanyl 15 μg	Hyperbaric bupivacaine 12 mg + fentanyl 15 μg + morphine 150 μg
Rescue vasopressor protocol	Metaraminol bolus (not phenylephrine)	Phenylephrine rate-doubling + supplementary bolus	Phenylephrine rate-doubling + 100 μg bolus
Outcome reporting	Complete	Reactive hypertension not reported	Complete

Certainty of Evidence Assessment

The certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Results

Study selection

The database searches identified 239 records: PubMed (n=32), ScienceDirect (n=24), the Cochrane Library (n=80), and Scopus (n=103). After 42 duplicates were removed, 197 records underwent title and abstract screening, and 177 were excluded. Twenty reports were sought for retrieval; one could not be retrieved because the full text was unavailable. Nineteen reports underwent full-text assessment, of which three met all eligibility criteria. Sixteen reports were excluded because they included participants with BMI <30 kg/m² (n=5), excluded participants with BMI >30 kg/m² (n=3), did not report BMI (n=5), included participants with comorbidities (n=2), or were not published in English (n=1). The selection process is shown in Figure 1.

Risk of Bias Assessment

Two of the three studies were judged to have a low risk of bias across all RoB 2 domains. Hassan et al. was rated as having some concerns in Domain 3 because six participants were excluded after randomisation, with limited reporting of the reasons or whether exclusions were balanced between groups. Allocation concealment was adequate in all three trials, which used sequentially numbered, opaque envelopes opened by personnel not involved in patient management. George et al. reported blinding of participants, clinicians, and outcome assessors. Hassan et al. blinded participants and the anaesthesia team but did not report assessor blinding. Xing et al. described the study as double-blind in the Discussion but did not provide corresponding details in the Methods. Xing et al. had no post-randomisation exclusions, whereas Hassan et al. excluded 6 of 74 participants and George et al. assessed 178 participants for eligibility; 18 were excluded before randomisation, and the remaining 160 participants underwent randomisation and were included in the analysis. Prospective trial registration supported outcome prespecification in Xing et al. and George et al.; Hassan et al. did not report a registration number. The risk-of-bias summary is presented in Figure 2.

Characteristics of the Included Studies

Three randomised controlled trials contributed data from 334 parturients with BMI ≥30 kg/m² who underwent caesarean delivery and had no history of hypertension, diabetes mellitus, or preeclampsia. Definitions of hypotension differed across studies and used relative, absolute, or algorithm-based systolic blood pressure thresholds. Hassan et al. excluded six participants from the analysis because of missing data. Phenylephrine was administered as a fixed-rate infusion beginning at 50 μg/min or as one of four fixed weight-based doses (0.375, 0.5, 0.625, or 0.75 μg/kg/min). Comparators included rescue bolus administration or alternative infusion doses. Study characteristics and outcomes are summarised in Tables 2a and 2b.

Table 2a. Study Characteristics and Intervention

Author, Year	Country	Design	Sample Size	BMI (Mean ± SD)	PE Dose & Type	Comparator
Xing et al., 2024	China	RCT	100	32.1–32.4 (range across 4 dose groups)	PE infusion 0.375–0.75 μg/kg/min	Dose-response design (4 fixed dose)
Hassan et al., 2024	Malaysia	RCT	74 (68 analysed)	33.7 ± 3.3 (A), 34.5 ± 3.5 (B)	PE infusion 50–100 μg/min (Group A)	100 μg PE bolus (Group B)
George et al., 2018	Canada & USA	RCT	160	40.8 ± 4.2 (Inf), 41.1 ± 4.5 (Bolus)	PE infusion 50 μg/min (adjusted)	100 μg PE bolus

Table 2b. Maternal, Adverse Event, and Neonatal Outcomes

Author, Year	Hypotension	Reactive Hypertension	Adverse effects	Neonatal Outcomes
Xing et al., 2024	1) Dose-dependent reduction (52% → 0%, P<0.001) 2) ED_{50} 0.42, ED_{90} 0.68 μg/kg/min	Dose-dependent ↑ (0–40%)	No significant differences across dose groups for nausea/vomiting, shivering or bradycardia	Apgar 10/10, pH 7.29–7.32
Hassan et al., 2024	Lower mean SBP, DBP and MAP in bolus compared to infusion (P<0.01)	Not reported	No adverse effects reported.	Apgar 8/9 (both groups)
George et al., 2018	Lower incidence and fewer episodes with infusion (P<0.01)	More frequent pre-delivery with infusion (P=0.002); no difference in hypertensive episodes overall	1) Lower intraoperative nausea/vomiting (P<0.001); lower 0–2h postoperative vomiting (P=0.02); lower antiemetic use (P=0.04) with infusion; higher pruritus scores with infusion (1 vs 0, P=0.048) 2) No difference in 2–24h vomiting or post-delivery haemodynamic stability	Not reported

BMI : body mass indeks, DBP : diastolic blood pressure, MAP : mean arterial pressure, PE : phenylephrine, RCT : randomised controlled trial, SBP : systolic blood pressure

Table 3a. GRADE Summary of Findings Table : Prophylactic Phenylephrine Infusion Versus Rescue bolus

Outcome	Studies/participants	Main finding	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty
Maternal hypotension	1 RCT/160	Hypotension was less frequent with infusion	Not serious	Not assessable	Serious[1]	Not serious	Not strongly suspected[6]	⊕⊕⊕◯ Moderate
Maternal blood-pressure control	1 RCT/68	SBP, DBP, and MAP were better maintained with infusion	Serious[2]	Not assessable	Not serious	Serious[3]	Not strongly suspected[6]	⊕⊕◯◯ Low
Intraoperative nausea and vomiting	1 RCT/160	46% versus 75%; RR 0.61 (95% CI 0.47–0.80)	Not serious	Not assessable	Serious[1]	Not serious	Not strongly suspected[6]	⊕⊕⊕◯ Moderate
Vomiting within 2 hours after delivery	1 RCT/160	11% versus 25%; RR 0.44 (95% CI 0.21–0.90)	Not serious	Not assessable	Serious[1]	Serious[4]	Not strongly suspected[6]	⊕⊕◯◯ Low
Reactive hypertension	1 RCT/160	Pre-delivery reactive hypertension was more frequent with infusion	Not serious	Not assessable	Serious[1]	Serious[3]	Not strongly suspected[6]	⊕⊕◯◯ Low
Bradycardia	1 RCT/160	No significant between-group difference	Not serious	Not assessable	Serious[1]	Very serious[5]	Not strongly suspected[6]	⊕◯◯◯ Very low
Neonatal Apgar scores	1 RCT/68	No significant between-group difference	Serious[2]	Not assessable	Not serious	Very serious[5]	Not strongly suspected[6]	⊕◯◯◯ Very low

Table 3b. GRADE Summary of Findings Table : Comparison of Fixed Weight-Based Infusion Doses

Outcome	Studies/participants	Main finding	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty
Maternal hypotension and dose requirement	1 RCT/100	Hypotension decreased from 52% to 0% across increasing doses; ED_{50} 0.42 and ED_{90} 0.68 μg/kg/min	Not serious	Not assessable	Not serious	Serious[3]	Not strongly suspected[6]	⊕⊕⊕◯ Moderate
Reactive hypertension	1 RCT/100	Dose-dependent increase from 0% to 40%	Not serious	Not assessable	Not serious	Serious[3]	Not strongly suspected[6]	⊕⊕⊕◯ Moderate
Bradycardia, nausea, and vomiting	1 RCT/100	No significant differences across dose groups	Not serious	Not assessable	Not serious	Very serious[5]	Not strongly suspected[6]	⊕⊕◯◯ Low
Neonatal outcomes	1 RCT/100	Apgar scores and umbilical arterial pH were comparable	Not serious	Not assessable	Not serious	Very serious[5]	Not strongly suspected[6]	⊕⊕◯◯ Low

Legend: ⊕⊕⊕⊕ High, ⊕⊕⊕◯ Moderate, ⊕⊕◯◯ Low, ⊕◯◯◯ Very low

1. Downgraded for indirectness because George et al. predominantly included women with BMI >35–55 kg/m²; therefore, applicability to the broader BMI ≥30 kg/m² population is uncertain.
2. Downgraded because Hassan et al. excluded 6 of 74 participants after randomisation, with limited explanation regarding the missing data and group distribution.
3. Downgraded because the evidence came from one relatively small trial and did not provide a sufficiently precise pooled estimate.
4. Downgraded because the confidence interval remained compatible with effects ranging from a large to a relatively small benefit.
5. Downgraded by two levels because events were infrequent or absent and the study was not powered to exclude clinically important differences
6. Formal assessment of publication bias was not possible with only three included studies. No downgrade was applied because no specific evidence of publication bias was identified

Publication bias: not formally tested, as funnel-plot asymmetry testing requires a minimum of approximately 10 studies; reported as undetected given the small number of included trials (n=3).

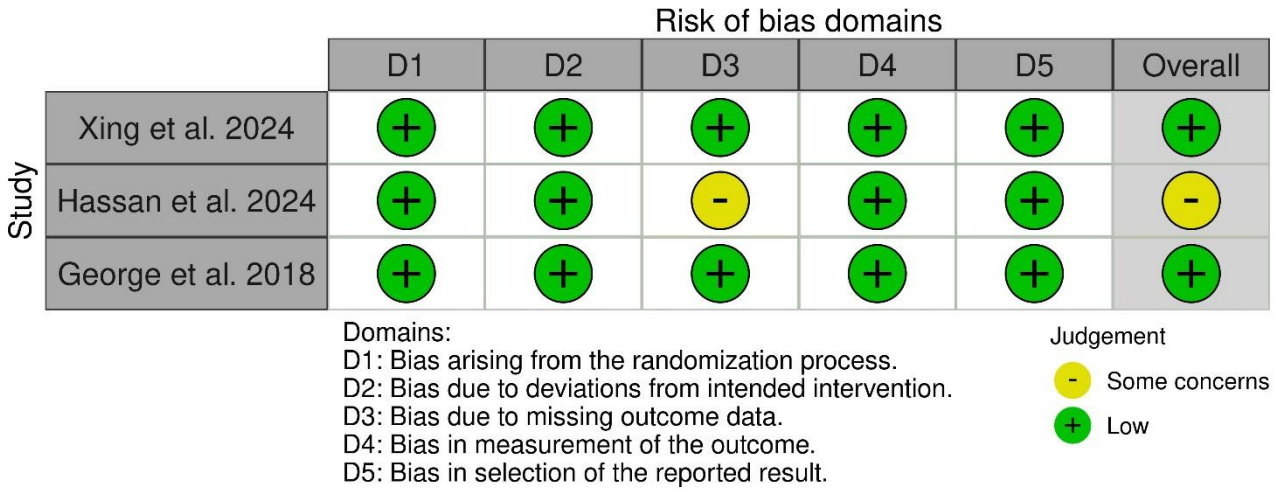

Figure 2. Quality assessment of the risk of bias assessment of 3 controlled trials

Effects of phenylephrine infusion

Xing et al. evaluated four phenylephrine infusion doses. Hypotension occurred in 52% of the 0.375 µg/kg/min group, 40% of the 0.5 µg/kg/min group, 20% of the 0.625 µg/kg/min group, and 0% of the 0.75 µg/kg/min group ($p<0.001$). The estimated ED_{50} and ED_{90} were 0.42 and 0.68 µg/kg/min, respectively.[4] These single-trial estimates should be regarded as preliminary pharmacological benchmarks rather than general dosing recommendations. Reactive hypertension increased with dose, reaching 40% in the 0.75 µg/kg/min group, whereas other adverse events did not differ significantly across groups.

Hassan et al. compared a prophylactic phenylephrine infusion starting at 50 µg/min with 100-µg rescue boluses. Systolic, diastolic, and mean arterial pressures were significantly higher in the infusion group ($p<0.05$). No adverse events were reported, and neonatal Apgar scores were comparable between groups.[7]

Across the included studies, phenylephrine infusion tended to reduce hypotensive episodes compared with bolus or control strategies, although certainty in the estimated benefit was limited. George et al. reported less intraoperative hypotension and fewer associated symptoms with phenylephrine infusion than with bolus administration. Intraoperative nausea and vomiting occurred in 46% versus 75% of participants, respectively ($p<0.001$). Post-delivery hypotension (7% vs 43%), intraoperative antiemetic use (26% vs 42%), and vomiting 0-2 h after delivery (11% vs 25%) were also less frequent with infusion. The infusion group had more pre-delivery reactive hypertension and higher pruritus scores, whereas post-delivery hypertension and bradycardia did not differ significantly.[9]

Discussion

International consensus guidance recommends prophylactic vasopressor administration for preventing spinal anaesthesia-induced hypotension during caesarean delivery, with phenylephrine remaining a widely used first-line agent.6 Across the included studies, haemodynamic outcomes generally favoured infusion over rescue bolus administration, although the magnitude and nature of benefit varied according to the dosing strategy.[7,9]

Safety comparisons were limited because Hassan et al. did not report reactive hypertension. In the dose-response trial,

hypotension decreased as the infusion dose increased (ED_{50} 0.42 μg/kg/min; ED_{90} 0.68 μg/kg/min), but reactive hypertension became more frequent at higher doses.[4]

Obesity-related cardiovascular and pharmacokinetic differences may contribute to variation in vasopressor response. Fixed-rate regimens are straightforward to administer but may not account for differences in body size, whereas weight-based regimens may provide more individualised dosing. Nevertheless, the ED_{50} and ED_{90} values reported by Xing et al. were derived from a single dose-response trial in parturients with a mean BMI of approximately 32 kg/m².[4] They should therefore not be interpreted as broadly applicable dosing recommendations. No included trial directly compared fixed-rate with weight-based infusion, so the relative advantages of these approaches remain uncertain.

Obesity may increase susceptibility to spinal anaesthesia-induced hypotension through several mechanisms. Greater abdominal mass and the gravid uterus increase intra-abdominal pressure and may aggravate inferior vena cava compression. Engorgement of the epidural venous plexus can reduce cerebrospinal fluid volume and intrathecal space, potentially promoting cephalad spread of spinal anaesthesia.[10]

Higher BMI is also associated with changes in cardiac output and vascular function that may increase variability in vasopressor response across obesity classes.[11] In addition, obesity increases the risk of chronic hypertension, preeclampsia, and gestational diabetes mellitus.[12,13]

George et al. similarly reported more pre-delivery reactive hypertension with a fixed-rate infusion of 50 μg/min.9 Hassan et al. found smaller reductions in diastolic and mean arterial pressures with infusion than with rescue boluses.[7]

An observational study found no difference in vasopressor requirements between participants with BMI <30 kg/m² and those with BMI 30-45 kg/m², but reported differences in hypotensive episodes, fluid administration, and phenylephrine requirements among participants with BMI >45 kg/m².14 The present review did not include sufficient data to determine whether phenylephrine requirements differ across obesity classes.

