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Perioperative Management of Patients using GLP-1 Receptor Agonists Current Evidence, Risks, and Practical Recommendations-A Narrative Review

Uğur Serkan Çitilcioğlu, Hatice Kaya Özdoğan

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Perioperative Management of Patients using GLP-1 Receptor Agonists Current Evidence, Risks, and Practical Recommendations-A Narrative Review

Uğur Serkan Çitilcioğlu, Hatice Kaya Özdoğan

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Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dual glucose-dependent insulinotropic polypeptide GLP-1 RAs are increasingly prescribed for diabetes and obesity, leading to a growing number of surgical patients receiving these agents. Their ability to delay gastric emptying has raised concerns about residual gastric contents (RGCs) and potential aspiration during anaesthesia. Available evidence from mechanistic studies, clinical investigations, and case reports indicates that GLP-1-based therapies consistently impair solid-phase gastric emptying and may increase RGC, particularly during early treatment and dose escalation, with effects that can persist despite standard fasting and short-term drug interruption. Although clinically apparent aspiration events remain uncommon, multiple reports have described perioperative regurgitation or unexpected solid gastric contents at induction. Early guidance favoured routine preoperative drug interruption; however, more recent multisociety recommendations increasingly support continuation of therapy in most asymptomatic patients and endorse enhanced perioperative mitigation strategies, such as dietary modification, strict adherence to fasting, selective use of point-of-care gastric ultrasound, preference for regional anaesthesia when feasible, and tailored airway management. Overall, current data support an individualised, risk-adapted approach rather than uniform interruption of GLP-1 therapy. Continuation of structured mitigation appears reasonable for many patients, whereas heightened caution and full-stomach precautions remain appropriate in higher-risk situations. Further prospective studies are required to define true perioperative aspiration risk and to establish evidence-based management pathways.

Keywords: Glucagon-like peptide-1 receptor agonists, anaesthesia, gastric emptying, pulmonary aspiration, obesity

Main Points

- Glucagon-like peptide-1 (GLP-1) receptor agonists delay solid-phase gastric emptying and may increase residual gastric contents despite standard fasting and short-term drug interruption.
- Clinically evident aspiration appears uncommon; however, perioperative regurgitation and unexpected solid gastric contents have been reported, particularly during early treatment and dose escalation.
- Contemporary multisociety guidance increasingly supports continuation of GLP-1 therapy in most asymptomatic patients, coupled with enhanced perioperative mitigation rather than routine drug interruption.
- Risk-adapted management incorporating dietary modification, strict fasting adherence, selective use of point-of-care gastric ultrasound, and tailored airway and anaesthetic strategies is central to safe perioperative care.

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Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 RAs, initially developed for the treatment of type 2 diabetes mellitus, are now widely prescribed for obesity and metabolic diseases owing to their potent effects on glycaemic control, appetite suppression, and weight reduction.[1-3] With the rising global prevalence of obesity, perioperative clinicians are increasingly encountering patients receiving agents such as semaglutide, liraglutide, and tirzepatide for both approved and off-label indications.[4,5] Although these medications confer substantial metabolic and cardiovascular benefits, they also modify gastrointestinal physiology—most notably by slowing gastric emptying via vagal and peripheral mechanisms—which may result in residual gastric contents (RGC) despite standard fasting, and may raise concern for regurgitation and pulmonary aspiration during anaesthesia.[6-8]

These concerns are particularly relevant in patients with obesity or type 2 diabetes mellitus, who frequently exhibit baseline vulnerabilities such as gastro-oesophageal reflux, autonomic dysfunction, delayed gastric transit, reduced pulmonary reserve, and increased difficulty in airway management.[9-12] The addition of a therapy that further impairs gastric motility may therefore amplify existing perioperative risks and necessitate tailored management strategies. However, the available evidence remains limited.[13] Current data are derived largely from gastric physiology studies, case reports of peri-induction regurgitation, and small observational cohorts, and there are few controlled clinical trials.[14] Moreover, findings are heterogeneous: while several studies demonstrate increased retention of solids after standard fasting—sometimes persisting even after treatment interruption—others report minimal or variable effects, depending on dose, duration of therapy, indication, and comorbid conditions.[15]

In keeping with this uncertainty, professional recommendations vary considerably. Early anaesthesia-focused guidance advocated interrupting long-acting GLP-1 RAs prior to elective procedures, based on pharmacokinetic considerations and emerging case reports.[16,17] More recent multidisciplinary statements favour an individualised approach incorporating symptom assessment, modified fasting protocols, and selective perioperative gastric evaluation, rather than routine treatment interruption.[18-21] Such divergence underscores the absence of consensus and highlights the need to integrate mechanistic, clinical, and guideline-based perspectives.

Accordingly, this narrative review aims to summarise the current evidence on the perioperative implications of GLP-1 RAs, integrate mechanistic insights, clinical studies, and contemporary guideline recommendations, and propose a practical, risk-adapted framework for perioperative management.

Literature Identification Strategy

A comprehensive literature search was conducted using PubMed, Embase, Web of Science, and Scopus to identify publications relevant to the perioperative management of patients receiving GLP-1 RAs. The search included studies published in English up to February 2026 and encompassed original research articles, clinical studies, case reports, guideline statements, review articles, and perioperative consensus documents. Keywords and search term combinations included "GLP-1 RA," "GIP/GLP-1 RA," "semaglutide," "liraglutide," "tirzepatide," "gastric emptying," "gastric motility," "gastroparesis," "RGC," "perioperative," "aspiration risk," "regurgitation," "airway management," and "preoperative fasting." In addition, the reference lists of relevant articles were screened to identify further relevant studies.

Pharmacology and Mechanisms of Action of GLP-1 RAs

GLP-1 RAs are incretin-based therapies that activate GLP-1 receptors expressed in pancreatic β-cells, the gastrointestinal tract, vagal afferent pathways, and central satiety centres.[22] In contrast to native GLP-1, which is rapidly degraded by dipeptidyl peptidase-4, pharmacological analogues are engineered with structural modifications—such as albumin binding, peptide acylation, or increased molecular size—to prolong circulation time and resist enzymatic degradation.[23] These properties permit once-daily or once-weekly administration and result in sustained metabolic effects that are relevant to perioperative care.

Agent-Specific Pharmacological Profiles

Semaglutide (Ozempic®, Wegovy®-subcutaneous weekly; Rybelsus®-oral daily) has an elimination half-life of approximately 6-7 days and reaches steady state after 4-5 weeks of therapy. Complete elimination may require more than five half-lives (approximately 30-35 days). Consequently, clinically meaningful effects on gastric emptying may persist for 2-4 weeks after discontinuation, particularly when discontinued early in therapy.

Liraglutide (Saxenda®, Victoza®-subcutaneous daily) has a shorter half-life of approximately 11-13 hours, with near-complete clearance within 3-4 days. Gastric emptying delay is typically mild to moderate during early treatment and tends to diminish with long-term use. Residual effects beyond 48-72 hours are unlikely, although symptomatic patients may remain at increased risk.