Maternal hypotension is an important contributor to intraoperative nausea and vomiting. George et al. reported less intraoperative nausea and vomiting and lower rescue antiemetic use with prophylactic infusion.[9] By contrast, Hassan et al. reported no adverse events with its infusion protocol, although adverse events were not the primary focus of that trial.[7] Bradycardia did not differ significantly between infusion and comparator groups in the trials that reported this outcome.[4,9]

Prolonged maternal hypotension may compromise uteroplacental perfusion and contribute to fetal acidosis. However, neonatal outcomes were reported in only two of the three included studies, and neither trial was adequately powered to establish neonatal equivalence.[4,7]

Fluid administration may also modify vasopressor requirements. Although this question was not directly evaluated by the included trials, a separate study found that crystalloid co-loading rates of 10 and 20 mL/kg/h produced different phenylephrine ED_{50} estimates, suggesting that fluid strategy should be considered when comparing dose requirements.[15]

Certainty of Evidence

The certainty of evidence was assessed separately for the comparison of prophylactic phenylephrine infusion versus rescue bolus administration and for comparisons among fixed weight-based infusion doses. These comparisons were not combined because they addressed different intervention questions. For infusion versus rescue bolus administration, the certainty was moderate for maternal hypotension and intraoperative nausea and vomiting, low for maternal blood-pressure control, early postoperative vomiting, and reactive hypertension, and very low for bradycardia and neonatal outcomes. For the dose-response comparison, moderate-certainty evidence supported a dose-dependent reduction in maternal hypotension accompanied by an increase in reactive hypertension. Evidence regarding bradycardia, nausea and vomiting, and neonatal outcomes was of low certainty because these outcomes were infrequent and the trial was not adequately powered to exclude clinically important differences. Publication bias could not be formally assessed because only three trials were included; however, no downgrade was applied in the absence of specific evidence suggesting publication bias.

Limitations

This review included only three randomised controlled trials, and substantial clinical and methodological heterogeneity precluded meta-analysis. Definitions of hypotension, infusion strategies, fluid protocols, spinal anaesthetic regimens, and outcome reporting differed across studies. The small evidence base also prevented formal assessment of publication bias.

Applicability is limited to obese parturients without major comorbidities. Evidence was insufficient for parturients with severe obesity (BMI ≥45 kg/m^2), chronic hypertension, preeclampsia, or gestational diabetes mellitus. Studies in preeclampsia suggest different vasopressor dose requirements from those in normotensive parturients[16,17], while non-obstetric diabetes studies cannot provide direct dosing guidance for pregnancy.[18,19] Fluid management was also not standardised and may have influenced phenylephrine requirements.[15]

Finally, restricting eligibility to English-language publications may have introduced language bias. These limitations require cautious interpretation of any proposed dosing range, particularly for high-risk subgroups.

Recommendations for Future Research

Future trials should determine prophylactic infusion requirements in parturients with severe obesity and directly compare fixed-rate with weight-adjusted regimens. Maternal outcomes should include hypotension, reactive hypertension, bradycardia, cardiac output, rescue vasopressor use, and nausea and vomiting; neonatal outcomes should include Apgar scores, umbilical arterial pH, and base excess.[4,7,9] Studies should also evaluate common comorbidities, particularly gestational diabetes and chronic hypertension. Standardised blood pressure targets, dosing units, fluid protocols, and core outcomes would improve comparability across trials.[6]

Conclusion

Current evidence is insufficient to define the optimal phenylephrine infusion

strategy for preventing hypotension in obese parturients because the certainty was low for most outcomes. Infusion generally improved haemodynamic control compared with rescue bolus administration, but reactive hypertension increased at higher doses. Bradycardia did not differ significantly, although estimates were imprecise. These findings apply only to obese parturients without major comorbidities. Larger, standardised randomised controlled trials are required before definitive dosing recommendations can be made.

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Conflict of Interest

The author(s) report no conflict of interest.

Data Availability Statement

All data analyzed in this study were extracted from previously published articles. The extracted dataset used for the meta-analysis is available from the corresponding author upon reasonable request.

Author's Contributions

Conceptualization: AA, SD. Methodology: AA, SD. Literature search: AA, FK, GH. Data curation: AA, FK, GH. Formal Analysis: AA, FK, GH. Writing – original draft: AA. Writing – review & editing: AA, FK, GH. Supervision: SD. All authors have read and approved the final version of the manuscript.

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Supplementary Table 1. Databases Search Strategies

Database	Keywords	Last Search
Pubmed	((((((obesity) OR (obese)) OR (bmi)) OR (body mass index)) AND (((phenylephrine[Title/Abstract]) OR (phenylephrine infusion[Title/Abstract])) OR (vasopressor[Title/Abstract]))) AND (((((((hypotension[Title/Abstract]) OR (blood pressure[Title/Abstract])) OR ("bradycardia"[Title/Abstract])) OR ("hypertension"[Title/Abstract])) OR ("hemodynamic stability"[Title/Abstract])) OR (nausea[Title/Abstract])) OR (vomiting[Title/Abstract]))) AND (((((((((cesarean section[Title/Abstract]) OR (caesarean section[Title/Abstract])) OR (cesarean delivery[Title/Abstract])) OR (spinal anesthesia[Title/Abstract])) OR (neuraxial block[Title/Abstract]))) OR ("pregnant"[Title/Abstract])) OR ("pregnancy"[Title/Abstract])) OR (c-section[Title/Abstract])) Filters**:** from 2010 - 2025	14th July 2025
Cochrane	“obesity” OR “obese” OR “BMI” OR “body mass index” and “phenylephrine” OR “phenylephrine infusion” OR “vasopressor” and hypotension OR blood pressure OR bradycardia OR hypertension OR hemodynamic stability OR nausea OR vomiting and “cesarean section” OR “caesarean section” OR “cesarean delivery” OR “spinal anesthesia” OR “neuraxial block” OR “pregnant” OR “pregnancy” OR “c-section” Filter applied: - Publication year: 2010–2025	14th July 2025
Scopus	(TITLE-ABS-KEY (obesity OR obese OR bmi OR "body mass index") AND TITLE-ABS-KEY (phenylephrine OR "phenylephrine infusion" OR vasopressor) AND TITLE-ABS-KEY (hypotension OR "blood pressure" OR bradycardia OR hypertension OR "hemodynamic stability" OR nausea OR vomiting) AND TITLE-ABS-KEY ("cesarean section" OR "caesarean section" OR "cesarean delivery" OR "spinal anesthesia" OR "neuraxial block" OR pregnant OR pregnancy OR "c-section"))	02nd September 2025

	AND (PUBYEAR > 2009 AND PUBYEAR < 2026)	
ScienceDirect	(obesity OR obese OR bmi OR "body mass index") AND (phenylephrine OR "phenylephrine infusion" OR vasopressor) AND (hypotension OR "blood pressure" OR bradycardia OR hypertension OR "hemodynamic stability" OR nausea OR vomiting) AND ("cesarean section" OR "caesarean section" OR "cesarean delivery" OR "spinal anesthesia" OR "neuraxial block" OR pregnant OR pregnancy OR "c-section") Filter applied: from 2010 to 2025	14th July 2025

Suppelmentary Table 2. Studies Excluded After Full-Text Assessment and Reasons for Exclusion

No.	Author Name	Title	Reason for Exclusion
1	Benevides et al., 2024	Phenylephrine Infusion for the Prevention of Hypotension in Obese Patients During Cesarean Delivery Under Spinal Anesthesia: A Randomized, Placebo-Controlled, Double-Blind Study	Did not exclude patients with comorbidities
2	Singh et al., 2023	Comparing the Effect of Phenylephrine Bolus and Phenylephrine Infusion for Maintaining Arterial Blood Pressure During Cesarean Delivery Under Spinal Anesthesia: A Randomized Prospective Study.	Obese patients (BMI >30 kg/m²) were excluded
3	Nivatpumin et al., 2022	Comparison of perioperative outcomes and anesthetic-related complications of morbidly obese and super-obese parturients delivering by cesarean section	Did not exclude patients with comorbidities
4	Shafeinia et al., 2020	The Effect of Phenylephrine Infusion on Maternal Hemodynamic Changes During Spinal Anesthesia for Cesarean Delivery	Obese patients (BMI >30 kg/m²) were excluded
5	Odekon et al., 2015	The Effect of β2-Adrenoceptor Genotype on Phenylephrine Dose Administered During Spinal Anesthesia for Cesarean Delivery.	Did not exclude patients with BMI <30 kg/m²

6	Sakuma et al., 2010	Effects of intravenous vasopressor on spread of spinal anesthesia with 0.5% hyperbaric bupivacaine for caesarean delivery	Did not exclude patients with BMI <30 kg/m²
7	Guo et al., 2022	Prophylactic norepinephrine or phenylephrine infusion for bradycardia and post-spinal anaesthesia hypotension in patients with preeclampsia during Caesarean delivery: a randomised controlled trial	Did not report participant BMI
8	Yao et al., 2024	Effect of pneumatic leg compression on phenylephrine dose for hypotension prophylaxis via variable rate infusion at cesarean delivery: an unblinded randomized controlled trial	Did not report participant BMI
9	Park et al., 2022	Colloid coload versus crystalloid coload to prevent maternal hypotension in women receiving prophylactic phenylephrine infusion during caesarean delivery: a randomised controlled trial	Did not report participant BMI
10	Wang et al., 2020	Comparison of Continuous Infusion of Epinephrine and Phenylephrine on Hemodynamics During Spinal Anesthesia for Cesarean Delivery: A Randomized Controlled Trial	Did not exclude patients with BMI <30 kg/m²
11	Hasanin et al., 2019	Norepinephrine versus phenylephrine infusion for prophylaxis against post-spinal anaesthesia hypotension during elective caesarean delivery: A randomised controlled trial	Did not report participant BMI
12	Theodoraki et al., 2020	Prevention of hypotension during elective cesarean section with a fixed-rate norepinephrine infusion versus a fixed-rate phenylephrine infusion. A double-blinded randomized controlled trial	Did not exclude patients with BMI <30 kg/m²
13	Marni et al., 2024	Comparison Of The Effect Of Ephedrine And Phenylephrine In The Treatment Of Hypotension After Spinal Anesthesia During Caesarean Section And Their Effect On Fetal Outcome	Did not report participant BMI
14	Nani et al., 2011	Correlation between the Body Mass Index (BMI) of pregnant women and the development of hypotension after spinal anesthesia for cesarean section	Obese patients (BMI >30 kg/m²) were excluded

15	Fakhari et al., 2019	Comparing the effect of hypotension treatment due to spinal anesthesia with ephedrine or phenylephrine on arterial blood gases and neonatal Apgar score during cesarean delivery in obese mothers: Randomized clinical trial	Published in other language than English
16	Rana et al., 2020	Comparison of Variable Rate Phenylephrine Infusion with Rescue Phenylephrine Boluses Versus Rescue Boluses Alone for Prevention of Hypotension During Spinal Anesthesia for Elective Cesarean Delivery	Did not exclude patients with BMI <30 kg/m²

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ORIGINAL ARTICLE

Eleveld versus Schnider TCI Model for Propofol Sedation in Outpatient Colonoscopy: A Randomized Trial

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Abstract

Introduction: Outpatient colonoscopy is commonly performed under sedation, and propofol is frequently selected because of its rapid onset and short recovery profile. Target-controlled infusion (TCI) may improve dosing precision, but the comparative performance of the Eleveld and Schnider models during outpatient colonoscopy remains insufficiently defined. This study compared the Eleveld and Schnider TCI models for propofol sedation in patients undergoing outpatient colonoscopy.

Patients and Methods: This randomized, participant- and assessor-blinded, parallel-group controlled trial included 36 adults aged 20-65 years with ASA physical status I-III and BMI <30 kg/m2 who underwent elective outpatient colonoscopy. Participants were allocated to receive propofol using either the Eleveld or Schnider TCI model. The initial effect-site concentration was 2 µg/mL and was titrated by 0.5 µg/mL until a BIS value of 70 was achieved. The primary outcome was induction time, defined as the time from propofol infusion initiation to BIS 70. Secondary outcomes were mean propofol consumption, number of effect-site concentration adjustments, post-procedural agitation assessed using RASS, and recovery time to GCS 15.

Results: The Eleveld model was associated with shorter induction time than the Schnider model (4.03 ± 0.81 vs 5.32 ± 0.98 minutes; p <0.001) and lower propofol consumption (92.47 ± 28.29 vs 119.24 ± 31.56 µg/kg/min; p = 0.011). Recovery time was also shorter in the Eleveld group (5.27 ± 1.71 vs 7.88 ± 1.94 minutes; p <0.001). The number of effect-site concentration adjustments and post-procedural agitation did not differ significantly between groups.

Conclusion: The Eleveld TCI model was associated with faster induction, lower propofol consumption, and faster recovery than the Schnider model during outpatient colonoscopy, with comparable sedation adjustment requirements and post-procedural agitation. These findings suggest that the Eleveld model may improve sedation efficiency in this setting, although larger studies are needed to confirm its clinical and safety advantages.

Keywords: Colonoscopy; Drug delivery systems; Pharmacokinetics; Propofol; Sedation

Introduction

Colonoscopy is an important diagnostic and therapeutic procedure for lower gastrointestinal disease, particularly for colorectal cancer screening and early intervention.[1,2] The increasing use of outpatient colonoscopy has strengthened the need for sedation strategies that provide patient comfort, procedural efficiency, and rapid recovery. Despite its clinical value, colonoscopy may cause discomfort and anxiety, making sedation an important component of care.[3,4]

Propofol, an intravenous hypnotic agent, has emerged as the sedative of choice for endoscopic procedures because of its rapid onset, predictable recovery, and favorable safety profile.[5,6] Administering propofol, however, requires careful titration to balance adequate sedation with minimal adverse events, such as hypotension, bradycardia, and respiratory depression. Conventional methods, including intermittent bolus and continuous infusion via syringe pumps, often lead to fluctuating plasma concentrations, increasing the risk of over- or under-sedation.[7,8]

Target-controlled infusion (TCI) systems were developed to improve the precision of intravenous anesthetic administration by using pharmacokinetic and pharmacodynamic models to estimate plasma or effect-site concentrations, tailored to patient-specific factors such as age, body mass, and sex.[9,10] Among propofol TCI models, Schnider and Eleveld are commonly used. The Schnider model was developed from an adult population and uses covariates such as lean body mass, offers rapid onset and tight control in standard adult populations but may be less reliable in elderly or obese patients.[10,11] In contrast, the Eleveld was developed from a broader dataset and incorporates covariates including fat-free mass, potentially providing more adaptable sedation across different patient groups, although its induction may be slower and initial overshoot is possible.[12,13]

Despite the widespread adoption of both models, direct comparative studies evaluating the efficacy and safety of Eleveld versus Schnider TCI during outpatient colonoscopy remain limited. Most available literature assesses these models in surgical or intensive care settings, with varying patient demographics and procedural requirements, leaving a gap in knowledge regarding their relative performance in endoscopic sedation. Therefore, this study aimed to compare induction time, propofol consumption, effect-site concentration adjustments, recovery time, and post-procedural agitation between the Eleveld and Schnider TCI models during outpatient colonoscopy.

Patients and Methods

This randomized, participant- and assessor-blinded, parallel-group controlled trial was conducted at the Endoscopy Unit of a central general hospital in Bali, Indonesia, between July and August 2025. Ethical approval was obtained from the Udayana University Ethical Clearance Commission on July 20, 2025 (approval number: 2131/UN14.2.2.VII.14/LT/2025). Written informed consent was obtained from all participants before enrollment.

The sample size was calculated based on a previous study by Cuiabano et al. (2022) evaluating TCI propofol for colonoscopy sedation and expecting a clinically significant difference in induction time between the Eleveld and Schnider models, the sample size was calculated using an

alpha (α) of 0.05 and a statistical power of 80%. Anticipating a large effect size (Cohen's d = 0.98) based on pilot data/literature, a minimum sample size of 18 patients per group (total n=36) was determined to be sufficient. No dropouts occurred during the study, resulting in a final analysed sample of 36 patients.

Participants were recruited consecutively until the required sample size was achieved. Eligible participants were adults aged 20-65 years, of both sexes, with American Society of Anesthesiologists (ASA) physical status I-III and body mass index (BMI) <30 kg/m2 who were scheduled for elective outpatient colonoscopy. Patients were excluded if they had allergy to any sedative drug used in the study, neurodegenerative or psychiatric disorders, significant cardiovascular or hepatic dysfunction, chronic sedative use, or obstructive sleep apnea.

Participants were randomly assigned in a 1:1 ratio to the Eleveld or Schnider group using a computer-generated randomization sequence prepared by an independent statistician. Allocation concealment was maintained using sequentially numbered, sealed, opaque envelopes prepared by a third party not involved in recruitment, clinical care, or data collection. The envelopes were opened by the attending anesthesiologist only after eligibility had been confirmed and written informed consent had been obtained

Participants and outcome assessors were blinded to group allocation. The attending anesthesiologist could not be blinded because the assigned TCI model had to be selected and patient parameters had to be entered into the B. Braun Perfusor Space IITM system. Outcome measurements, including BIS threshold timing, propofol consumption, effect-site concentration adjustment, Richmond Agitation-Sedation Scale (RASS) assessment, and recovery evaluation, were performed by an independent trained assessor who was blinded to group assignment and had no access to the TCI interface.

Table 1. Baseline Characteristics of Study Participants

Characteristic	TCI-Eleveld (n=18)	TCI-Schnider (n=18)	*p*-value
Age, years (median, range)	57 (31–65)	56 (40–65)	0.937[M]
Male, n (%)	8 (44.4)	7 (38.9)	0.735[C]
Female, n (%)	10 (55.6)	11 (61.1)	0.735[C]
ASA I, n (%)	5 (27.8%)	5 (27.8%)	
ASA II, n (%)	9 (50%)	9 (50%)	1.000[C]
ASA III, n (%)	4 (22.2%)	4 (22.2%)	
BMI, kg/m² (mean ± SD)	23.89 ± 2.97	23.26 ± 3.39	0.563[T]
Procedure duration, min (mean ± SD)	26.44 ± 8.76	27.33 ± 8.49	0.759[T]

[M]Analysis of the variables was performed using the Mann-Whitney U test; results were considered significant if $p \leq 0,05$

[C]Analysis of the variables was performed using the Chi-square test; results were considered significant if $p \leq 0,05$

[T]Analysis of the variables was performed using the Independent T-test; results were considered significant if $p \leq 0,05$

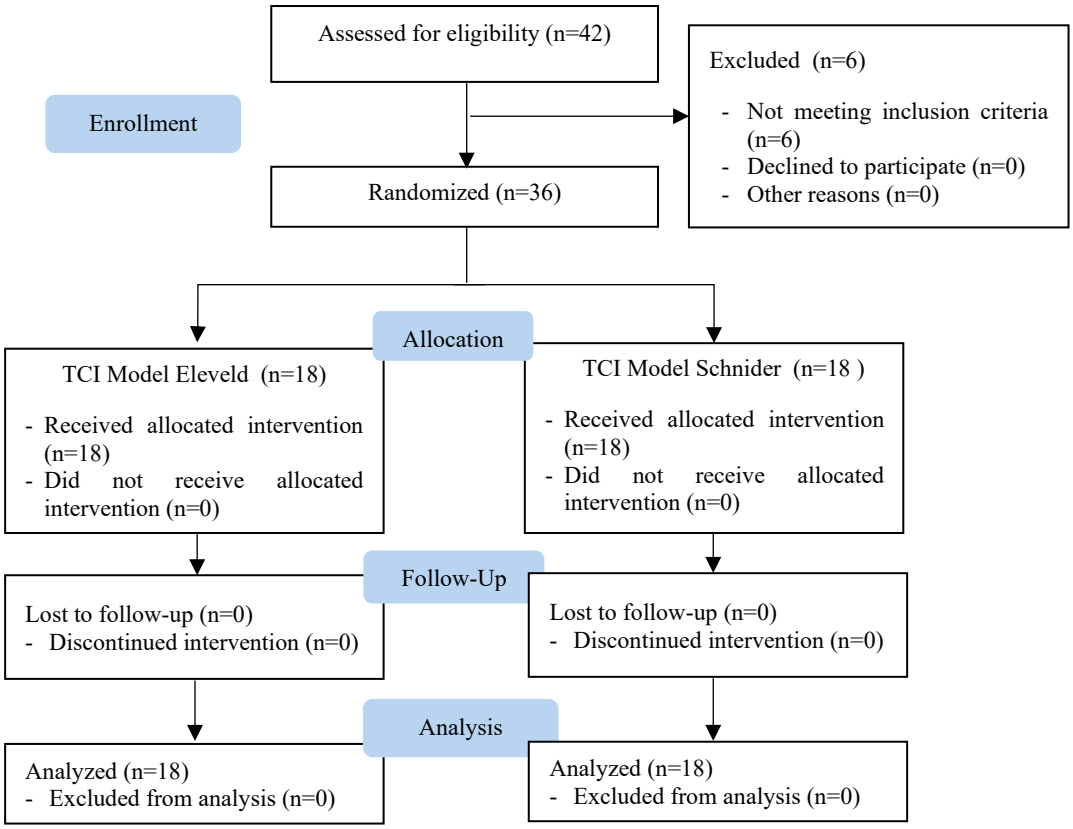

Figure 1. CONSORT Flow Chart

In the endoscopy unit, all participants received standard monitoring, including non-invasive blood pressure, electrocardiography, pulse oximetry, and Bispectral Index (BIS) monitoring. Supplemental oxygen was administered at 3 L/min through a nasal cannula throughout the procedure. Fentanyl 1 µg/kg was administered intravenously before propofol infusion. Propofol sedation was delivered using the assigned TCI model. In both groups, the initial effect-site concentration was set at 2 µg/mL and titrated in 0.5 µg/mL increments until a BIS value of 70 was achieved. During the procedure, effect-site concentration adjustments were made if BIS deviated outside the target range of 65-75 for more than 30 seconds or if clinical signs of inadequate sedation or over-sedation occurred.

The primary outcome was induction time, defined as the interval from initiation of propofol infusion to achievement of BIS 70. Secondary outcomes were mean propofol consumption (µg/kg/min), number of effect-site concentration adjustments, post-procedural agitation assessed using RASS, and recovery time, defined as the interval from cessation of propofol to GCS 15.

Predefined rescue protocols were used for adverse respiratory or hemodynamic events. Respiratory depression, defined as peripheral oxygen saturation <90% or respiratory rate <8 breaths/min, was managed with jaw-thrust maneuver, increased supplemental oxygen flow, or temporary cessation of the TCI pump until spontaneous ventilation recovered. Hypotension, defined as a decrease in mean arterial pressure >20% from baseline, was treated with a 250-mL intravenous fluid bolus and, if persistent, intravenous ephedrine 5-10 mg. Bradycardia, defined as heart rate <50 beats/min, was treated with intravenous atropine 0.5 mg.

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 29.0 (IBM Corp., Armonk, NY, USA). Data normality was assessed using the Kolmogorov-Smirnov test. Normally distributed continuous variables were presented as mean ± standard deviation and compared using the independent-samples t-test. Non-normally distributed variables were presented as median (minimum-maximum) and compared using the Mann-Whitney U test. Categorical variables were presented as frequency and percentage and compared using the Chi-square test or Fisher exact test, as appropriate. Statistical significance was set at $p < 0.05$.

Results

A total of 42 patients scheduled for elective outpatient colonoscopy were assessed for eligibility. Six patients were excluded because they did not meet the inclusion criteria. The remaining 36 participants were randomized equally into the Eleveld and Schnider groups, with 18 participants in each group. All randomized participants received the allocated intervention and were included in the final analysis. No protocol deviations, dropouts, or losses to follow-up were reported. Baseline demographic and clinical characteristics, including age, sex, BMI, ASA physical status, and procedure duration, were comparable between groups (Table 1).

The primary outcome, induction time, was significantly shorter in the Eleveld group than in the Schnider group (4.03 ± 0.81 vs 5.32 ± 0.98 minutes; $p < 0.001$). Mean propofol consumption was also significantly lower in the Eleveld group than in the Schnider group (92.47 ± 28.29 vs 119.24 ± 31.56 μg/kg/min; $p = 0.011$). Recovery time was significantly shorter in the Eleveld group than in the Schnider group (5.27 ± 1.71 vs 7.88 ± 1.94 minutes; $p < 0.001$). The median number of effect-site concentration adjustments did not differ significantly between the Eleveld and Schnider groups (3 [range, 1–6] vs 2 [range, 0–6]; $p = 0.710$). Post-procedural agitation occurred in one participant in each group (5.6% vs 5.6%; $p = 1.000$). The comparison of clinical outcomes between groups is presented in Table 2.

Table 2. Test of Normality

Variable	Kolmogorov – Smirnov Statistic	*p*-value[K]
Age	0.136	0.91
BMI	0.09	0.200
Procedure duration	0.089	0.200
Induction time	0.093	0.200
Mean Propofol Consumption	0.110	0.200
Effect-Site Concentration Adjustments	0.173	0.008
Recovery time	0.108	0.200

[K] The Kolmogorov-Smirnov test was used to assess normality; data were considered normally distributed if $p > 0,05$

Discussion

This study showed that the Eleveld TCI model provided faster induction, lower propofol consumption, and shorter recovery time than the Schnider model during outpatient colonoscopy sedation. Both models required a comparable number of effect-site concentration adjustments and showed similarly low rates of post-procedural agitation. These

findings suggest that the Eleveld model may offer greater dosing efficiency without compromising sedation stability in this outpatient setting.

The shorter induction time observed with the Eleveld model may be explained by differences in the pharmacokinetic and pharmacodynamic structures of the two models. The Eleveld model was developed using a broader and more heterogeneous population dataset and incorporates covariates such as age, sex, weight, height, and fat-free mass to estimate propofol distribution and clearance.[12,13] This structure may allow more individualized prediction of effect-site concentration and faster achievement of the intended sedation depth. In contrast, the Schnider model was developed from a more limited adult population and uses lean body mass as one of its key covariates, which may reduce its adaptability across varying patient characteristics.10 Previous comparative data in endoscopic sedation also reported shorter induction with the Eleveld model, supporting the direction of the present findings.[14] Although the absolute difference in induction time was modest, it may be relevant in high-volume outpatient endoscopy units, where small reductions in induction time can influence workflow efficiency.

Table 3. Clinical Variables

Outcome	TCI-Eleveld (n=18)	TCI-Schnider (n=18)	*p*-value (CI*)	Effect Size**
Induction time, minute (mean ± SD)	4.03 ± 0.81	5.32 ± 0.98	<0.001^{T} (-2.156 – -0.658)*	-1.429
Mean propofol consumption, µg/kg/min (mean ± SD)	92.47 ± 28.29	119.24 ± 31.56	0.011^{T} (-1.574 – -0.201)*	-0.893
Effect-Site concentration adjustments, times (median, range)	3 (1–6)	2 (0–6)	0.710^{M} (0.870 – 1.000)*	-0.062
Recovery time, minute (mean ± SD)	5.27 ± 1.71	7.88 ± 1.94^{T}	<0.001^{T} (-2.161 – -0.689)*	-1.433
Post procedural agitation, n (%)	1 (5.6)	1 (5.6)	1.000^{F}	

*95% Confidence Interval; **Effect size value based on Cohen's D; ^{T}Analysis of the variables was performed using the Independent T-test; results were considered significant if $p \leq 0,05$.
^{M}Analysis of the variables was performed using the Mann-Whitney U test; results were considered significant if $p \leq 0,05$. ^{F}Analysis of the variables was performed using the Fisher's Exact test; results were considered significant if $p \leq 0,05$.

This finding may be partly explained by the pharmacokinetic and pharmacodynamic differences between the two models. The Schnider model was developed from a relatively limited adult population and uses fixed compartmental assumptions with lean body mass as an important covariate. These characteristics may reduce its flexibility in predicting effect-site propofol concentrations across patients with varying physiological profiles. In contrast, the Eleveld model was developed from a broader population dataset and incorporates individual covariates, including age, weight, height, sex, and fat-free mass, to estimate propofol distribution and clearance.[10,15,16] This more individualized structure may allow more adaptive prediction of effect-site concentration, thereby contributing to faster achievement of the target BIS level and more efficient propofol use. In outpatient sedation, such differences may be practically relevant because even modest reductions in induction time and drug exposure can support smoother procedural workflow, although this study did not directly measure room turnover or operational efficiency.

The lower propofol consumption in the Eleveld group (92.47 μg/kg/min vs. 119.24 μg/kg/min in the Schnider group) supports the concept that a more individualized pharmacokinetic model may reduce unnecessary drug exposure while maintaining adequate sedation depth. This finding is clinically relevant because higher cumulative propofol doses may increase the risk of dose-related adverse effects, including hypotension, respiratory depression, and delayed recovery.[17] This result is consistent with findings from previous studies showing that the Eleveld model's more individualized dosing approach leads to a more efficient use of propofol while maintaining adequate sedation levels14. The Eleveld model incorporates individual physiological covariates, including age, weight, height, sex, and fat-free mass, allowing more adaptive estimation of propofol distribution and clearance. This may reduce unnecessary dose overshoot and improve dosing efficiency compared with the Schnider model, which uses a more limited pharmacokinetic structure. Despite this lower propofol requirement, the number of effect-site concentration adjustments was comparable between groups, indicating that both models were able to maintain sedation within the intended BIS-guided target range after adequate sedation had been achieved. Therefore, the main advantage of the Eleveld model in this study appears to be related to induction efficiency and lower drug requirement rather than superior intra-procedural sedation stability. This distinction is important because it suggests that the Eleveld model may be more efficient, while the Schnider model remains clinically usable for maintaining stable sedation during outpatient colonoscopy.[10,12,14]

Both TCI models required similar numbers of effect-site concentration adjustments during sedation (3 vs. 2, $p = 0.710$), indicating that both systems were effective in maintaining stable sedation with minimal need for titration. This result suggests that, although Eleveld is more efficient in terms of induction and drug consumption, both models can achieve comparable levels of sedation stability. The similarity in adjustment requirements between the two models aligns with the findings of other studies, which suggest that both Schnider and Eleveld models are equally capable of maintaining sedation

during a range of procedures, including those requiring relatively deep sedation like colonoscopy.[18]

Recovery time was also shorter in the Eleveld group (5.27 ± 1.71 min vs. 7.88 ± 1.94 min in the Schnider group). This may be related to lower propofol exposure and more efficient effect-site targeting during the procedure, resulting in less residual sedative effect after cessation of infusion. This finding supports the notion that more accurate effect-site targeting with the Eleveld model allows for a quicker return to full consciousness and may reduce the overall time spent in the recovery room19. Quicker recovery times also enhance patient satisfaction and operational efficiency, making Eleveld an ideal choice for outpatient colonoscopy and similar procedures. The relationship between cumulative propofol dosage and recovery duration is well-established; lower total doses promote faster drug elimination from the body, thereby shortening the recovery phase. The Schnider model calculates the induction bolus based on distribution to the central (plasma) compartment, but often lacks precision in predicting effect-site concentrations—particularly in elderly patients or those with extreme body mass indices, who represent common demographics in colonoscopy. Consequently, anesthesiologists must frequently adjust target concentrations or administer supplemental boluses. In contrast, the Eleveld model is derived from a larger, more diverse database and utilizes a more sophisticated algorithm, enabling it to predict how propofol distributes into tissues and reaches therapeutic effect-site (brain) concentrations with greater accuracy and efficiency. Because the Eleveld group utilizes propofol more efficiently and at a lower cumulative dose, patients naturally regain consciousness faster, facilitating a prompter transfer to the recovery room and, ultimately, timely discharge home.[19]

Post-procedural agitation was rare and similar between groups. This suggests that both Eleveld and Schnider models provided acceptable emergence quality when sedation was guided by BIS monitoring and titrated using a standardized protocol. The low agitation rate may also reflect the advantage of TCI-based propofol administration, which allows more stable plasma or effect-site concentrations than intermittent bolus techniques.[7] Thus, although the Eleveld model showed advantages in induction, drug consumption, and recovery time, both models appeared comparable in terms of sedation stability and immediate emergence profile

This study has several limitations. First, the sample size was relatively small and the study was conducted at a single center, which may limit generalizability. Second, the study included patients aged 20–65 years with BMI <30 kg/m²; therefore, the findings cannot be directly extrapolated to elderly, obese, or higher-risk populations, even though these groups are often central to discussions of TCI model performance. Third, the anesthesia operators could not be blinded because the selected TCI model had to be entered manually into the infusion system. Although participants and outcome assessors were blinded, operator awareness may still have influenced titration behavior. Fourth, this study focused mainly on short-term procedural outcomes and did not assess detailed cardiorespiratory adverse events, discharge readiness, patient satisfaction, endoscopist satisfaction, or cost-effectiveness. Finally, fentanyl was

used as an adjunct in both groups, which may have influenced propofol requirements and recovery profile, although the same protocol was applied to all participants.