Dulaglutide (Trulicity®-subcutaneous, weekly) has a half-life of approximately 4.5-5 days, and full elimination may take up to four weeks depending on the dose. Effects

on gastric motility are generally modest, becoming more apparent at higher doses or during dose escalation. Delayed gastric emptying may therefore persist for 1-3 weeks after cessation in selected patients.

Tirzepatide (Mounjaro®, Zepbound®-subcutaneous weekly; dual GLP-1/GIP RA) has an approximate half-life of five days, reaches steady state after approximately four weeks, and may require four weeks or longer for elimination. Gastric motility effects are less well characterised; however, early data suggest a dose-dependent delay comparable to that observed with long-acting GLP-1 RAs. Pending further evidence, persistence of delayed gastric emptying for 2-4 weeks after discontinuation should be assumed.

Exenatide (Byetta®-subcutaneous twice daily; Bydureon®-subcutaneous weekly) is available in short-acting and extended-release formulations: the short-acting formulation has a half-life of approximately 2.4 hours and produces a pronounced postprandial delay in gastric emptying, whereas the extended-release formulation has a half-life of approximately 6-7 days and a less pronounced effect on gastric emptying. Clearance of the twice-daily formulation typically occurs within 24 hours, whereas the extended-release formulation may require three to four weeks for elimination.

Perioperative Physiologic and Anaesthetic Implications

Gastric Emptying and Aspiration Risk

Delayed gastric emptying represents the central perioperative concern associated with GLP-1 RAs.[24] These agents slow gastric motility by reducing antral contractions, increasing pyloric tone, and modulating vagal pathways, which collectively prolong solid-phase retention even when patients adhere to standard fasting instructions.[25] Consequently, gastric contents may not reliably clear despite 8-12 hours of fasting, particularly in individuals receiving long-acting weekly formulations.[26]

Evidence from case reports, prospective gastric ultrasonography studies, and endoscopic cohorts consistently demonstrates a higher prevalence of retained solid gastric contents among GLP-1 RA users.[27-29] Unexpected solid residues have been observed during induction, sometimes accompanied by regurgitation despite appropriate fasting. Although increased RGC raises concern regarding perioperative aspiration risk, this physiological finding does not necessarily translate into a proven increase in clinically evident aspiration. Moreover, the current evidence regarding aspiration risk remains limited and is largely derived from observational studies and case reports.[30,31]

Haemodynamic and Endocrine Considerations

Beyond their effects on gastrointestinal motility, GLP-1 RAs also produce endocrine and modest cardiovascular changes that may be relevant in the perioperative setting. These agents lower blood glucose by stimulating insulin secretion in a glucose-dependent manner; therefore, the risk of significant hypoglycaemia is generally low unless they are coadministered with insulin or sulfonylureas.[32,33] This profile may facilitate perioperative glycaemic management compared with some other antidiabetic therapies, particularly during prolonged fasting or when caloric intake is uncertain.

Long-term GLP-1 RA therapy may also modestly reduce blood pressure and sympathetic tone through weight loss, natriuresis, and improvement in metabolic parameters.[34] Clinically significant intraoperative haemodynamic instability directly attributable to GLP-1 RA therapy has not been clearly demonstrated in the perioperative literature; however, the available evidence remains limited. Accordingly, GLP-1 RA therapy alone does not justify routine modification of anaesthetic drug selection or monitoring; perioperative management should be guided by the overall clinical context. These physiological effects and their potential perioperative implications are schematically summarised in Figure 1.

Evidence from Clinical Studies

Observational and Interventional Studies

Available clinical evidence regarding the perioperative effects of GLP-1 RAs remains limited, but generally points in a consistent direction. Across prospective gastric ultrasonography studies, retrospective endoscopic series, and mechanistic investigations, GLP-1 RA use is associated with delayed solid-phase gastric emptying and increased RGC, particularly during early treatment phases and periods of dose escalation. Notably, these effects have been observed despite standard fasting protocols and short-term drug interruption, suggesting that routine preoperative fasting may be insufficient in a subset of patients.[26-28,35] A recent prospective multicentre matched-control study by Vlaeminck et al.[36] further supports these findings, demonstrating a significantly higher prevalence of a "full stomach" on preoperative gastric ultrasound in semaglutide users compared with matched controls despite guideline-compliant fasting.

Although increased RGC and impaired gastric clearance are frequently documented, clinically apparent aspiration events remain rare. Gastrointestinal symptoms have been reported to be strongly associated with increased RGC, independent of the duration of preoperative drug interruption; emerging data indicate variability among agents, with long-acting formulations and dual agonists conferring higher risk.[28,37-39] An integrated overview of the included clinical studies is presented in Table 1.

Table 1. Summary of Clinical Studies on Perioperative Effects of GLP-1 RAs

Study/year	Population	Method of assessment	Key findings	Clinical implication
Sherwin et al.[26]	Volunteers without obesity recently started on semaglutide	Gastric ultrasound after ≥10 h overnight fasting	Retained solids in 70-90% of semaglutide users vs. 10-20% of controls	Early semaglutide use causes marked solid-phase delay even in non-obese subjects
Nersessian et al.[27]	Elective surgery patients who used SG≤10 days preop. No diabetes, no obesity	Preoperative point-of-care gastric ultrasound	Increased RGC in 40% vs. 3% of controls; younger male patients at highest risk	Semaglutide within 10 days markedly increases RGC; even 10-day cessation may be insufficient
Jensterle et al.[35]	Obese women with PCOS	Gastric scintigraphy with solid meal	37% retention at 4 h vs. 0% in controls; T½ prolonged from 118 → 171 min	Mechanistic evidence in obese endocrine population
Vlaeminck et al.[36]	Elective surgery patients receiving semaglutide vs. matched controls	Prospective multicentre gastric ultrasound study	Full stomach: 49% vs. 18% (OR 4.29); solids 42% vs. 7%	Semaglutide associated with increased RGC despite guideline-compliant fasting
Gabe et al.[37]	Adults with obesity	Paracetamol absorption (liquid emptying surrogate)	No change in gastric emptying; no delay detected	Possible tachyphylaxis; liquid-phase tests may underestimate effects
Silveira et al.[38]	EGD under sedation/ general anaesthesia SG use within 30 days	Direct endoscopic measurement of RGC (solids or >0.8 mL kg^{-1} fluid)	Increased RGC 24.2% vs. 5.1%; interruption interval irrelevant	GLP-1 RA users show higher RGC despite ~10-day drug withdrawal
Santos et al.[28]	Adults undergoing EGD under deep sedation/ general anaesthesia	Endoscopic quantification of residual gastric content (solids or >0.8 mL kg^{-1} fluid)	Higher RGC (20.3% vs. 3.2%); GI symptoms key predictor; risk persists if semaglutide withheld ≤14 days, normalizing only after >14-21 days.	Perioperative semaglutide markedly increases RGC withholding >14-21 days may be required
Robalino Gonzaga et al.[39]	Ambulatory EGD cohort	Direct endoscopic visualization of solid food retention	GLP-1 use ↑ RGC risk ~9-fold; tirzepatide highest (45%)	Strong association between GLP-1 use and RGC; but aspiration remains rare
Dahl et al.[40]	Well-controlled T2D adults	Paracetamol absorption test (liquid-phase GE surrogate)	Early gastric emptying reduced by 31%, with no delay observed in the later 5-hour phase	Only early liquid-phase GE is delayed; no sustained GE delay demonstrated
Muranaka et al.[41]	Elective surgery patients taking semaglutide <7 days pre-op	Gastric POCUS; solid content or >1.5 mL kg^{-1} ="full stomach"	20% had RGC. 1-3 day interval → 75% full stomach, 4-6 day interval → 10%. Dose/BMI/ diabetes not predictive	G-POCUS prevents unnecessary cancellations; semaglutide within <3 days carries highest RGC risk
Skidmore et al.[42]	Diabetics with GLP-1 using ambulatory urology surgeries	Postop $DSpO_2$ as surrogate for micro-aspiration/ atelectasis	GLP-1 hold <7 vs. ≥7 days → no difference in $DSpO_2$	GLP-1 hold duration does not impact pulmonary risk
Sen et al.[43]	Fasted elective surgery patients; weekly GLP-1 RA users vs. controls	Gastric ultrasonography; solids, thick liquids or >1.5 mL kg^{-1}=increased RGC	RGC: 56% vs. 19%; GLP-1 use ↑ risk (adjusted prevalence ratio 2.48); no association between stop duration (≤7 days) and RGC	GLP-1 RA is independent risk factor for high RGC. Stopping for 7 days does not normalize, GUS-based assessment recommended