Conclusion

Eleveld TCI model was associated with faster induction, lower propofol consumption, and shorter recovery time than the Schnider model during outpatient colonoscopy sedation, while maintaining comparable sedation stability and emergence quality. These findings suggest that the Eleveld model may be an efficient option for propofol TCI sedation in outpatient endoscopy, particularly in settings where time efficiency, rapid recovery, and optimized drug use are important. The lower propofol requirement may also offer potential safety advantages by reducing dose-related adverse effects, although this study was not powered to assess differences in clinical complications. Therefore, while the Eleveld model appears promising for outpatient colonoscopy sedation, larger multicenter studies involving broader patient populations and more comprehensive safety, recovery, patient satisfaction, and workflow outcomes are needed to confirm whether these advantages translate into meaningful clinical and operational benefits.

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Conflict of Interest

The author(s) report no conflict of interest.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author's Contributions

Conceptualization: AW. Methodology: MW and TA. Investigation: AW, MW, and TA. Data curation: AW, IGAMWK. Formal analysis: AW and MW. Writing – original draft: AW and MW. Writing – review & editing: AW, IGAMWK and MW. Supervision: MW. All authors approved the final manuscript.

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ORIGINAL ARTICLE

Efficacy of Pregabalin Versus Gabapentin as Preemptive Analgesia in Patients Undergoing Modified Radical Mastectomy: a Randomized Controlled Trial

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Abstract

Introduction: Postoperative pain after modified radical mastectomy (MRM) increases morbidity, opioid use, and recovery time. Gabapentinoids may reduce central sensitization when administered before surgical injury. This study compared pregabalin and gabapentin as preemptive analgesics in patients undergoing MRM.

Patients and Methods: This double-blind randomized controlled trial was conducted at Ngoerah Hospital, Denpasar. Forty-two patients scheduled for elective MRM were allocated to oral pregabalin 150 mg (n = 21) or oral gabapentin 900 mg (n = 21), administered two hours before surgery. The primary outcome was Visual Analogue Scale (VAS) pain score at 12, 24, and 48 hours postoperatively. Secondary outcomes were time to first rescue analgesia and cumulative opioid consumption during the first 24 postoperative hours. Between-group comparisons used the independent t-test or Mann-Whitney U test, as appropriate.

Results: Pregabalin produced lower VAS scores than gabapentin at 12 hours (2.18 +/- 0.65 vs 2.65 +/- 0.74; p = 0.034), 24 hours (2.27 +/- 0.66 vs 2.71 +/- 0.63; p = 0.030), and 48 hours (1.90 +/- 0.65 vs 2.36 +/- 0.71; p = 0.033). Time to first rescue analgesia was longer with pregabalin (232.69 +/- 19.88 vs 219.88 +/- 17.81 minutes; p = 0.034), and 24-hour opioid consumption was lower (240 [145] vs 360 [155] micrograms fentanyl equivalent; p = 0.034). No adverse hemodynamic.

Conclusion: Preoperative oral pregabalin 150 mg provided statistically superior analgesia and reduced opioid consumption compared with gabapentin 900 mg after MRM. However, the absolute differences in pain scores and rescue-analgesia time were modest; therefore, safety monitoring and larger studies are warranted

Keywords: Analgesia; Gabapentin; Mastectomy, Modified radical; Postoperative pain; Pregabalin.

Introduction

Postoperative pain is common after breast-cancer surgery and remains clinically important after modified radical mastectomy (MRM). The prevalence of post-mastectomy pain has been reported to range from 25% to 60% among women undergoing the procedure.[1] Recent evidence on pain after mastectomy has shown that approximately 68.9% of women experience moderate-to-severe acute postoperative pain, while 22.1% develop subacute pain.[2] These findings indicate a substantial

postoperative pain burden and highlight the need for effective preemptive analgesic strategies in breast surgery.

The pathophysiology of postoperative pain involves complex interactions between the immune and nervous systems, leading to peripheral and central sensitization. In mastectomy, neuropathic pain may occur due to injury to the intercostobrachial nerve or smaller peripheral branches in the axillary region, causing sensory disturbance and persistent pain. Because MRM-related pain has both nociceptive and neuropathic components, optimal analgesic management is essential to prevent pain chronification and enhance postoperative recovery.[3]

Gabapentinoids, particularly pregabalin and gabapentin, are commonly used as preemptive analgesic agents because they attenuate central sensitization by modulating calcium channel activity at the $\alpha_2\delta$ subunit. Although both drugs share a similar mechanism of action, their pharmacokinetic differences may influence clinical efficacy.[4] Meta-analyses have shown that both agents can reduce postoperative pain and opioid consumption.[5] However, direct comparative evidence between pregabalin and gabapentin in patients undergoing MRM remains limited, particularly in Indonesia.[6]

Therefore, this study aimed to evaluate the comparative efficacy of preoperative oral pregabalin 150 mg and gabapentin 900 mg in patients undergoing MRM. The evaluated outcomes included postoperative pain intensity measured using visual analogue scale (VAS) at 12, 24, and 48 hours after surgery, time to first rescue analgesia, and total opioid consumption within the first 24 postoperative hours.

Patients and Methods

This double-blind randomized controlled trial was conducted at Ngoerah Hospital, Denpasar, Bali, Indonesia, between August and October 2025. Ethical approval was obtained from the Health Research Ethics Committee of Universitas Udayana Faculty of Medicine/Ngoerah Hospital (approval number: 1423/UN14.2.2.VII.14/LT/2025). Written informed consent was obtained from all participants before enrollment.

The target population consisted of patients scheduled for elective MRM under general anesthesia. Participants were recruited consecutively according to predefined eligibility criteria. The inclusion criteria were female patients aged 30–65 years, American Society of Anesthesiologists (ASA) physical status I–II, and body mass index (BMI) of 18–30 kg/m². Patients with chronic pain disorders, current anticonvulsant or antidepressant use, hepatic or renal impairment, or a history of allergy to the study drugs were excluded.

The sample size was calculated using the formula for comparison of two independent means, with a two-sided alpha of 0.05 ($Z\alpha$ = 1.96) and 90% power ($Z\beta$ = 1.28). Calculations were based on postoperative VAS scores, time to first rescue analgesia, and total postoperative opioid consumption. The estimated sample sizes were 16, 3, and 19 participants per group, respectively. The largest estimate was selected as the basis for sample size determination. After accounting for an anticipated 10% dropout rate, the minimum required sample size was 21 participants per group, resulting in 42 participants in total.

Randomization was performed using a computer-generated random number table by an independent statistician. Allocation

concealment was maintained using sequentially numbered, sealed, opaque envelopes. The randomization list was kept by an independent hospital pharmacist and remained inaccessible to the recruiting investigators, anesthesiologists, and outcome assessors throughout the study.

Pregabalin and gabapentin were prepared by the hospital pharmacist through over-encapsulation into identical opaque gelatin capsules. Therefore, the study drugs were indistinguishable to participants, anesthesiologists, and outcome assessors. The randomization code could only be broken in the event of a severe allergic reaction or other clinical emergency requiring immediate drug identification.

Both study drugs were administered orally with a small amount of water two hours before anesthesia induction. Group P1 received gabapentin 900 mg, while Group P2 received pregabalin 150 mg. All patients underwent standardized general anesthesia consisting of preoxygenation, propofol induction, sevoflurane maintenance in an oxygen–air mixture, and muscle relaxation with atracurium. Intraoperative analgesia was provided using fentanyl 2 μg/kg, followed by standard postoperative care in the recovery unit.

Postoperative pain intensity was assessed using the VAS at 12, 24, and 48 hours after surgery. All participants received intravenous paracetamol 1 g every 8 hours and intravenous ketorolac 30 mg every 8 hours as scheduled analgesia. Time to first rescue analgesia was defined as the interval from the end of surgery to the first request for supplemental analgesia. Rescue analgesia was administered as intravenous ketorolac 30 mg. Total opioid consumption during the first 24 postoperative hours was calculated in micrograms of fentanyl equivalents. All outcomes were assessed by trained blinded assessors.

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 29.0 (IBM Corp., Armonk, NY, USA). Data distribution was assessed using the Shapiro–Wilk test. Normally distributed continuous variables were presented as mean ± standard deviation, while non-normally distributed variables were presented as median and interquartile range. Between-group comparisons were performed using the independent-samples t-test, Mann–Whitney U test, Chi-square test, or Fisher's exact test, as appropriate. A p-value of <0.05 was considered statistically significant.

Results

A total of 42 eligible patients were included and randomly allocated into two equal groups, with 21 patients in each group. All participants completed the study according to the protocol, with no dropouts or protocol deviations. Baseline demographic and clinical characteristics, including age, BMI, and ASA physical status, were comparable between groups, with no significant intergroup differences ($p > 0.05$) (Table 1).

Postoperative VAS scores were significantly lower in the pregabalin group than in the gabapentin group at 12 hours (2.18 ± 0.65 vs 2.65 ± 0.74), 24 hours (2.27 ± 0.66 vs 2.71 ± 0.63), and 48 hours (1.90 ± 0.65 vs 2.36 ± 0.71) after surgery (all $p <0.05$) (Table 2). This finding indicates superior postoperative analgesic control in the pregabalin group, with pain levels progressively declining over time in both groups, though more

pronounced in the pregabalin cohort. The mean trend of postoperative pain reduction in both groups is presented in Figure 1, illustrating the consistently lower VAS scores among patients treated with pregabalin.

The time to first rescue analgesia was significantly longer in the pregabalin group than in the gabapentin group (232.69 ± 19.88 vs 219.88 ± 17.81 minutes; p = 0.034) (Table 3). Total opioid consumption during the first 24 postoperative hours was also significantly lower in the pregabalin group than in the gabapentin group (240 [145] µg vs 360 [155] µg fentanyl equivalent; p = 0.034) (Table 4). This reduction reflects the opioid-sparing effect of pregabalin when used as a preemptive analgesic adjunct.

Table 1. Demographic Characteristics

Characteristics	Preemptive Analgesia						p-value
	Gabapentin 900 mg (n = 21)			Pregabalin 150 mg (n = 21)			
	N,%	Average	SD	N,%	Average	SD	
Age (year)		51.75	7.27		50.43	8.46	0.434*)
ASA							
I	1 (4.8)			3 (14.3)			0.757**)
II	20 (95.2)			18 (85.7)			
BMI (kg/m^2)		23.21	3.56		23.54	3.44	0.108*)

*) Independent t-Test; **) chi-square test; ASA: American Society of Anesthesiologists physical status classification; BMI: body mass index

Table 2. Comparison of Postoperative VAS scores

Time after surgery	Preemptive Analgesia				p-value
	Gabapentin 900 mg (n = 21)		Pregabalin 150 mg (n = 21)		
	Average	SD	Average	SD	
12 hours	2.65	0.74	2.18	0.65	0.034*)
24 hours	2.71	0.63	2.27	0.66	0.030*)
48 hours	2.36	0.71	1.90	0.65	0.033*)

*) Independent t-Test

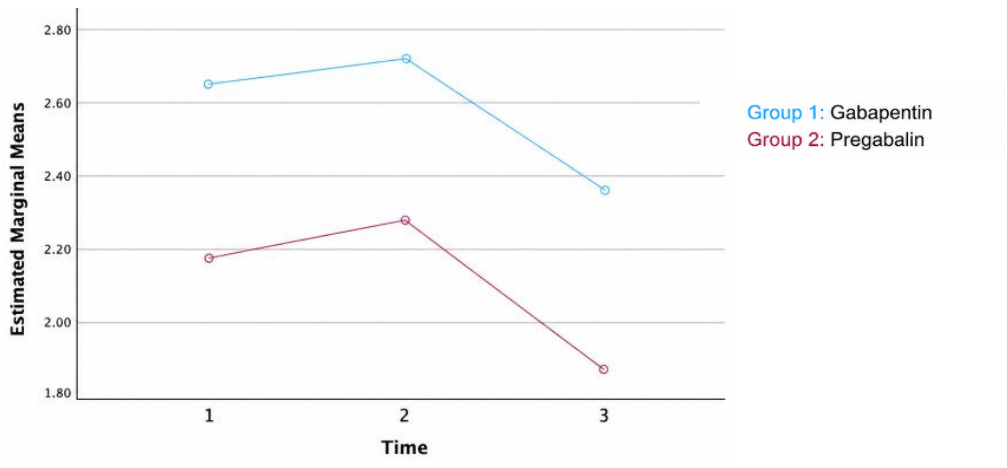

Figure 1. Visual Analog Scale (VAS) scores at 12, 24, and 48 hours postoperatively between the two groups.

Overall, the pregabalin group showed better analgesic efficacy, longer duration of analgesia, and reduced postoperative opioid requirements compared to the gabapentin group, without any reported adverse hemodynamic events.

Discussion

This study showed that preoperative oral pregabalin 150 mg provided better postoperative analgesic outcomes than gabapentin 900 mg in patients undergoing MRM. Patients who received pregabalin had lower postoperative VAS scores at 12, 24, and 48 hours, a longer time to first rescue analgesia, and lower opioid consumption during the first 24 postoperative hours. These findings suggest that pregabalin may be more effective than gabapentin as a preemptive analgesic adjunct in this surgical population.

The lower postoperative pain scores in the pregabalin group may be explained by the pharmacologic properties of gabapentinoids. These agents bind to the $\alpha_2\delta$ subunit of presynaptic voltage-gated calcium channels, reducing calcium influx and suppressing the release of excitatory neurotransmitters such as glutamate, norepinephrine, and substance P.[7] This mechanism decreases neuronal hyperexcitability in the dorsal horn and attenuates central sensitization, which is particularly relevant in MRM because postoperative pain may involve both nociceptive and neuropathic components. Compared with gabapentin, pregabalin has greater $\alpha_2\delta$-subunit affinity, more predictable absorption, higher bioavailability, and a more rapid onset of action, which may contribute to more consistent analgesic effects.[1,5]

The present findings are consistent with previous evidence showing that preemptive gabapentinoids can reduce postoperative pain and analgesic requirements across several surgical settings.[8,9] In breast surgery, pregabalin has also been associated with reduced acute postoperative pain and improved analgesic outcomes.

Table 3. Comparison of Total Opioid Consumption

Variable	Preemptive Analgesia				p-value
	Gabapentin 900 mg (n = 21)		Pregabalin 150 mg (n = 21)		
	Median	IQR	Median	IQR	
Fentanyl (μg)	360	155	240	145	0.034*)

*) Mann-Whitney U test

Table 4. Comparison of Time to First Rescue Analgesia

Variable	Preemptive Analgesia				p-value
	Gabapentin 900 mg (n = 21)		Pregabalin 150 mg (n = 21)		
	Average	SD	Average	SD	
Time (minutes)	219.88	17.81	232.69	19.88	0.034*)

*) Independent T-test

These findings support the role of pregabalin as part of multimodal analgesia, particularly in procedures associated with moderate-to-severe postoperative pain and potential neuropathic mechanisms.