RGC, residual gastric content; EGD, esophagogastroduodenoscopy; GI, gastrointestinal; PCOS, polycystic ovary syndrome; T2D, type 2 diabetes; GE, gastric emptying; POCUS, point-of-care ultrasound; GUS, gastric ultrasonography; RLD, right lateral decubitus; $DSpO_2$, difference between preoperative and postoperative oxygen saturation; SG, semaglutide group; NSG, non-semaglutide group; RA, receptor agonist; GLP-1, glucagon-like peptide-1; OR, odds ratio

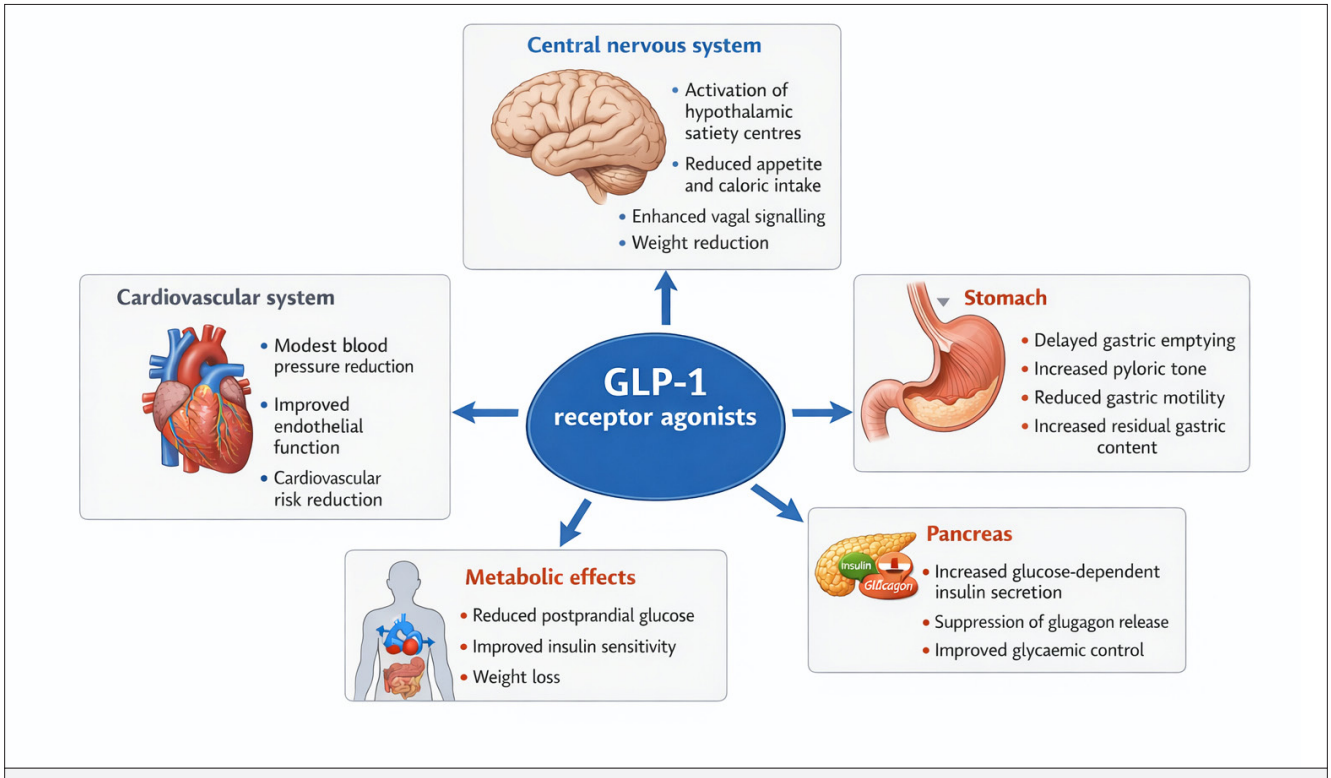

Figure 1. Physiological effects and mechanisms of GLP-1 receptor agonists.

GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide.

Case Reports and Case Series

Published case reports and small case series provide important early clinical signals regarding the perioperative implications of GLP-1 RAs. Across the literature, delayed gastric emptying, RGC, and perioperative regurgitation or aspiration have been reported despite adherence to standard—and in some cases prolonged—fasting protocols. Although these reports represent low-level evidence, they illustrate scenarios in which routine perioperative precautions failed to ensure gastric emptying, particularly in patients receiving long-acting GLP-1 RAs such as semaglutide.[30,31,44,45]

One illustrative case involved a non-obese, non-diabetic patient who was using semaglutide for weight loss and experienced large-volume regurgitation during induction of anaesthesia after approximately 20 hours of fasting from solid food. Notably, the last semaglutide dose had been administered two days prior to surgery, underscoring the persistence of pharmacological effects beyond both prolonged fasting and short-term drug interruption.[30] Similar cases have described aspiration events despite residue-free diets and withholding periods of up to six days, suggesting that neither dietary modification nor brief cessation reliably mitigates risk in susceptible individuals.[31,44] In other reports, retained solid gastric contents were incidentally identified intraoperatively or on imaging, with previously undisclosed GLP-1 RA use later recognised as the likely contributor.[45]

Additional case series describe reversible drug-induced gastroparesis and severe gastrointestinal dysmotility associated with GLP-1 RA therapy, often following rapid dose escalation or occurring in patients with pre-existing motility disorders. Symptoms—including nausea, vomiting, abdominal pain, and delayed transit—consistently improved after drug discontinuation, supporting a causal and potentially reversible effect.[46-48] Rare pulmonary complications, such as silent microaspiration and organising pneumonia, have also been reported, indicating that delayed gastric emptying may have clinically relevant consequences even outside the immediate perioperative setting.[49]

Guideline and Consensus Recommendations

Early guidance on the perioperative management of GLP-1 RAs was driven largely by precaution rather than high-quality evidence. The American Society of Anesthesiologists (ASA) 2023 consensus-based guidance was the first formal response to emerging case reports of regurgitation and aspiration associated with long-acting GLP-1 agents.

Acknowledging the very low quality of available evidence, ASA adopted a conservative, safety-first strategy centred on preoperative drug withholding, recommending interruption of daily agents on the day of surgery and of weekly agents for seven days before elective procedures.[17] Symptomatic patients were advised to be managed as though having a full stomach; gastric ultrasound or full-stomach precautions were suggested if withholding was incomplete.

Subsequent European guidance introduced greater nuance. The European Society of Anaesthesiology and Intensive Care (ESAIC) 2025 guideline, developed using a structured patient/population, intervention, comparison, outcome framework, retained drug withholding as a core strategy but emphasised patient- and procedure-specific risk stratification.[18] While recommending the interruption of weekly agents for at least one week—and up to two weeks in high-risk contexts such as obesity or bariatric surgery—the guideline explicitly recognised that even prolonged interruption may not normalise gastric emptying. Compared with ASA, ESAIC placed greater emphasis on mitigation strategies, including point-of-care gastric ultrasound, clear-liquid diets for selected patients, and airway-protection measures when aspiration risk was suspected.

More recent multidisciplinary statements have shifted away from routine drug interruption towards continuation-focused strategies. The Society for Perioperative Assessment and Quality Improvement 2025 consensus, the Australian-New Zealand joint recommendations led by the Australian and New Zealand College of Anaesthetists, and the 2025 United Kingdom multisociety consensus endorsed by the Association of Anaesthetists, all concluded that the evidence linking GLP-1 continuation to clinically significant aspiration is weak, whereas the metabolic and cardiovascular consequences of drug interruption are well established.[19-21] These documents favour the continuation of GLP-1 and dual GIP/GLP-1 RAs in most patients, with risk mitigation achieved through dietary modification, strict adherence to fasting, selective use of gastric ultrasound, and tailored anaesthetic and airway strategies, rather than by routine interruption. The key recommendations, conceptual differences, and risk-mitigation strategies across major guidelines and consensus statements are summarised in Table 2.

Current Clinical Recommendations and Practical Considerations

Clinicians are increasingly encountering patients treated with GLP-1 RAs and dual GIP/GLP-1 RAs, while the perioperative evidence base remains indirect and heterogeneous. Consequently, current recommendations do not reflect a single universal standard but rather an evolving synthesis across professional societies, largely informed by observational data and expert consensus.

There is broad agreement that GLP-1 RAs delay solid-phase gastric emptying and increase RGC; however, the clinical relevance of these physiological changes in terms of aspiration risk remains uncertain. This uncertainty underlies the observed divergence in guidance. The ASA and ESAIC adopt a precautionary approach, recommending temporary interruption of daily agents on the day of surgery and of weekly formulations for at least one week, while acknowledging that cessation may neither normalise gastric emptying nor be metabolically benign (a consensus-based recommendation).

In contrast, more recent multisociety statements favour continuation of GLP-1 therapy in most asymptomatic patients, emphasising that prolonged interruption rarely restores gastric motility and may expose patients to hyperglycaemia, weight rebound, and loss of cardio-renal benefit. These groups instead prioritise mitigation strategies, including strict adherence to fasting, selective use of a 24-hour clear-fluid diet, regional anaesthesia, when feasible, and point-of-care gastric ultrasound for individualised risk assessment. However, gastric point-of-care ultrasound is operator-dependent and its availability may be limited in some perioperative settings. These recommendations are supported mainly by observational data and expert opinion.

Across all guidance, symptomatic patients and those in early dose-escalation phases are consistently identified as higher-risk groups, requiring heightened caution, postponement of procedures, or precautions related to a full stomach. When uncertainty persists, full-stomach precautions with appropriate airway protection remain the default. Overall, contemporary practice is shifting from routine drug interruption toward a continuation-plus-mitigation model that balances the uncertain aspiration risk against the clearer metabolic harms.

Proposed Perioperative Management Strategy

This proposed approach is informed by clinical experience in the perioperative care of patients with obesity, in whom airway management is often more complex and tolerance for aspiration-related complications is limited.

From an anaesthesiology perspective, the possibility of a "full stomach" remains a central concern, particularly when associated with factors such as obesity. Although documented aspiration events are uncommon, reports of regurgitation and aspiration with solid gastric contents—even after prolonged fasting—suggest that this risk cannot be considered purely theoretical.[30,31]

Table 2. Comparative Summary of Major Guidelines and Multisociety Consensus Statements on Perioperative Management of GLP-1 and GIP/GLP-1 RAs

Feature	ASA 2023	ESAIC 2025	SPAQI 2025	ADS/ANZCA/ GESA/NACOS 2025	United Kingdom multisociety 2025
Document type	Consensus-based guidance (expert opinion)	Formal guideline with clinical practice suggestions (CPS)	Multidisciplinary consensus with graded recommendations	Multisociety practice recommendations (conditional GRADE)	Multidisciplinary consensus (Delphi-based)
Evidence appraisal	Narrative evidence from case reports and small observational series; no GRADE	Structured PICO; CPS issued due to low-quality evidence	Systematic review + modified Delphi; graded (B, C, E)	Abbreviated Delphi; conditional GRADE	Directed review and three-round Delphi; largely observational data
Overall evidence quality	Very low	Low	Low to moderate	Low	Low
Perioperative GLP-1 strategy	Withhold: daily agents on DOS; weekly agents 7 days prior	Withhold: daily on DOS; weekly ≥1 week (up to 2 weeks for high-risk patients)	Continue in asymptomatic patients	Continue routinely; cessation generally not advised	Continue perioperatively; avoid routine cessation
Fasting/diet strategy	Standard ASA fasting; no changes recommended	Standard fasting; consider 24-h clear-liquid diet in high-risk patients	Extend solid-food restriction to 24 h; carbohydrate-adjusted clear liquids	Universal 24-h clear-liquid diet and standard fasting	Standard national fasting; emphasise strict adherence
Core risk concept	Aspiration risk mitigated primarily through drug interruption and full-stomach precautions	All GLP-1 users at potential risk; amplified by obesity, diabetes, bariatric surgery	Aspiration risk small and uncertain; continuation favored due to metabolic benefit	Delayed emptying persists despite brief cessation; focus on diet with procedural mitigation	Aspiration risk real but small; metabolic destabilization outweighs theoretical benefit of withholding
Risk stratification	Symptom-based (nausea, vomiting, abdominal discomfort)	Indication- and risk-profile based (obesity, diabetes, bariatric surgery, agent type)	Based on symptom burden, comorbidities, and procedure type	Fasting completeness, procedure type, adherence to clear-fluid protocol	Integrated: drug (dose/timing), patient (diabetes/obesity/ gastroparesis), procedure/ anaesthetic factors
Role of gastric ultrasound	Optional if drug not withheld; informs full-stomach precautions	Strongly encouraged, if RGC present → consider postponement	Mentioned but not central; more emphasis on fasting modification	Key tool if clear-fluid protocol not followed; alternative is ultrathin endoscopy	Recommended where appropriate; guides airway planning and aspiration risk
Airway/anaesthetic mitigation	Full-stomach precautions; consider RSI and tracheal intubation	RSI/intubation in high-risk patients; full-stomach approach if ultrasound unavailable	Mitigation tailored to overall risk; no universal RSI	Prefer regional anaesthesia with minimal sedation; RSI/full-stomach precautions when risk high	Prefer regional anaesthesia; selective use of RSI, prokinetics, gastric decompression, head-up position
Cardiometabolic impact of cessation	Acknowledged mainly for diabetic patients; endocrinology input advised	Briefly discussed; less emphasis than others	Strongly emphasized (hyperglycemia; loss of cardio-renal protection)	Highlighted (hyperglycemia, weight and BP destabilization)	Strong emphasis on hyperglycemia, stress hyperglycemia, loss of long-term cardio-renal benefit
Conceptual stance	Precautionary, drug-withholding, aspiration-focused	Risk-tailored withholding with procedural mitigation	Continuation-forward with fasting modification	Continuation and strengthened mitigation (diet/imaging/procedure-level)	Continuation-focused, system-level risk stratification and shared decision-making