The longer time to first rescue analgesia in the pregabalin group suggests a more sustained analgesic effect. Pregabalin has linear pharmacokinetics and high bioavailability of approximately 90%, resulting in more predictable plasma concentrations.[10,11] In contrast, gabapentin has saturable intestinal absorption at higher doses, which may lead to more variable clinical effects. This pharmacokinetic difference may explain why pregabalin produced a longer duration of analgesia despite both drugs acting through a similar mechanism.[12]

The prolonged analgesic duration observed in this study corresponds with how pregabalin reduces the hyperexcitability of neuronal membranes and delays the recurrence of nociceptive transmission following tissue injury. Inhibition of calcium channel–mediated neurotransmitter release leads to decreased sensitization of pain pathways, prolonging the analgesic effect beyond the early postoperative phase.[13]

Total opioid requirement during the first 24 postoperative hours was significantly lower in the pregabalin group than in the gabapentin group, indicating a stronger opioid-sparing effect of pregabalin. Pregabalin reduces the central sensitization that amplifies pain signaling and indirectly minimizes opioid requirements. Jiang et al. (2018) also found that gabapentinoids, when used as preemptive analgesics, effectively decreased total perioperative opioid consumption.

The reduction in opioid use is clinically important because it reduces the incidence of opioid-related side effects such as nausea, vomiting, sedation, and respiratory depression. The findings align with Routray et al. (2018) and Khetarpal et al. (2016), who reported that pregabalin use led to better postoperative pain relief with fewer opioid-related complications. Additionally, a recent study supported that preoperative pregabalin minimized opioid dependency and improved recovery quality.[14,15]

Pregabalin and gabapentin are GABA analogues in terms of structure; however, their pharmacologic effects are not mediated through direct interaction with GABA receptors. Their primary mechanism involves binding to the $\alpha_2\delta$ subunit of voltage-gated calcium channels, thereby suppressing neurotransmitter release and decreasing neuronal excitability. Pregabalin's stronger receptor affinity enhances its ability to prevent central sensitization and postoperative hyperalgesia. Moreover, Chincholkar (2020) described that gabapentinoids stabilize neuronal membranes and inhibit ectopic discharge from injured nerves, contributing to their analgesic and antihyperalgesic properties.[7]

The results of this study are consistent with Routray et al. (2018), which concluded that pregabalin administration before surgery significantly reduced postoperative pain intensity and opioid requirements compared with gabapentin. Khetarpal et al. (2016) also reported that pregabalin was more effective in providing postoperative analgesia in patients undergoing abdominal surgery. Likewise, Hetta et al. (2016) demonstrated similar findings in gynecologic surgery, where pregabalin resulted in lower pain scores and fewer analgesic demands.[6,14,15]

Furthermore, Jiang et al. (2018) found that pregabalin provided prolonged analgesia and a greater reduction in opioid consumption compared to gabapentin, supporting the analgesic superiority of pregabalin. These consistent results across multiple studies validate the effectiveness of pregabalin as a preemptive analgesic in various surgical populations, including breast, gynecologic, and orthopedic surgery.[16]

From a clinical perspective, preoperative pregabalin offers several advantages: effective pain reduction, prolonged analgesia, and lower opioid use, which together contribute to improved patient satisfaction and recovery. These findings are in line with multimodal analgesic concepts that emphasize opioid-sparing approaches to reduce postoperative complications and enhance early mobilization.[17] The current study supports incorporating pregabalin into multimodal pain management strategies for surgeries associated with moderate to severe postoperative pain.

Although the differences in VAS scores between groups were statistically significant, the absolute magnitude of these differences (approximately 0.4–0.5 points on a 0–10 scale) was relatively small and may fall below the minimal clinically important difference (MCID) commonly reported for acute postoperative pain, which ranges from approximately 1.0 to 1.3 points. This suggests that while pregabalin demonstrated statistically superior analgesic control compared with gabapentin, the clinical relevance of this difference for individual patient comfort may be modest. The more clinically meaningful findings of this study may instead lie in the secondary outcomes, namely the prolonged time to first rescue analgesia and the reduction in total opioid consumption, both of which carry direct implications for opioid-sparing strategies and recovery quality. Nevertheless, the absolute difference in time to first rescue analgesia (approximately 13 minutes) was itself relatively modest, and although statistically significant, its practical impact on patient comfort or clinical decision-making may be limited. Similarly, the magnitude of opioid-sparing observed should be interpreted with caution given the modest absolute difference in consumption between groups.

This study has several noteworthy limitations. The modest sample size (21 patients per group) and single-center setting may limit the statistical power to detect smaller treatment effects and reduce the generalizability. Furthermore, although statistically significant, the absolute differences observed in VAS scores and time to first rescue analgesia were relatively modest in clinical terms, and these results should therefore be interpreted with caution rather than as definitive evidence of clinical superiority. This study also did not assess chronic postsurgical pain or broader quality-of-recovery outcomes, both of which are clinically relevant endpoints following mastectomy and warrant evaluation in future studies with longer follow-up. In addition, serum concentrations of the investigated drugs were not evaluated, and adverse effects such as dizziness and somnolence were not systematically documented. The findings of this study may also have limited applicability to centers that routinely employ regional analgesic techniques (e.g., paravertebral or pectoral nerve blocks) or opioid-free anesthesia strategies for modified radical mastectomy, as the comparative benefit of gabapentinoids in

such settings remains unclear. Therefore, further multicenter studies involving larger populations, longer follow-up duration, and comparison across different anesthetic and analgesic protocols are needed to confirm these results and clarify the broader clinical applicability of pregabalin as a preemptive analgesic.

Conclusion

Preoperative oral pregabalin 150 mg was associated with lower postoperative pain scores, longer time to first rescue analgesia, and reduced opioid consumption compared with gabapentin 900 mg in patients undergoing modified radical mastectomy. These findings suggest that pregabalin may be a useful component of multimodal analgesia for postoperative pain management in this surgical population. However, given the modest absolute differences in pain scores and rescue analgesia timing, its clinical benefit should be interpreted with caution.

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Conflict of Interest

The author(s) report no conflict of interest.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author's Contributions

Conceptualisation: Y.J.P, M.S.P.A. Methodology: Y.J.P, I.P.P.S, I.P.K. Investigation: I.P.P.S, M.S.P.A. Data curation: Y.J.P, I.P.P.S. Formal analysis: Y.J.P. Writing – original draft: Y.J.P. Writing – review & editing: Y.J.P, M.S.P.A. Supervision: I.P.P.S, I.P.K. All authors approved the final manuscript.

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ORIGINAL ARTICLE

Comparison of Continuous and Intermittent Bolus Enteral Nutrition in Patients with Severe Traumatic Brain Injury: a Randomized Controlled Trial

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Abstract

Introduction: Severe traumatic brain injury (TBI) is associated with impaired gastric motility and dysregulated glucose homeostasis, making optimal enteral nutrition challenging. This study compared continuous and intermittent bolus enteral nutrition in terms of gastric residual volume (GRV), glycemic variability, and gastrointestinal tolerance in patients with severe TBI.

Patients and Methods: An assessor-blinded, randomized controlled trial was conducted in 60 adult patients with severe TBI admitted to the intensive care unit. Participants were randomly assigned to continuous (n = 30) or intermittent bolus enteral nutrition (n = 30) during the first 24 hours after ICU admission. GRV was measured every 4 hours using gastric ultrasonography. Glycemic variability was assessed using the coefficient of variation (CV), and diarrhea was recorded as a marker of gastrointestinal tolerance. GRV was analyzed using repeated-measures analysis of variance (ANOVA), while glycemic fluctuation and diarrhea incidence were analyzed using Fisher's exact and chi-square tests.

Results: Sixty patients were analyzed, with comparable baseline characteristics between groups. Repeated-measures ANOVA demonstrated a significant overall effect of feeding method on GRV ($F(1,58) = 158.235$, $p < 0.001$) and a significant time × group interaction (Greenhouse–Geisser corrected $F(3.980,230.814) = 3.437$, $p = 0.010$). During the 24-hour observation period, continuous feeding resulted in a lower overall GRV than intermittent bolus feeding (mean difference 18.9 mL; 95% CI 15.9–21.9). Glycemic fluctuation was similar between groups ($p = 0.500$), whereas diarrhea occurred less frequently with continuous feeding (20.0% vs 50.0%, $p = 0.008$).

Conclusion: During the first 24 hours of ICU admission, continuous enteral nutrition was associated with lower overall GRV and a lower incidence of diarrhea than intermittent bolus feeding, while glycemic fluctuation was comparable between groups. Further studies are warranted to evaluate long-term clinical outcomes.

Keywords: Enteral nutrition, Brain injuries; Intensive care units; Blood glucose; Gastric emptying

Introduction

Severe traumatic brain injury (TBI) continues to be a leading cause of morbidity and mortality globally, especially in critically ill patients in need of intensive care. These patients frequently develop a hypermetabolic and hypercatabolic state, accompanied by impaired gastric motility and metabolic dysregulation, which contribute to poor clinical outcomes.

Early nutritional support plays a pivotal role in mitigating catabolism and promoting recovery. However, nutritional management remains challenging due to feeding intolerance and glycemic instability.[1,2]

Approximately 68% of patients with severe TBI develop malnutrition as a result of the systemic stress response, while stress-induced insulin resistance contributes to hyperglycemia.1 In Indonesia, traumatic brain injury accounts for 11.9% of trauma cases, highlighting its clinical burden.[3]

Enteral nutrition is recommended as the preferred route of nutritional support in critically ill patients with preserved gastrointestinal function, as it maintains gut integrity and reduces infectious complications compared with parenteral nutrition.4 Nevertheless, the optimal method for delivering enteral nutrition remains controversial. Intermittent bolus feeding is generally considered more physiological and practical, whereas continuous feeding has been hypothesized to improve gastrointestinal tolerance and metabolic stability. Previous studies and meta-analyses have demonstrated inconsistent results, with no clear superiority of either method in general critically ill populations. Importantly, evidence specifically evaluating patients with severe TBI remains limited.[5,6]

Given the high risk of gastric intolerance, glycemic fluctuation, and diarrhea in severe TBI, determining the optimal enteral

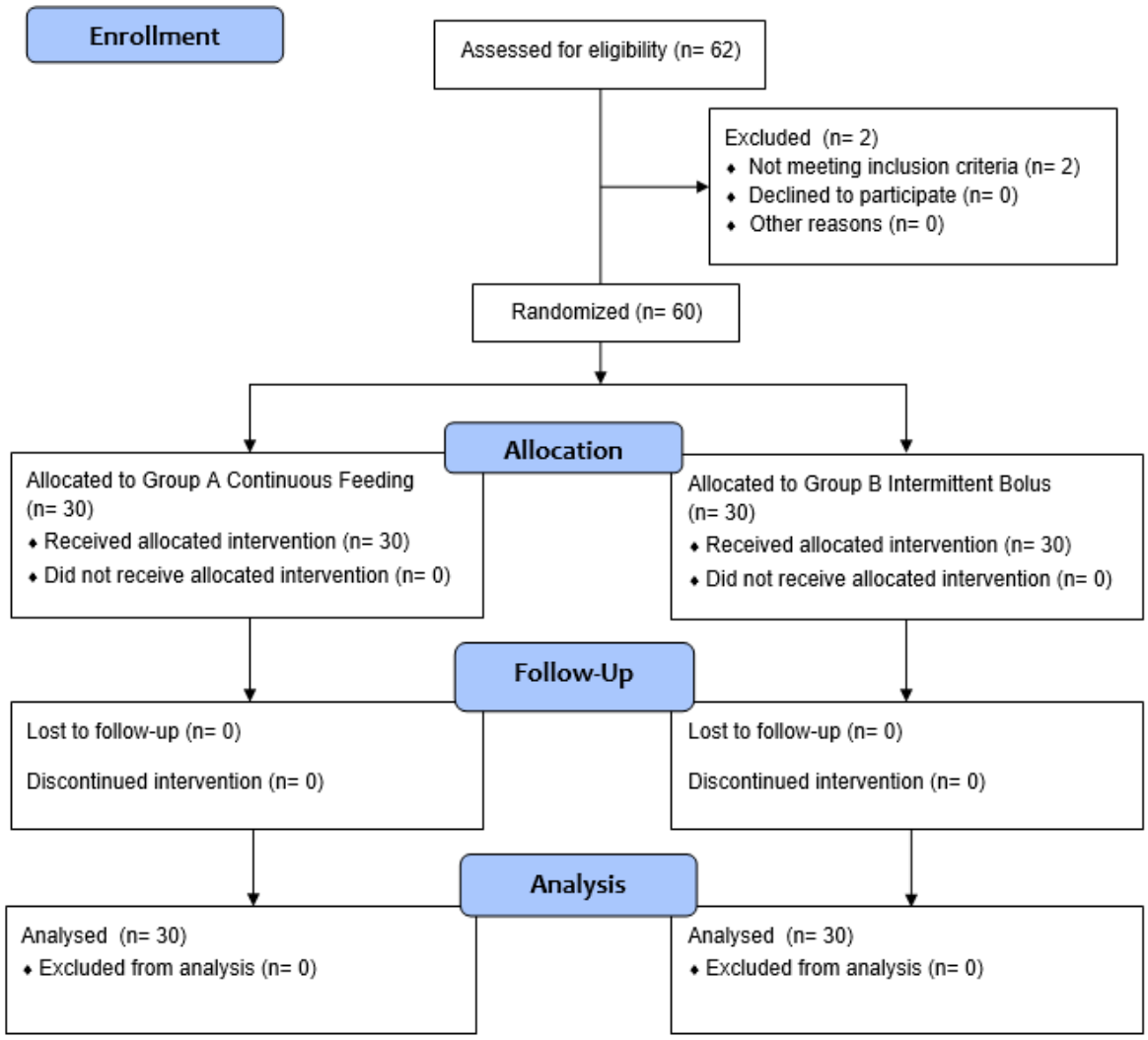

Figure 1. CONSORT Flow Diagram

feeding strategy is clinically relevant. This study aimed to compare continuous and intermittent bolus enteral feeding in terms of gastric residual volume, glycemic variability, and diarrhea in patients with severe TBI.

Patients and Methods

Trial Design

This study was a prospective, assessor-blinded, randomized controlled trial conducted in the intensive care unit of a tertiary referral hospital between November and December 2025. Patient recruitment commenced only after approval had been obtained from the Institutional Ethics Committee on 14 November 2025 (2767/ UN14.2.2.VII.14/LT/2025). Informed written consent was obtained from all participants or their legally authorized representatives before enrolment.

Participants

Eligible participants were adult patients (≥18 years) with severe TBI, defined as a Glasgow Coma Scale (GCS) score ≤8 confirmed by clinical and radiological assessment. Eligible patients were required to have an indication for enteral nutrition via nasogastric tube and to initiate feeding within 24 hours of admission. Predicted body weight was restricted to 50–70 kg to ensure homogeneity in nutritional requirements.

Patients were excluded if they had pre-existing severe gastrointestinal disorders (including paralytic ileus or intestinal obstruction), required high-dose vasopressor support (norepinephrine >0.3 μg/kg/min), had treatment-limitation decisions, or declined participation.

Participants were withdrawn if they developed hemodynamic instability requiring escalation of vasopressors, aspiration events, endocrine complications, were discharged from the intensive care unit within 24 hours, or died during the study period.

Interventions

All participants received enteral nutrition via a nasogastric tube using a standardized enteral formula to ensure consistency of nutritional composition across groups. The formula used in this study was a commercially available peptide-based enteral formula (Peptibren®, PT Kalbe Farma, Tbk), specifically formulated to support patients with neurological injury and high metabolic stress. This formula provides an energy density of approximately 1 kcal/mL, allowing adequate caloric delivery while minimizing fluid overload, which is particularly relevant in patients with severe TBI.