ASA, American Society of Anesthesiologists; ESAIC, European Society of Anaesthesiology and Intensive Care; SPAQI, Society for Perioperative Assessment and Quality Improvement; ADS, Australian Diabetes Society; ANZCA, Australian and New Zealand College of Anaesthetists; GESA, Gastroenterological Society of Australia; NACOS, National Association of Clinical Obesity Services; GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide; RGC, residual gastric content; RSI, rapid sequence induction; CPS, Clinical Practice Suggestions; DOS, day of surgery; PICO, patient/population, intervention, comparison, outcome

In the context of an evolving, evidence-limited literature, patient safety should remain the primary consideration. Increased perioperative awareness of GLP-1 and dual GIP/GLP-1 RA therapy among patients and healthcare providers is essential, as incomplete disclosure or under-recognition of these agents may contribute to avoidable risks.

Decisions regarding continuation or temporary interruption of therapy should be individualised and, when feasible, involve multidisciplinary input from anaesthesiology, endocrinology, and cardiology. For elective procedures, a longer interruption period and enhanced dietary preparation may be reasonable in selected high-risk patients, while recognising that drug interruption alone may not reliably normalise gastric emptying. Accordingly, such patients should continue to be approached with a degree of caution regarding aspiration risk.

When discontinuation is not feasible—such as in urgent or emergent settings—risk mitigation becomes central. Regional anaesthesia should be preferred when appropriate. If general anaesthesia is required, strategies may include rapid sequence induction, tracheal intubation, selective use of prokinetics or gastric decompression, minimising opioid exposure, and close postoperative monitoring. Overall, this approach aligns with an emerging consensus favouring

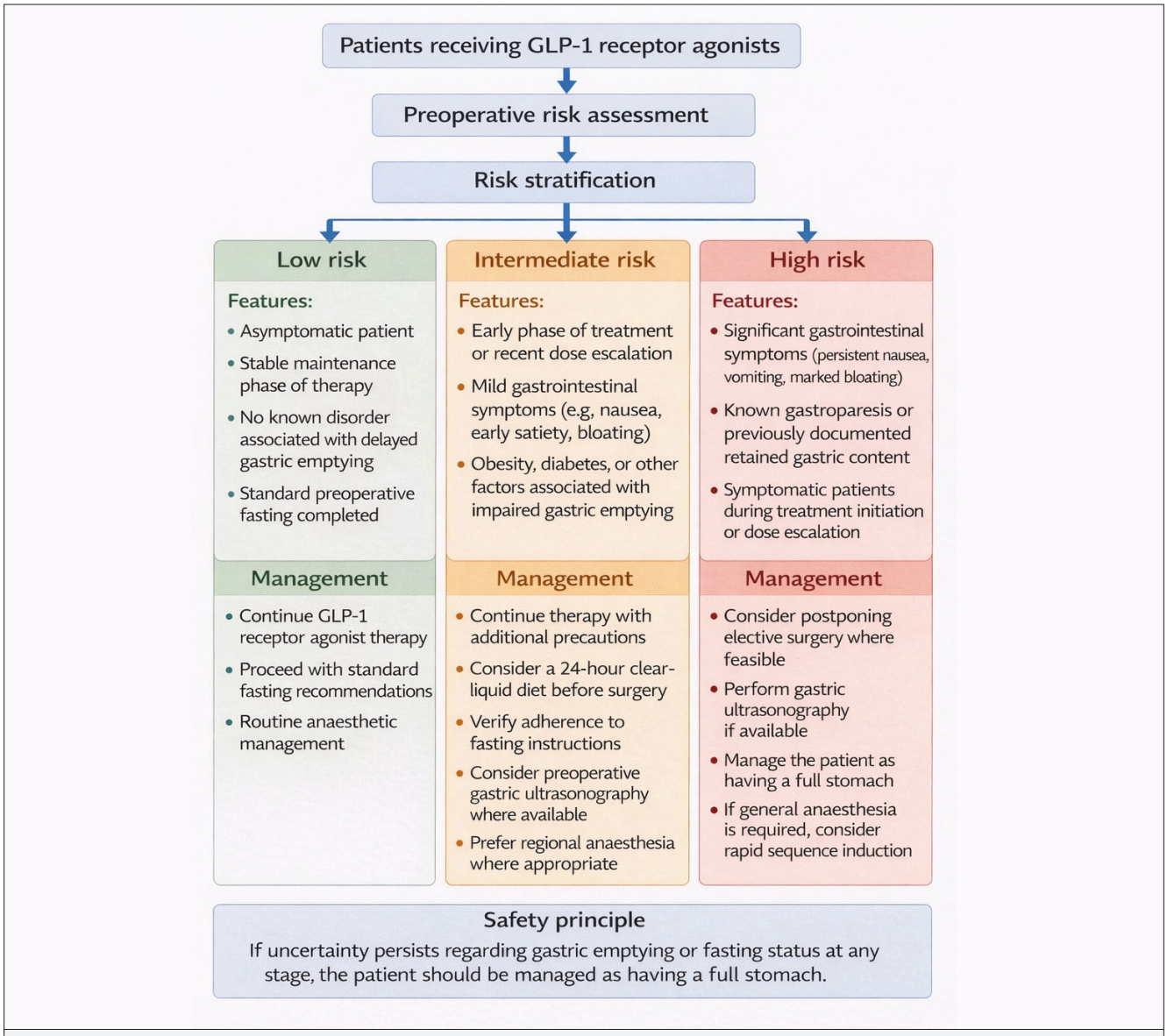

Figure 2. Proposed risk-adapted perioperative management algorithm for patients receiving GLP-1 and dual GIP/GLP-1 receptor agonists.

GLP-1, glucagon-like peptide-1.

individualised mitigation-based perioperative management rather than uniform drug interruption, thereby balancing aspiration risk against the metabolic benefits of continued therapy. A proposed risk-adapted perioperative management algorithm is presented in Figure 2.