The use of a single standardized enteral formula in both intervention groups was intended to eliminate potential confounding effects related to differences in nutrient composition, thereby ensuring that the observed outcomes were attributable solely to the feeding method.

Participants assigned to the continuous group received enteral nutrition via infusion using a nutritional bag system. Feeding was initiated at 50 mL/h for the first 3 hours, followed by a 1-hour rest period, and continued cyclically over 24 hours. Water flushes of 50 mL were administered prior to each rest period. Gastric residual volume was monitored every 4 hours during feeding.

Participants assigned to the intermittent bolus group received enteral nutrition divided into six equal portions over 24 hours. Each bolus (approximately 150 mL) was administered every 4 hours by gravity

over 5–10 minutes. Water flushes of 50 mL were administered after each feeding.

In both groups, enteral feeding was initiated within the first 24 hours following ICU admission and monitoring of outcomes was conducted during this period.

Outcomes

The primary outcome was GRV, measured every 4 hours using bedside gastric ultrasonography. All ultrasound examinations were performed by a single senior anesthesiology resident who had received formal training in gastric ultrasonography, thereby minimizing inter-operator variability. Patients were positioned in the right lateral decubitus position, and a low-frequency curved-array probe was placed over the epigastric paramedian region to identify the gastric antrum. The antero-posterior and craniocaudal diameters of the antrum were measured, and the antral cross-sectional area was calculated using the validated Perlas formula to estimate GRV. Measurements were obtained using a standardized scanning protocol without averaging multiple acquisitions. Formal intra- or inter-observer reliability testing was not performed.

Secondary outcomes included glycemic variability and incidence of diarrhea. Blood glucose levels were measured at baseline, 2 hours after feeding initiation, and subsequently every 4 hours using a portable glucometer. Glycemic variability was assessed using the coefficient of variation (CV), calculated by dividing the standard deviation by the mean glucose level and multiplying by 100%. A CV ≤36% was considered indicative of stable glycemic control.

Diarrhea was established as the passage of loose or watery stools occurring more than three times within a 24-hour period or stool volume exceeding 200 g/day, as documented by ICU nursing staff.

Sample Size

Sample size was calculated based on the primary outcome (gastric residual volume), using the formula for comparison of two independent means:

$$n = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \times (\sigma_1^2 + \sigma_2^2)}{(\mu_1 - \mu_2)^2}$$

In this formula, n represents the required sample size per group. The term $Z\alpha/2$ corresponds to the standard normal deviate for a significance level (α) of 5%, while $Z\beta$ corresponds to a statistical power of 80%. The parameters σ_1 and σ_2 denote the standard deviations of the outcome in each group, and $(\mu_1 - \mu_2)$ represents the expected difference in mean GRV between the two groups.

The calculation was based on data reported by Banaei et al. (2022), which reported a mean GRV of 39.78 mL in the continuous group and 43.98 mL in the intermittent bolus group, with standard deviations of 4.94 and 7.18, respectively.[5] Using these parameters ($Z\alpha/2$ = 1.96 and $Z\beta$ = 0.84), the minimum required sample size was 27 participants in each group.

To account for potential dropout, an additional 10% was added, resulting in a final sample size of 30 participants per group. Therefore, a total of 60 participants were included in this study.

Randomisation

Participants were enrolled through consecutive sampling and randomly assigned in a 1:1 ratio using a computer-generated randomization sequence. Allocation concealment was maintained with sealed opaque envelopes that were

opened immediately before the intervention.

Blinding

Due to the nature of the intervention, personnel administering enteral nutrition could not be blinded. However, outcome assessments, including gastric residual volume, blood glucose measurements, and gastrointestinal outcomes, were performed by an independent investigator blinded to group allocation. The treating clinical team was also blinded to treatment allocation, except for the personnel responsible for administering the assigned feeding protocol.

Statistical Methods

Statistical analyses were performed using IBM SPSS Statistics (IBM Corp., Armonk, NY, USA). All analyses followed the intention-to-treat principle. Continuous variables were summarized as mean ± standard deviation or median (interquartile range), according to data distribution, while categorical variables were expressed as frequencies and percentages. Data normality was assessed using the Kolmogorov–Smirnov test.

The primary outcome, gastric residual volume (GRV), was analyzed using repeated-measures analysis of variance (ANOVA), with feeding method as the between-subject factor and time as the within-subject factor. Mauchly's test was used to assess sphericity, and the Greenhouse–Geisser correction was applied when the assumption of sphericity was violated. Continuous baseline variables were compared using the independent *t*-test or Mann–Whitney *U* test, as appropriate. Categorical variables were analyzed using the chi-square test or Fisher's exact test. A two-tailed P <0.05 was considered statistically significant.

Results

A total of 60 patients with severe TBI were enrolled and included in the final analysis, with 30 patients allocated to the continuous enteral nutrition group and 30 to the intermittent bolus feeding group. The mean age was 38.67 ± 12.88 years in the continuous group and 38.37 ± 11.48 years in the intermittent bolus group. Male patients predominated in both groups, accounting for 63.3% vs 60.0% of participants in the continous and intermitten bolus groups, respectively. Body mass index and other baseline characteristics were comparable between the groups, with no statistically significant differences observed (Table 1).

Group A: continuous feeding group; Group B: intermittent bolus group; BMI: Body Mass Index, [T]= Independent T-test, [C]: *Chi-square test*.

Table 1. Baseline characteristics of the study participants

Variables	Group A (n=30)	Group B (n=30)	*p-value*
Age (years), mean ± SD	38.67 ± 12.88	38.37 ± 11.48	0.462[T]
Sex, n(%)			
Male	19 (63.3)	18 (60)	0.791[C]
Female	11 (36.7)	12 (40)	
Body weight (kg), mean ± SD	55.57 ± 7.76	58.60 ± 9.89	0.096[T]
Height (cm), mean ± SD	162.50 ± 8.10	162.20 ± 7.30	0.359[T]
BMI (kg/m^2), mean ± SD	21.21 ± 3.46	22.20 ± 4.30	0.165[T]

Repeated-measures ANOVA demonstrated that GRV changed significantly over time (Greenhouse–Geisser corrected $F(3.980, 230.814) = 18.360$, $p < 0.001$, partial $\eta^2 = 0.240$). A significant interaction between time and feeding method was observed

($F(3.980, 230.814) = 3.437$, $p = 0.010$, partial $\eta^2 = 0.056$), indicating that the pattern of GRV over time differed between the continuous and intermittent bolus feeding groups. Moreover, the continuous enteral nutrition group had a significantly lower overall GRV than the intermittent bolus feeding group throughout the 24-hour observation period ($F(1, 58) = 158.235$, $p < 0.001$, partial $\eta^2 = 0.732$) (Tables 2 and 3).

Table 2. Comparison of gastric residual volume at 4, 8, 12, 16, 20, and 24 hours

Variables, GRV (mL), mean ± SD	Group A (n=30)	Group B (n=30)
GRV at 4 hours	69.67 ± 16.07	93.32 ± 9.93
GRV at 8 hours	67.73 ± 11.31	94.39 ± 9.93
GRV at 12 hours	74.54 ± 10.67	93.43 ± 10.51
GRV at 16 hours	85.73 ± 9.53	98.18 ± 12.90
GRV at 20 hours	83.79 ± 10.53	101.33 ± 13.47
GRV at 24 hours	88.60 ± 11.18	102.61 ± 15.31

Group A: continuous feeding group; Group B: intermittent bolus group, GRV: Gastric Residual Volume

Glycemic variability did not differ significantly between groups. Stable glycemic control was observed in 29 patients (96.7%) in the continuous group and 28 patients (93.3%) in the intermittent bolus group, with no statistically significant difference (p = 0.500) (Table 4).

In contrast, the incidence of diarrhea was significantly lower in the continuous enteral nutrition group than in the intermittent bolus group. Diarrhea was observed in 6 patients (20.0%) in the continuous group compared with 15 patients (50.0%) in the intermittent bolus group, representing a statistically significant difference (Table 5).

Discussion

Patients with severe TBI in the intensive care unit experience a hypermetabolic and hypercatabolic state, which predisposes them to malnutrition, impaired gastric emptying, and metabolic instability. This condition is driven by neuroendocrine stress responses, including increased catecholamines, cortisol, and insulin resistance, which contribute to hyperglycemia and secondary brain injury.[1,2,7] Enteral nutrition remains the preferred route of nutritional support as it preserves gut barrier integrity, reduces infectious complications, and is more physiologically appropriate than parenteral nutrition.[4] However, impaired gastric motility in this population makes the choice of feeding method an important determinant of gastrointestinal tolerance and clinical outcomes.

The primary finding of this study was that continuous enteral nutrition was associated with significantly lower gastric residual volume than intermittent bolus feeding throughout the 24-hour observation period. Repeated-measures ANOVA demonstrated both a significant overall effect of feeding method and a significant interaction between feeding method and time. This finding is consistent with the physiological mechanism of gastric emptying, where gradual nutrient delivery reduces intragastric pressure, improves antral motility, and prevents vagally mediated inhibition of gastric emptying. In contrast, bolus feeding introduces a large volume within a short period, leading to gastric distension, increased intragastric pressure, and delayed gastric emptying.[8]

Table 3. Results of repeated-measures ANOVA for gastric residual volume during the 24-hour observation period

Repeated-measures ANOVA (Greenhouse–Geisser correction)	F (df)	*p-value*	partial η^2
Time effect	18.360 (3.980, 230.814)	<0.001	0.240
Group effect	158.235 (1, 58)	<0.001	0.732
Time × Group interaction	3.437 (3.980, 230.814)	0.010	0.056

GRV = gastric residual volume; η^2 = partial eta squared. Data were analyzed using repeated-measures ANOVA. Because Mauchly's test indicated violation of the sphericity assumption (W = 0.584, p = 0.007), Greenhouse–Geisser correction was applied to the within-subject (time) and time × group effects

Table 4. Comparison of glycemic variability between groups

Glycemic Variability, n (%)	Group A (n=30)	Group B (n=30)	*p-value*
Stable	29 (96.7)	28 (93.3)	0.500[f]
Unstable	1 (3.3)	2 (6.7)	

Group A: continuous feeding group; Group B: intermittent bolus group, [f]: Fisher's exact test (two cells had expected counts < 5)

Table 5. Comparison of gastrointestinal tolerance based on diarrhea incidence

Diarrhea Incidence, n (%)	Group A (n=30)	Group B (n=30)	*p-value*
Yes	6 (20)	15 (50)	0.008[C]
No	24 (80)	15 (50)	

Group A: continuous feeding group; Group B: intermittent bolus group, [C]: *Chi-square test.*

These findings are consistent with previous randomized trials and recent meta-analyses demonstrating improved gastrointestinal tolerance and reduced feeding intolerance with continuous feeding.[6,9] Current clinical guidelines also support this approach, recommending continuous enteral nutrition in patients with severe neurological injury due to better tolerance profiles.[4]

From a clinical perspective, lower gastric residual volume may indicate better enteral feeding tolerance and fewer interruptions in nutritional delivery. However, this study did not evaluate aspiration-related complications or other longer-term clinical outcomes; therefore, these potential benefits should be interpreted cautiously. These factors are particularly important in patients with severe TBI, where maintaining adequate nutritional support plays a critical role in recovery and prevention of complications.[10,11]

Although the reduction was modest, even small improvements in feeding tolerance may reduce interruptions in nutritional delivery during the early phase of neurocritical care. Therefore, its clinical

significance should be interpreted cautiously, particularly because routine GRV monitoring alone is no longer recommended to assess feeding intolerance or aspiration risk. Nevertheless, the lower GRV observed in the continuous feeding group was accompanied by a significantly lower incidence of diarrhea, suggesting improved gastrointestinal tolerance. Whether this reduction translates into clinically important outcomes such as fewer aspiration events, reduced pneumonia, shorter ICU stay, or improved survival remains to be determined in future studies.

No statistically significant difference was identified between the two feeding methods for glycemic fluctuation. This finding suggests that glycemic control in critically ill patients is influenced predominantly by the systemic stress response rather than by the method of enteral nutrient delivery. Severe TBI triggers a neuroendocrine cascade characterized by increased catecholamines, cortisol, glucagon, and insulin resistance, leading to stress-induced hyperglycemia.[1,7] Elevated glucose levels can exacerbate cerebral edema, oxidative stress, and ischemic injury, contributing to worse neurological outcomes.[2] However, previous studies and meta-analyses have shown that the method of enteral nutrition does not significantly affect glycemic fluctuation in critically ill populations. Therefore, glycemic management should primarily rely on standardized insulin protocols and close glucose monitoring rather than modification of feeding strategy alone.[12,13]

The incidence of diarrhea was significantly lower in the continuous feeding group, indicating better gastrointestinal tolerance compared with intermittent bolus feeding. This finding may be explained by differences in intestinal physiology. Continuous feeding provides a steady nutrient flow that maintains stable intestinal osmolality and promotes efficient absorption, whereas bolus feeding increases osmotic load and stimulates rapid intestinal transit, leading to diarrhea.[8] Additionally, rapid nutrient delivery may reduce mucosal contact time, impairing absorption and increasing luminal fluid secretion. Similar findings have been reported in critically ill populations, where intermittent feeding is associated with higher rates of diarrhea and gastrointestinal intolerance.[6,9,11,14]

Clinically, reduced diarrhea may improve fluid balance, electrolyte homeostasis, and continuity of enteral nutrition. However, whether these benefits translate into improved patient recovery or other long-term clinical outcomes was not evaluated in the present study.[7]

This study provides additional evidence supporting continuous enteral nutrition may improve short-term gastrointestinal tolerance in patients with severe TBI without adversely affecting glycemic fluctuation during the first 24 hours of ICU care.

This study has several limitations should be acknowledged. First, clinically important outcomes such as aspiration, ventilator-associated pneumonia, adequacy of nutritional delivery, ICU length of stay, and mortality were not evaluated. Second, this study did not assess gastrointestinal hormonal biomarkers such as motilin or gastrin, which could provide further insight into the mechanisms underlying gastric motility and feeding tolerance. Future studies with longer observation periods and inclusion of mechanistic biomarkers are needed to better understand the long-

term impact of enteral feeding strategies in this population.

A further limitation is that detailed data on concomitant ICU therapies that may influence gastric emptying and glycemic control, such as sedatives, opioids, neuromuscular blocking agents, prokinetics, antiemetics, and stress-ulcer prophylaxis, were not systematically collected. Although all patients received routine ICU care according to institutional practice, the potential influence of these co-interventions cannot be excluded. Finally, the relatively small sample size may have limited the statistical power to detect differences in secondary outcomes.

Conclusion

Continuous enteral nutrition was associated with lower gastric residual volumes and a lower incidence of diarrhea than intermittent bolus feeding during the first 24 hours of ICU admission in patients with severe traumatic brain injury, while glycemic fluctuation did not differ significantly between groups. These findings are limited to the 24-hour observation period, and further studies are needed to determine whether they translate into improved long-term clinical outcomes.

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Conflict of Interest

The author(s) report no conflict of interest.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author's Contributions

Conceptualization: AFC, SS. Methodology: AFC. Investigation: AFC, IWA, SS. Data curation: AFC, IWA, SS. Formal analysis: AFC, IBK. Writing – original draft: AFC. Writing – review & editing: AFC, IWA, SS. Supervision: IBK, IWA. All authors approved the final manuscript.