Clinical and Research Consequences

The expanding use of GLP-1 RAs and dual GIP/GLP-1 RAs has important implications for everyday anaesthetic practice. Current evidence supports a shift away from uniform drug interruption towards an individualised, risk-adapted approach that integrates patient symptoms, treatment phase, comorbidities, and procedural risk. For clinicians, this necessitates heightened awareness of these agents, routine preoperative enquiry about their use, and consideration of mitigation strategies, such as dietary modification, regional anaesthesia, when feasible, and selective application of point-of-care gastric ultrasound.

From a research perspective, substantial knowledge gaps remain. Prospective studies evaluating the true incidence of perioperative aspiration, the duration of gastric emptying impairment after drug interruption, and the comparative risks associated with different GLP-1 and dual agonist formulations are needed. Further studies should explore whether perioperative continuation or interruption of therapy influences glycaemic stability, cardiovascular outcomes, and postoperative complications. Addressing these gaps will be essential for developing evidence-based, standardised perioperative management pathways.

Study Limitations

This review has several limitations. First, it was conducted as a narrative rather than a systematic review, reflecting the limited and evolving nature of the available evidence in this field. Second, much of the current knowledge regarding the perioperative implications of GLP-1 RAs is derived from physiological studies, case reports, and relatively small observational cohorts rather than large prospective clinical trials. Finally, differences in study populations, drug formulations, treatment duration, and perioperative protocols contribute to substantial heterogeneity across the available literature.

Conclusion

Current evidence regarding the anaesthetic implications of GLP-1 RAs remains limited and largely observational. Available data suggest that delayed gastric emptying and increased RGCs may persist despite standard fasting and short-term drug interruption; however, the clinical significance of these findings in terms of aspiration risk has not yet been clearly defined. Recent multisociety guidance increasingly supports continuation of therapy in selected patients, although this approach is consistently coupled with enhanced perioperative risk-mitigation strategies rather than unconditional continuation of therapy.

Accordingly, perioperative management should be individualised and guided by multidisciplinary input, particularly in patients with obesity, diabetes, or additional risk factors for impaired gastric emptying. In lower-risk, asymptomatic patients, continuation of GLP-1 therapy may be reasonable provided that extended solid-food restriction, clear-liquid dietary preparation, and strict adherence to fasting are observed. In higher-risk situations or when uncertainty persists, heightened caution—including full-stomach precautions and selective use of point-of-care gastric ultrasound—remains appropriate. Until prospective data more precisely define true perioperative risk, a risk-adapted strategy combining therapy continuation with structured mitigation represents a balanced and defensible approach.

Footnotes

Authorship Contributions: Concept - U.S.Ç., H.K.Ö.; Design - U.S.Ç., H.K.Ö.; Data Collection and/or Processing - U.S.Ç., H.K.Ö.; Analysis and/or/Interpretation - U.S.Ç., H.K.Ö.; Literature Review - U.S.Ç., H.K.Ö.; Writing - U.S.Ç., H.K.Ö.

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Evaluating a Novel Regional Technique: Serratus Posterior Superior Intercostal Plane Block Reduces Opioid Consumption and Pain Scores after Breast-conserving Surgery: A Randomized Controlled Trial

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Abstract

Objective: Serratus posterior superior intercostal plane block (SPSIPB) provides thoracic analgesia. Our objective was to assess the analgesic effectiveness of SPSIPB in reducing pain scores and opioid consumption in patients undergoing breast-conserving surgery (BCS) with axillary dissection or sentinel lymph node biopsy.

Methods: Participants were individuals aged 18-65 years with American Society of Anesthesiologists physical status I-II who were scheduled for elective BCS under general anaesthesia. Participants were randomly assigned to Group SPSIPB (n = 30) or Group Control (n = 30); the control group received local infiltration anaesthesia. A total of 30 milliliters of 0.25% bupivacaine was during the SPSIPB procedure. The primary outcome of the study was the numerical rating scale (NRS) score at 1 hour postoperatively. Secondary outcomes included 24-hour opioid consumption, need for rescue analgesia, and adverse effects.

Results: During the first 24 hours after surgery, the median static and dynamic NRS scores were lower in the SPSIPB group than in the control group ($P < 0.005$). Fewer patients in the SPSIPB group required rescue analgesia than in the control group (3 vs. 26 patients, $P=0.001$), and opioid consumption was lower in the SPSIPB group ($P=0.001$). The incidence of adverse effects was significantly lower in the SPSIPB group ($P < 0.005$).

Conclusion: Opioid consumption and pain scores in the SPSIPB group were significantly lower compared with those in the control group. SPSIPB provides effective analgesia and reduces opioid requirements, offering a valuable opioid-sparing alternative for anaesthesia in breast surgery.

Keywords: Breast surgery, chest wall blocks, pain management, regional anaesthesia, serratus posterior superior intercostal plane block, ultrasound

Main Points

- Serratus posterior superior intercostal plane block (SPSIPB) is a novel regional anaesthesia method that provides thoracic analgesia.
- Case reports and limited studies report that SPSIPB provides effective analgesia for breast surgery.
- This is a prospective, randomized study of the efficacy of SPSIPB for breast surgery, reported in the literature.
- Our results indicate that SPSIPB provides effective analgesic management in patients who underwent breast surgery.

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Introduction

Breast-conserving surgery (BCS), commonly called lumpectomy, is a common procedure for treating breast cancer, one of the most prevalent cancers affecting women worldwide.[1] Breast cancer accounts for nearly one in three new cancer diagnoses among women, underscoring the need for effective, patient-centered surgical options. BCS involves removing the cancerous tumor while preserving as much of the breast as possible, often resulting in favorable cosmetic outcomes and psychological benefits.[1] However, a significant number of patients report persistent pain following breast surgery, ranging from mild discomfort to chronic pain.[2] This pain arises from multiple mechanisms, including nerve damage or irritation during surgery, tissue inflammation, and scarring, all of which can cause long-term discomfort. Other sources of pain after breast surgery include axillary procedures, such as axillary dissection and sentinel lymph node biopsy.[3] In the acute postoperative phase, patients who have undergone breast surgery, particularly axillary surgery, experience severe pain. Addressing these pain mechanisms early, through individualized pain-management strategies, is essential to improving quality of life in patients who have undergone BCS.[1-3]

The PROSPECT guidelines propose the use of regional anaesthetic procedures. More recently, the 2023 evidence-based guideline on the prevention and management of perioperative pain for breast cancer surgical patients emphasizes multimodal analgesia to minimize opioid use.