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CASE REPORT

Epidural Anesthesia for Cesarean Section in a Parturient with Chiari I Malformation: a Case Report

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Abstract

Chiari I malformation is a congenital neurological condition characterized by caudal herniation of the cerebellar tonsils, which may alter cerebrospinal fluid dynamics and complicate anesthetic management during pregnancy. The optimal anesthetic approach for parturients with this condition remains controversial, particularly regarding the safety of neuraxial anesthesia. We report the case of a 28-year-old woman with a known Chiari I malformation who presented at term gestation and underwent an urgent cesarean section after the onset of regular uterine contractions. Preoperative neurological evaluation and imaging demonstrated stable cerebellar tonsillar herniation without syringomyelia or signs of increased intracranial pressure. Following multidisciplinary consultation, epidural anesthesia was selected to minimize abrupt cerebrospinal fluid pressure changes and maintain hemodynamic stability. Epidural anesthesia was performed using 15 mL of 0.5% plain bupivacaine, achieving a T6 sensory block level. A healthy neonate was delivered with APGAR scores of 8 and 9 at 1 and 5 minutes, respectively. The procedure was performed uneventfully, with stable intraoperative parameters and no neurological complications. Postoperative recovery was smooth, and no neurological deterioration was observed during follow-up. This case highlights that carefully planned and titrated epidural anesthesia may be a feasible anesthetic option for cesarean section in selected parturients with Chiari I malformation following thorough multidisciplinary assessment.

Keywords: Chiari malformation type I; Cesarean section; Epidural anesthesia; Pregnancy

Introduction

Chiari I malformation is a congenital neurological condition characterized by caudal herniation of the cerebellar tonsils through the foramen magnum, which may disrupt cerebrospinal fluid (CSF) circulation and result in craniospinal pressure dissociation.[1] Advances in neuroimaging have led to increased detection of this condition, revealing that many individuals remain asymptomatic until adulthood and are often diagnosed incidentally. Nevertheless, physiological changes during pregnancy, including increased intra-abdominal and intrathoracic pressures, may influence CSF dynamics and raise concerns regarding neurological stability during labor and delivery.[2] The anesthetic management of parturients with Chiari I malformation remains challenging, particularly with respect to the use of neuraxial anesthesia.

Theoretical risks include cerebellar tonsillar herniation and neurological deterioration following dural puncture or sudden alterations in CSF pressure gradients. Conversely, general anesthesia avoids neuraxial manipulation but may be associated with airway difficulties, hemodynamic instability, and increases in intracranial pressure during laryngoscopy and intubation.[3] Due to the rarity of this condition, current evidence guiding anesthetic decision-making is limited and primarily derived from case reports and small retrospective studies, resulting in variability in clinical practice.[4]

Despite increasing reports of successful neuraxial anesthesia in parturients with Chiari I malformation, the available evidence remains limited to case reports and small retrospective studies, with no standardized guidelines to support anesthetic decision-making. This case contributes additional clinical evidence by illustrating the use of carefully titrated epidural anesthesia in a neurologically stable parturient with spontaneous labor onset requiring urgent cesarean section.

Case Presentation

A 28-year-old woman, primigravida at 39 weeks of gestation, presented to the emergency department with regular uterine contractions occurring two to three times every 10 minutes. She reported no vaginal bleeding, no abnormal discharge, and normal fetal movements. There were no accompanying symptoms such as fever, cough, headache, visual disturbance, limb weakness, or sensory changes. Her antenatal course had been uneventful, with regular obstetric follow-up throughout pregnancy. Initially scheduled for elective cesarean section, the patient experienced regular contractions at 39 weeks of gestation, and the procedure was converted to an urgent cesarean section to avoid prolonged labor.

The patient had a known history of Chiari I malformation diagnosed during adolescence following evaluation for intermittent neck discomfort. Previous prepregnancy magnetic resonance imaging (MRI) demonstrated cerebellar tonsillar herniation measuring approximately 13 mm below the foramen magnum without evidence of brainstem compression or syringomyelia. She had no history of progressive neurological deficits, raised intracranial pressure symptoms, or previous neurosurgical intervention. Additional medical history included mitral valve prolapse and a thyroid cystic goiter, both of which were asymptomatic and managed conservatively. There was no relevant family history of neurological disorders, and she did not report any psychosocial issues. She was not receiving regular neurological medication.

During the antenatal period, the patient underwent multidisciplinary evaluation involving obstetrics and gynecology, neurology, anesthesiology, cardiology, and internal medicine to determine the optimal mode of delivery and anesthetic strategy. Neurological assessment confirmed stable neurological status with no focal deficits. The neurologist recommended cesarean delivery to minimize the risk of increased intracranial pressure associated with prolonged labor and forceful pushing. Cardiological evaluation, including echocardiography, revealed preserved left ventricular systolic function with no significant valvular abnormalities requiring intervention. Thyroid function tests were within normal limits.

Upon admission, cardiotocography showed a reassuring fetal status. The patient had stable vital signs, a Mallampati class II airway, a thyromental distance of more than 6 cm, and full neck mobility despite the presence of a cystic thyroid goiter. A comprehensive neurological examination revealed intact cranial nerve function, normal motor strength of 5/5 in all extremities, preserved sensation, normal deep tendon reflexes, and no clinical signs of increased intracranial pressure. The patient was classified as American Society of Anesthesiologists physical status II. Urgent cesarean section was performed under epidural anesthesia, based on the previously established multidisciplinary plan. The anesthetic goal was to maintain hemodynamic stability and avoid abrupt changes in cerebrospinal fluid pressure.

Standard monitoring was applied in the operating room, including non-invasive blood pressure, electrocardiography, pulse oximetry, respiratory rate, and temperature monitoring. Epidural anesthesia was performed by an experienced anesthesiologist under strict aseptic conditions with the patient in the lateral decubitus position. The epidural space was identified at the L3-L4 lumbar level with an 18G Tuohy needle using loss of resistance (LOR) to saline at 4 cm depth, and the catheter was secured at 9 cm at the skin. A 3 mL epidural test dose was administered, consisting of 1.8 mL lidocaine 2% and 1.2 mL of a commercial lidocaine–epinephrine preparation (Pehacaine®, lidocaine 2% with epinephrine 1:80,000), to detect inadvertent intravascular or intrathecal catheter placement. The main dose of 15 ml 0.5% plain bupivacaine was administered in 5 ml increments every 5 minutes to ensure hemodynamic stability and avoid sudden sympathetic blockade. The sensory block reached T6, while the Bromage score remained 0, indicating no motor block. The cesarean section proceeded uneventfully without additional epidural doses. A healthy neonate was delivered with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively, and a birth weight of 3500 grams. No complications such as accidental dural puncture or high block were observed. Fluid management included a co-load of 500 ml Ringer's Lactate. No vasopressors were required. Oxytocin 10 IU was administered as an infusion following delivery. Estimated blood loss was 400 ml.

Postoperatively, analgesia was administered via an epidural catheter using 0.1% bupivacaine, with a 10 mL bolus given when the pain score (VAS) exceeded 5. In addition, systemic analgesia was provided using an infusion consisting of fentanyl 400 mcg combined with ketamine 20 mg in 50 mL of normal saline, administered at a rate of 2.1 mL/hour. The patient was closely monitored for neurological symptoms, including headache, neck pain, sensory disturbances, or motor weakness. During the postoperative period, she remained neurologically intact, reported adequate pain control, and experienced no nausea or vomiting. Early mobilization was initiated on the first postoperative day.

The patient's postoperative course was uncomplicated. She demonstrated full neurological function and stable vital signs throughout her hospital stay. She was discharged on the second postoperative day in good condition, with no evidence of neurological deterioration or anesthetic-related complications at follow-up. The patient's status was evaluated seven days and six weeks after surgery, and she reported no neurological symptoms or pain.

Discussion

The anesthetic management of parturients with Chiari I malformation poses a significant clinical challenge due to altered cerebrospinal fluid (CSF) dynamics and the potential risk of neurological deterioration during labor and delivery. In the present case, epidural anesthesia was selected for cesarean section following comprehensive multidisciplinary evaluation, with the primary aim of maintaining intracranial pressure stability and avoiding abrupt changes in CSF pressure gradients.

Chiari I malformation is characterized by impaired CSF flow at the level of the foramen magnum, which may result in craniospinal pressure dissociation and altered intracranial compliance.1 Physiological changes associated with pregnancy, including increased intra-abdominal and intrathoracic pressures as well as painful uterine contractions, may further exacerbate fluctuations in CSF and intracranial pressures. These factors have historically raised concerns regarding the safety of neuraxial anesthesia in this patient population, particularly in the context of accidental dural puncture or rapid CSF leakage.[2]

The role of neuraxial anesthesia in parturients with Chiari I malformation remains controversial. Theoretical risks include cerebellar tonsillar herniation and worsening neurological symptoms following sudden alterations in CSF pressure. However, contemporary evidence suggests that neuraxial techniques may be safely considered in selected patients without signs of raised intracranial pressure or progressive neurological deficits. Neuraxial anesthesia is not an absolute contraindication in patients with intracranial pathology when careful patient selection and vigilant monitoring are applied.[3] More recent reviews have further supported this approach, highlighting that neuraxial anesthesia can be safely performed in parturients with stable intracranial pathology when meticulous technique and multidisciplinary planning are employed.[6] Furthermore, a multicenter retrospective study demonstrated favorable maternal and neurological outcomes in parturients with Chiari I malformation who received neuraxial anesthesia, supporting its feasibility in appropriately selected cases. [4]

In this case, the patient had a 13 mm cerebellar tonsillar herniation. Although tonsillar descent greater than 5 mm is generally considered radiologically diagnostic of Chiari I malformation, the extent of herniation does not necessarily correlate with clinical severity or predict neurological deterioration during neuraxial anesthesia. The decision to perform epidural anesthesia was based on the patient's stable neurological status, the absence of syringomyelia, and the lack of signs of increased intracranial pressure. Although spinal and combined spinal-epidural techniques have also been reported successfully in selected patients with Chiari I malformation, epidural anesthesia was preferred in this case because it allowed gradual titration and avoided intentional dural puncture. In contrast, general anesthesia, while avoiding neuraxial instrumentation, may still pose risks related to airway manipulation, hemodynamic instability, and transient increases in intracranial pressure during laryngoscopy and intubation.[5]

The strengths of this case include meticulous multidisciplinary planning, careful patient selection, and a conservative

anesthetic technique tailored to the underlying neurological condition. Nevertheless, this report is limited by its single-case design and the absence of direct intracranial pressure monitoring. In addition, long-term neurological follow-up was limited, which precludes definitive conclusions regarding delayed neurological outcomes.

In conclusion, Carefully titrated epidural anesthesia may be a feasible option for cesarean delivery in neurologically stable patients with Chiari I malformation after multidisciplinary assessment. While higher-quality prospective data remain limited, this report adds contemporary clinical evidence to guide individualized anesthetic decision-making in this challenging patient population.

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None.

Declaration of Patient Consent

The authors confirm that all necessary patient consent forms have been obtained. In these forms, the patient(s) provided informed consent for the publication of their images and relevant clinical information in the journal. The patients have been informed that while their names and initials will not be published and reasonable efforts will be made to protect their identity, complete anonymity cannot be guaranteed.

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Conflict of Interest

The author(s) report no conflict of interest.

Data Availability Statement

Deidentified patient data from this case report/series will be made available upon reasonable request to the corresponding author following publication, subject to institutional data-sharing policies and ethics approval.

Author's Contributions

Conceptualization: BW. Data curation: AP. Investigation: AP, BW. Writing – original draft: AP. Writing – review & editing: BW. Supervision: BW. All authors have read and approved the final version of the manuscript.

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CASE REPORT

Anesthesia Management in Aneurysm Clipping Surgery with Chilaiditi Sign : a Case Report

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Abstract

Chilaiditi sign is the asymptomatic interposition of the colon between the liver and diaphragm; when accompanied by gastrointestinal symptoms, it is termed Chilaiditi syndrome. Its coexistence with aneurysmal subarachnoid haemorrhage creates competing anaesthetic priorities, including aspiration prevention, lung protection, and control of cerebral haemodynamics. We report a 79-year-old woman who presented with sudden severe headache and transient loss of consciousness. Imaging demonstrated subarachnoid haemorrhage from a ruptured left posterior communicating artery aneurysm, together with incidental colonic interposition beneath an elevated right hemidiaphragm, bilateral pleural effusions, and partial right-lower-lobe collapse. After 10 hours of fasting and pharmacological aspiration-risk mitigation, general anaesthesia was induced with thiopental, remifentanil, and rocuronium using a modified rapid-sequence approach that included preoxygenation, cricoid pressure, gentle mask ventilation, and video laryngoscopy. Pressure-controlled ventilation and close haemodynamic control were maintained throughout aneurysm clipping. No intraoperative rupture, aspiration, haemodynamic instability, or respiratory deterioration occurred. The patient was extubated 36 hours after surgery and discharged on postoperative day 8 with a modified Rankin Scale score of 1. This case highlights the need to individualise induction and ventilation when Chilaiditi sign coexists with urgent intracranial surgery. The uneventful outcome of a single case should not be interpreted as evidence that modified induction is generally safer than classical rapid-sequence induction.

Keywords: Chilaiditi syndrome; Intracranial aneurysm; Subarachnoid hemorrhage; Anesthesia, general; Craniotomy

Introduction

Chilaiditi sign is the asymptomatic radiographic interposition of the colon or, less commonly, small intestine between the liver and right hemidiaphragm. When this finding is accompanied by gastrointestinal symptoms, it is termed Chilaiditi syndrome. The reported prevalence is 0.025-0.28%, with a predominance among older adults.[1] Although usually incidental, cephalad displacement of the diaphragm can reduce functional residual capacity and impair ventilation, particularly when increased intra-abdominal pressure or positive-pressure ventilation causes further diaphragmatic displacement. Interposed bowel may also raise concern about regurgitation during induction, although evidence quantifying aspiration risk is limited.[2] Patients with coexisting pulmonary or pleural abnormalities may have even less and controlled ventilation particularly important.[3]

When Chilaiditi sign coexists with aneurysmal subarachnoid haemorrhage (aSAH), the anaesthetic plan must reconcile competing priorities. The aneurysm should be secured promptly to reduce rebleeding, while anaesthetic management aims to maintain cerebral perfusion, limit changes in transmural pressure, provide brain relaxation, and avoid hypoxaemia and hypercapnia. Airway instrumentation can provoke sympathetic stimulation and abrupt haemodynamic changes, whereas strategies used to reduce aspiration risk may themselves influence oxygenation, gastric insufflation, and intracranial pressure. Evidence specific to neuroanaesthesia in patients with this anatomical variant is limited to isolated reports; decisions must therefore rely largely on general neuroanaesthetic and aspiration-risk principles.[4] This report describes the perioperative management of an older woman with a ruptured posterior communicating artery (PCom) aneurysm and incidental Chilaiditi sign who underwent emergency craniotomy and clipping. The case highlights how aspiration precautions, lung-protective ventilation, and cerebral haemodynamic control were balanced in an individualised modified rapid-sequence approach

Case Presentation

A 79-year-old woman (60 kg, 155 cm) presented five hours after a fall with head impact, followed by sudden severe headache and about five minutes of loss of consciousness. Her last meal was consumed six hours before the pre-anaesthetic evaluation. She reported choking while eating for five years, reduced oral intake for one week, and poorly controlled hypertension. She had no gastrointestinal symptoms, dyspnoea, fever, or seizures. The Glasgow Coma Scale score was E3V5M6 (14), and pain was 7/10. Peripheral oxygen saturation was 93% on room air and 97% with oxygen at 4 L/min through a nasal cannula. The respiratory rate was 22 breaths/min, with bilateral rhonchi; bowel sounds were audible over the right sixth intercostal space. Blood pressure was 157/72 mmHg and heart rate 95 beats/min. Arterial blood gas analysis on face-mask oxygen at 8 L/min showed mild compensated metabolic alkalosis (pH 7.50, $PaCO_2$ 46 mmHg, HCO_3^- 35.9 mmol/L, and base excess +12.7 mmol/L). Other laboratory findings are presented in Table 1

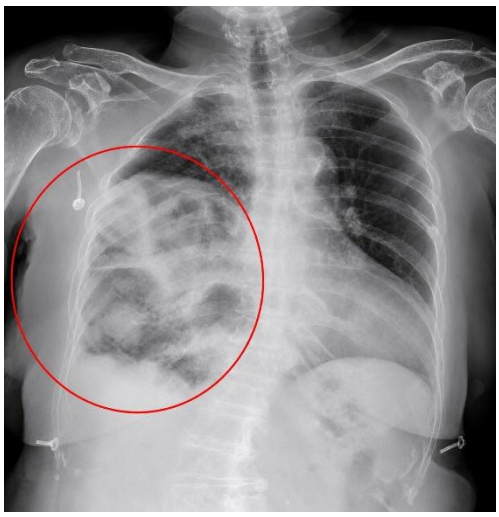

Figure 1. Posteroanterior chest radiograph showing elevation of the right hemidiaphragm with interposed bowel gas, consistent with Chilaiditi sign, together with bilateral pleural effusions and partial right-lower-lobe collapse.

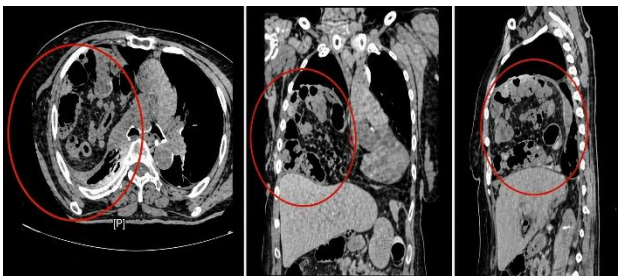

Figure 2. Contrast-enhanced thoracic CT images in axial, coronal, and sagittal planes showing interposition of the hepatic flexure between the liver and right hemidiaphragm (Chilaiditi sign), with cephalad displacement of the right hemidiaphragm

Table 1. Laboratory Findings

Test names	Values	Units
Complete Blood Count		
White Blood Cell	10.04	$\times 10^3/\mu L$
Hemoglobin	11.4	g/dL
Hematocrit	34.5	%
Platelets	267	$\times 10^3/\mu L$
Coagulation Profile		
PT	9.5	s
APTT	23.3	s
International Normalized Ratio (INR)	0.88	–
Clinical Chemistry		
BUN	17	mg/dL
Creatinine	0.65	mg/dL
eGFR	84.4	mL/min/1.73 m^2
AST	38	U/L
ALT	41	U/L
Electrolytes		
Sodium	137	mmol/L
Potassium	3.8	mmol/L
Chloride	103	mmol/L
Glucose	97	mg/dL
Arterial Blood Gas (FM 8 L/min)		
pH	7.5	–
pCO_2	46	mmHg
pO_2	189	mmHg
BEecf	12.7	mmol/L
HCO_3^-	35.9	mmol/L
SaO_2	100	%
TCO_2	37.3	mmol/L

ALT : alanine aminotransferase; APTT : activated partial thromboplastin time; AST : aspartate aminotransferase; BEecf : base excess; BUN: blood urea nitrogen; eGFR : estimated glomerular filtration rate; PT : prothrombin time; SaO_2 : arterial oxygen saturation; TCO_2 : Total carbondioxide

Chest radiography (Figure 1) showed an elevated right hemidiaphragm and bilateral pleural effusions. Thoracic computed tomography (CT; Figure 2) confirmed Chilaiditi sign, with the hepatic flexure in the subphrenic space, leftward mediastinal shift, and partial right-lower-lobe collapse.

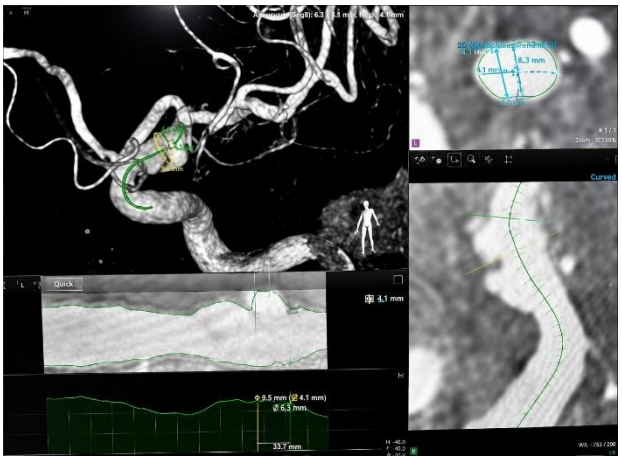

Figure 3. Three-dimensional rotational angiography and multiplanar reconstructions showing a saccular aneurysm at the origin of the left posterior communicating artery.

CT angiography demonstrated intracranial haemorrhage and subacute infarction involving the anterior limb of the internal capsule and left lentiform nucleus. Digital subtraction angiography (Figure 3) showed a saccular left PCom aneurysm, left vertebrobasilar-junction stenosis, and no additional anterior-circulation aneurysm. Severity was World Federation of Neurosurgical Societies grade 2, Hunt and Hess grade 2, and modified Fisher grade 1.

After 10 hours of fasting, premedication comprised midazolam 1 mg, omeprazole 40 mg, and dexamethasone 20 mg. The patient was classified as American Society of Anesthesiologists physical status IIIE. Standard monitoring was supplemented with a right radial arterial line. Preoxygenation used tidal-volume breathing with 100% oxygen at 6 L/min through a face mask. Anaesthesia was induced with thiopental 180 mg (3-5 mg/kg) and remifentanil target-controlled infusion (TCI; Minto model, 5-7 ng/mL). Cricoid pressure and gentle mask ventilation were applied. After rocuronium 40 mg, tracheal intubation was achieved on the first attempt using a video laryngoscope (Cormack-Lehane grade II). This modified rapid-

sequence approach maintained aspiration precautions while attenuating the pressor response to laryngoscopy. A right internal jugular catheter was inserted under ultrasound guidance.

Anaesthesia was maintained with air-oxygen (FiO_2 0.5), pressure-controlled ventilation (tidal volume 350 mL, approximately 7 mL/kg predicted body weight [50.5 kg]; respiratory rate 14 breaths/min; positive end-expiratory pressure 5 cmH_2O; plateau pressure 20 cmH_2O), thiopental infusion (3-4 mg/kg/h; total 600 mg), remifentanil TCI (3-5 ng/mL), and intermittent rocuronium. End-tidal carbon dioxide was 30-35 mmHg and mean arterial pressure 80-90 mmHg, without vasopressors. Ondansetron, tranexamic acid, and 20% mannitol 150 mL (30 g; approximately 0.5 g/kg) were administered before dural opening. A single permanent clip was applied, without temporary clipping or intraoperative rupture. Estimated blood loss was 300 mL, urine output 200 mL, crystalloid administration 1,800 mL, and temperature 36.1°C. Surgery lasted 2 hours 30 minutes.

The patient remained intubated and sedated and was transferred to intensive care. Analgesia comprised fentanyl 400 μg in 50 mL 0.9% saline at 2.1 mL/h and paracetamol 1 g every 8 hours. Nimodipine, started on admission, was continued for 21 days. Deep sedation was maintained for 24 hours; extubation was deferred until she was awake, cooperative, and breathing adequately. She was extubated 36 hours after surgery, stayed in intensive care for 5 days, and was discharged on postoperative day 8 with a modified Rankin Scale score of 1. Follow-up CT was not performed because of clinical improvement. No aspiration, pneumonia, or respiratory or neurological deterioration occurred. Figure 4 summarises the course.

Discussion

This case involved urgent clipping of a ruptured left PCom aneurysm in a patient with incidental Chilaiditi sign, an elevated right hemidiaphragm, bilateral pleural effusions, and partial right-lower-lobe collapse. The principal concerns were reduced pulmonary reserve and possible regurgitation if gastric insufflation or increased intra-abdominal pressure occurred. Chronic choking added uncertainty about aspiration risk despite fasting. The team retained aspiration precautions while avoiding hypoxaemia, hypercapnia, and abrupt haemodynamic changes that could worsen cerebral physiology.[5,6] Fasting was confirmed for 10 hours, but does not guarantee an empty stomach given her choking history, so aspiration precautions were maintained.

The modified rapid-sequence approach allowed controlled preoxygenation, cricoid pressure, low-pressure mask ventilation, and video laryngoscopy. Omeprazole could reduce gastric acidity but could not prevent aspiration.[7] Dexamethasone 20 mg was given as institutional practice intended to reduce cerebral oedema, with incidental antiemetic benefit.[8] Midazolam provided anxiolysis while lowering cerebral blood flow and oxygen consumption.[9] Gentle ventilation preserved oxygenation while minimising airway pressure and gastric insufflation. This approach differs from classical rapid-sequence induction and should be understood as an individualised balance of risks, not a generally preferable technique.

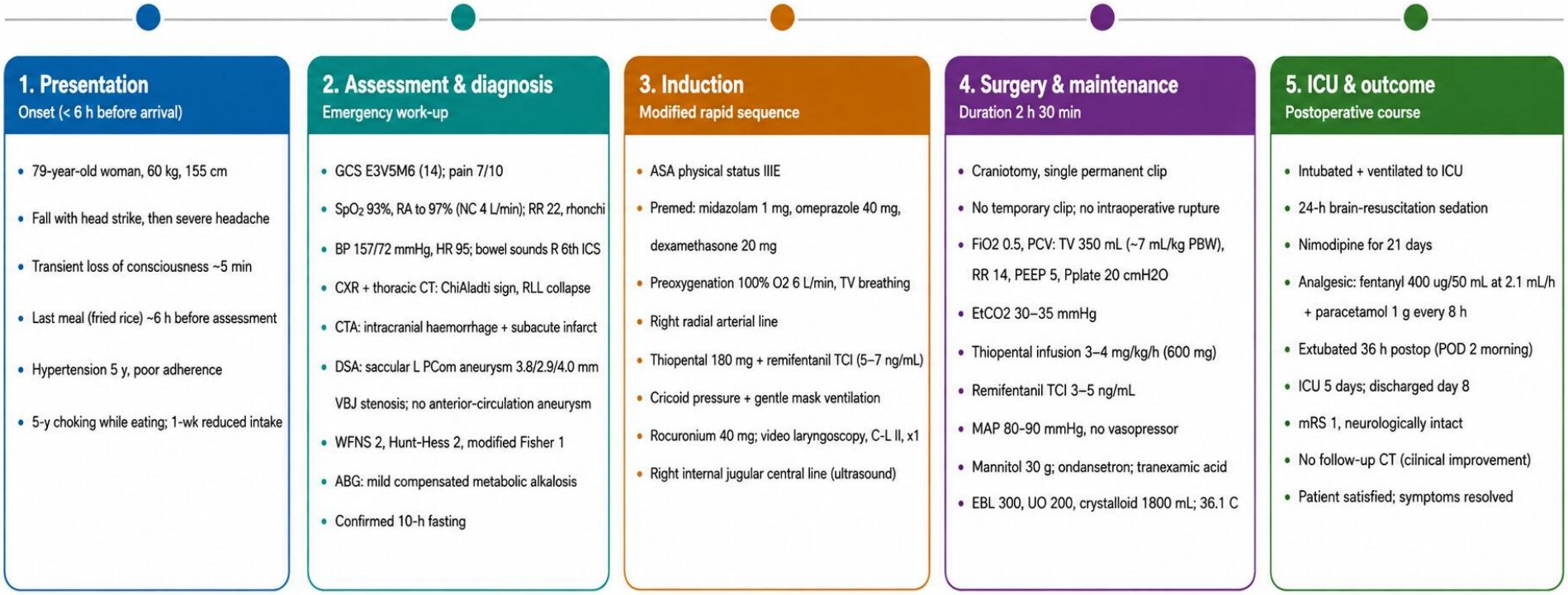

Figure 4. Timeline of the patient's presentation, perioperative management, and postoperative outcome.

10.24843/x59n1t02

Induction aimed to prevent rupture while preserving cerebral perfusion, avoiding a rise in transmural pressure and blunting the laryngoscopy pressor response.[4] General neuroanaesthetic principles for aneurysm surgery guided agent selection.[10] Thiopental, remifentanil, and rocuronium were selected for rapid hypnosis, attenuation of sympathetic responses, and prompt tracheal intubation. Thiopental reduces cerebral metabolic rate and blood flow, and observational data from unruptured aneurysm clipping have associated its use with fewer neurological complications; those findings cannot be directly extrapolated to ruptured aneurysms.[11] Remifentanil permits rapid titration with limited accumulation, whereas rocuronium provides rapid intubating conditions without clinically relevant histamine release.[12,13]

Classical RSI is usual when aspiration risk is high, but its main hazard here is the pressor response to laryngoscopy, with coughing, hypoxia and hypercapnia raising intracranial and transmural pressure. A modified rapid sequence approach, combining preoxygenation, cricoid pressure, gentle mask ventilation, rapid-onset agents and video laryngoscopy, preserved aspiration precautions with haemodynamic stability.[4]

Pressure-controlled ventilation with a tidal volume of approximately 7 mL/kg predicted body weight, positive end-expiratory pressure of 5 cmH_2O, plateau pressure of 20 cmH_2O, and end-tidal carbon dioxide of 30-35 mmHg provided lung-protective support. The elevated diaphragm, pleural effusions, and right-lower-lobe collapse were likely as relevant as the bowel interposition. Extubation was delayed until awakening and adequate respiratory assessment. The effusions were not further investigated or drained before urgent surgery, and no postoperative CT or formal pulmonary follow-up was performed; these are important limitations. Mannitol 30 g before dural opening gave satisfactory brain relaxation.[14]

Tranexamic acid was also administered; current aSAH guidance does not recommend routine antifibrinolytic therapy to improve functional outcome, so its use should be interpreted cautiously.[15] Depth-of-anaesthesia and quantitative neuromuscular monitoring were unavailable. These limitations and the uneventful outcome in one patient preclude causal conclusions about the selected strategy.

Published anaesthetic experience with Chilaiditi sign or syndrome is sparse. One abdominal surgery case emphasised aspiration prophylaxis and careful ventilation, and two patients underwent total intravenous anaesthesia without complications.[16,17] A cerebral-aneurysm report described an acceptable outcome with propofol-fentanyl TCI.[18] These heterogeneous reports support individualised planning but do not provide comparative evidence for any induction technique. This case adds a neuroanaesthetic example involving pulmonary compromise and modified rapid-sequence induction but remains limited by its single-patient design and incomplete postoperative imaging.

The principal lesson is that Chilaiditi sign should prompt assessment of respiratory mechanics and aspiration-related factors without allowing these concerns to compromise cerebral perfusion or aneurysm stability. In this patient, a carefully titrated modified rapid-sequence

approach, lung-protective ventilation, and delayed extubation were associated with an uneventful perioperative course. This outcome should not be interpreted as evidence that modified induction is safer than classical rapid-sequence induction; management should be individualised to the patient's pulmonary, gastrointestinal, and neurological risks.

Acknowledgement

None.

Declaration of Patient Consent

The authors confirm that all necessary patient consent forms have been obtained. In these forms, the patient(s) provided informed consent for the publication of their images and relevant clinical information in the journal. The patients have been informed that while their names and initials will not be published and reasonable efforts will be made to protect their identity, complete anonymity cannot be guaranteed.

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None reported.

Conflict of Interest

The author(s) report no conflict of interest.

Data Availability Statement

Deidentified patient data from this case report/series will be made available upon reasonable request to the corresponding author following publication, subject to institutional data-sharing policies and ethics approval.

Author's Contributions

Conceptualization: WW. Data curation: WW. Investigation: WW. Writing – original draft: WW. Writing – review & editing: IPPS. Supervision: IPPS. All authors have read and approved the final version of the manuscript.

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