Effective pain management is crucial for patients undergoing breast surgery, as it not only improves recovery but also reduces the risk of chronic pain.[2-3] The PROSPECT guidelines propose using regional anaesthetic procedures.[2] More recently, the 2023 Evidence-based Guideline on the Prevention and Management of Perioperative Pain for Breast Cancer Surgical Patients emphasizes multimodal analgesia to minimize opioid use.[4] Regional analgesia techniques have become popular for managing postoperative pain after breast surgery, offering targeted pain relief while minimizing the need for systemic opioids.[3] With the growing use of ultrasound (US) in daily anaesthesia practice, several fascial plane block techniques are used to provide analgesia for chest wall surgeries. By using these regional analgesia techniques, patients experience not only effective pain relief but also a reduced need for opioids, which can lower the risk of side effects and enhance post-operative recovery.[3] In recent years, novel techniques have emerged to address the limitations and inconsistencies in prior methods. The serratus posterior superior intercostal plane block (SPSIPB), introduced by Tulgar et al.[5] in 2023, represents a recent advancement in regional anaesthesia. In their study, which included one cadaver and five patients, they demonstrated that SPSIPB spreads from C7 to T7, effectively involving the intercostal nerves in the cadaver and providing a broad hemithoracic sensory blockade in the patients.[5] Existing case reports support that it is efficacious for various breast operations.[6-12] However, to our knowledge, no randomized clinical trials have investigated its use specifically in breast surgery. Therefore, we designed this study to evaluate the effectiveness of SPSIPB in this context, hypothesizing that it would offer superior analgesia compared to a control group receiving local infiltration. This study aims to compare SPSIPB and local infiltration with respect to pain scores, opioid requirements, and adverse events.

Methods

Study Design

This single-center, prospective, randomized study received approval from the Ethics and Research Committee of the İstanbul Medipol University Non-interventional Clinical Research Ethics Board (approval no.: 365, date: 13.04.2023). Following ethical approval, the study protocol was registered on ClinicalTrials.gov (NCT05972083). Participants were patients aged 18 to 65 with ASA classification I-II who were scheduled to undergo elective BCS with either axillary dissection or sentinel lymph node biopsy. Exclusion criteria included refusal to participate, posterior thoracic wall infection, coagulation disorders, pregnancy, inability to score pain, and a history of allergic reactions to local anaesthetics or study drugs. The study, conducted at Medipol Mega University Hospital, spanned from August 2023 to October 2024, and all participants provided written informed consent.

Grouping, Blinding, and Randomization

Prior to surgery, participants were randomized in a 1:1 ratio to the SPSIPB group (n = 30) or the control group (n = 30). The Research Randomizer computer program, which created a randomization table and assigned each patient an ID, was used to oversee the randomization process. The group allocations were concealed from the patients and the pain nurse-anaesthetist who evaluated the surgical outcomes. To maintain consistency, all blocks were performed by an anaesthesiologist skilled in regional anaesthesia.

General Anaesthesia Management and Surgical Technique

The clinic's standard anaesthesia protocol was used for induction and maintenance of general anaesthesia, with a multimodal analgesic regimen of 400 mg ibuprofen and 100 mg tramadol administered intravenously (IV) 20 minutes before surgery. Additionally, 4 mg IV ondansetron was administered for prophylaxis of postoperative nausea and vomiting. All surgeries, including BCS with axillary dissection or sentinel lymph node biopsy, were performed by the same surgical team following a standardized technique.

SPSIPB Procedure

Patients were placed in the lateral decubitus position (surgical side up) after completion of the sterile SPSIPB procedure and before extubation. The scapular spine serves as a crucial anatomical landmark for the SPSIPB.[5] After the manual palpation of the scapular spine, a high-frequency transducer (4-12 MHz) was placed sagittally on the scapula. The scapular spine was identified using US, and the transducer was moved toward the upper medial border of the scapula. The third rib was visualized adjacent to the medial border, with a slight oblique angulation applied to the transducer for optimal imaging.[4,8] The trapezius muscle, rhomboid major muscle, serratus posterior superior muscle (SPSM), third rib, and pleura were visualized. A 22G, 80-mm block needle (Stimuplex® Ultra 360®, B. Braun, Melsungen, Germany) was directed between the SPSM and the third rib. The block site was confirmed by injecting 5 mL of isotonic solution between the SPSM and the rib. Subsequently, 30 mL of 0.25% bupivacaine was administered into this plane (Figure 1).

In the control group, the surgical team performed wound infiltration along the incision line and into breast tissue. Additional infiltration was applied to the axillary fossa following dissection (a total of 30 ml of 0.25% bupivacaine). Surgical drains were placed in patients.

Postoperative Analgesia Regimen and Outcomes

For postoperative pain management, 400 mg of intravenous ibuprofen was prescribed every 8 hours as part of the routine analgesic protocol. Pain was measured using the numerical rating scale (NRS), with 0 indicating no pain and 10 indicating the worst imaginable pain. In the post-anaesthesia care unit and at 2, 4, 8, 16, and 24 hours after surgery, both static and dynamic NRS scores were recorded. As a rescue analgesic, 0.5 mg kg^{-1} intravenous meperidine was administered to patients with an NRS score of 4 or higher.

The NRS score one hour after surgery was the study's main endpoint. Use of meperidine, a rescue opioid analgesic, and the prevalence of adverse effects such as nausea, vomiting, and itching were secondary outcomes.

Sample Size

The G*Power program (version 3.1.9) was used to determine the study's sample size. The comparison of the first-hour NRS scores was the primary objective. In a preliminary analysis that included eight patients in each group, first-hour postoperative NRS score was 1 [standard deviation (SD) 0.55] in the SPSIPB block group and 3 (SD 2.25) in the control group. A minimum of 26 patients per group was needed to achieve 95% power, assuming an α error of 0.05 and a β error of 0.01. To account for potential dropouts, we decided to include at least 30 patients in each group.

Statistical Analysis

The shapes of the distributions of the study variables were evaluated using the Shapiro-Wilk test to assess normality and detect skewness. An independent samples t-test was used for group comparisons, and values for normally distributed data were displayed as the mean ± SD. The results were presented as median and interquartile range for continuous data that

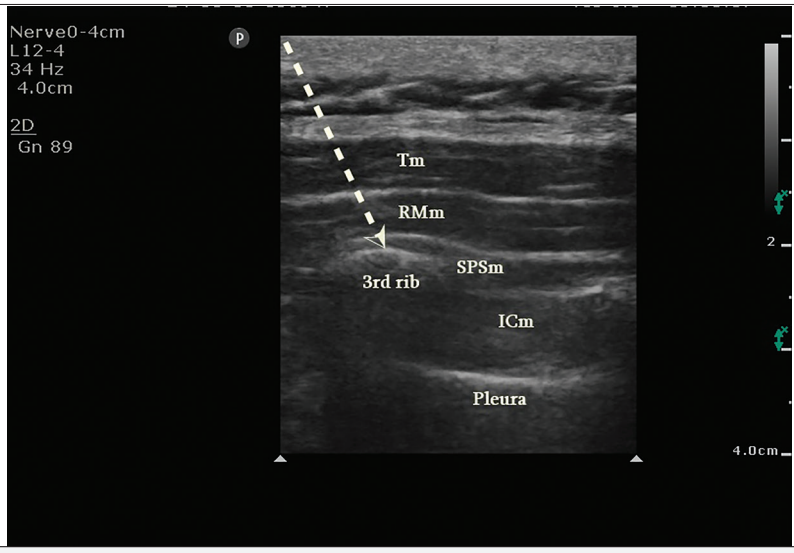

Figure 1. Sonographic visualization of SPSIPB. The Trapezius, rhomboid major, serratus posterior superior, the third rib, and the pleura are visualized. The arrow indicates the needle trajectory. The tip of the arrow is located between SPSm and the third rib.

Tm, trapezius muscle; RMm, rhomboideus major muscle; SPSm, serratus posterior superior muscle; ICm, intercostal muscle; SPSIPB, serratus posterior superior intercostal plane block.

were not normally distributed. Group differences were then examined using the Mann-Whitney U test. Statistical significance was defined as $P < 0.05$. SPSS (version 25, SPSS Inc., Chicago, IL, USA) was used for all analyses.

Results

The CONSORT flowchart (Figure 2) was used to track patient enrollment in this prospective, randomized study. Patient enrollment flow is detailed in Figure 2. Demographic data, surgery duration, and anaesthesia times were similar between groups (Table 1).

Table 2 presents a comparison of NRS scores at rest and during movement between groups. NRS scores were consistently lower in the SPSIPB group across all time points within the first 24 postoperative hours (P=0.001)

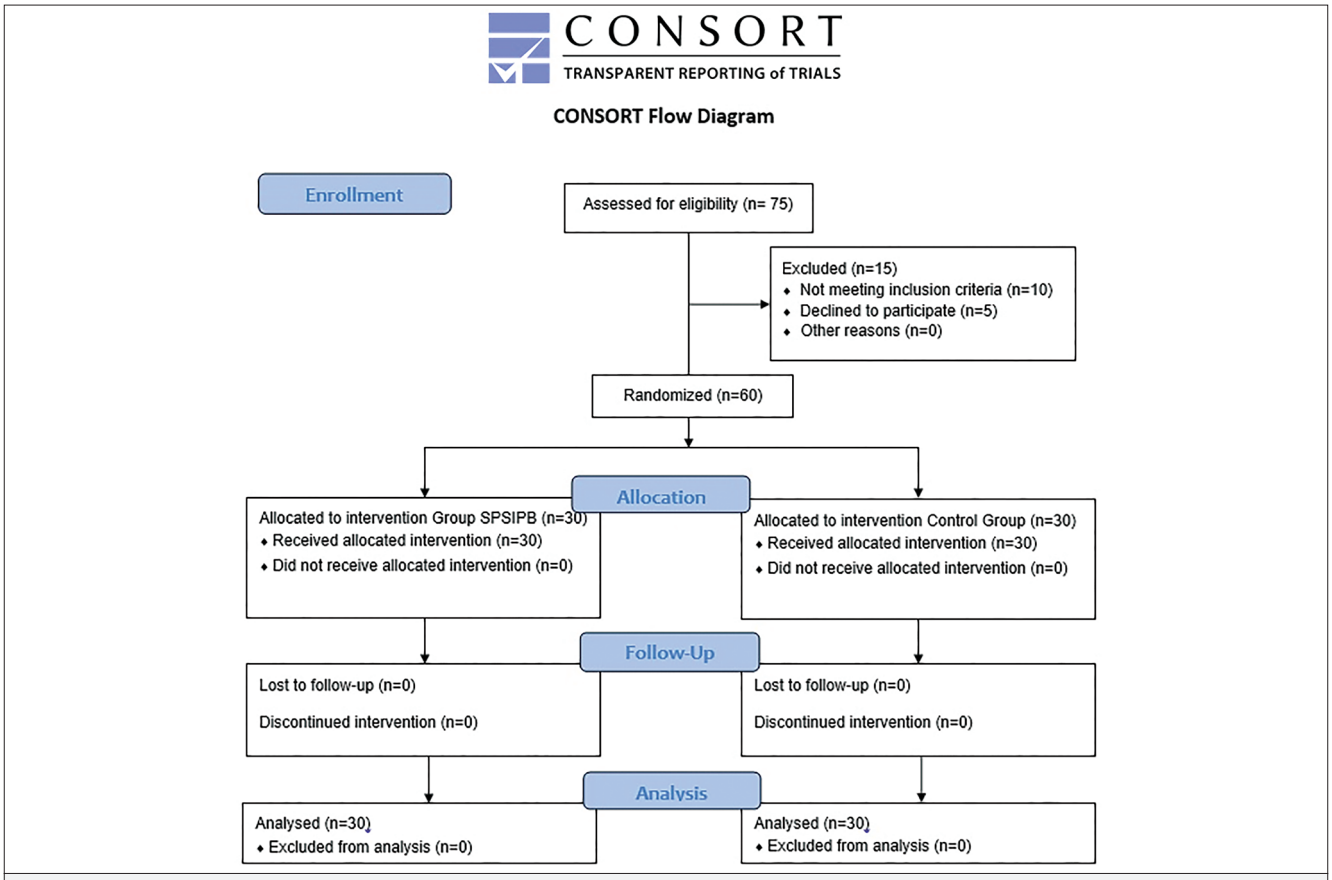

Figure 2. CONSORT flow diagram of the study.

Table 1. Comparison of Demographic Data and Duration Times of Surgery and Anaesthesia Between Groups

	Group SPSIPB (n = 30)	Group control (n = 30)	*P*
Age	53 (42-61)	49 (42-54)	*0,307
ASA (I/II)	7/23	7/23	†1
Height (cm)	162 (157-168)	162 (158-168)	*0.773
Weight (kg)	72 (65-80)	68 (35-76)	*0.251
Duration of surgery (min)	80 (71-93)	86 (80-98)	*0.125
Duration of anaesthesia (min)	95 (80-108)	101 (95-116)	*0.092

Values are expressed median (percentiles 25-75) or number, *: P value is obtained with Mann-Whitney U test, †: P value is obtained with Pearson's χ^2 test (n), P values were italicized and values that are written in bold represent statistical significance

ASA, American Society of Anesthesiologist; m, male; f, female; cm, centimeter; kg, kilogram; min, minutes; SPSIPB, Serratus posterior superior intercostal plane block

Table 2. Comparisons of Static and Dynamic NRS Assessment Between Groups			
	Group SPSIPB (n = 30)	**Group control (n = 30)**	***P***
At rest			
1st hour	0 (0-1)	2 (2-3)	**0.001**
2nd hour	0 (0-1)	2 (2-3)	**0.001**
4th hour	0 (0-0)	2 (1-3)	**0.001**
8th hour	0 (0-0)	2 (1-3)	**0.001**
16th hour	0 (0-0)	2 (1-2)	**0.001**
24th hour	0 (0-0)	1 (1-2)	**0.001**
On movement			
1st hour	0 (0-2)	4 (3-5)	**0.001**
2nd hour	1 (0-2)	4 (3-4)	**0.001**
4th hour	0 (0-1)	3 (3-3)	**0.001**
8th hour	0 (0-1)	3 (2-3)	**0.001**
16th hour	0 (0-0)	2 (2-3)	**0.001**
24th hour	0 (0-0)	2 (2-3)	**0.001**

Data are expressed as median (percentiles 25-75), *P* value is obtained with Mann-Whitney U test median (percentiles 25-75), *P* values were italicized and values that are written in bold represent statistical significance

NRS, numeretic rating pain scale; SPSIPB, serratus posterior superior intercostal plane block

Data concerning the number of patients requiring rescue analgesia and opioid consumption (meperidine) are presented in Table 3. Patients in the control group required rescue analgesia at a significantly higher rate than those in the SPSIPB group (26 vs. 3 patients; P=0.001). Furthermore, the control group consumed significantly more opioids than the SPSIPB group [0 (0-0) vs. 60 (30-70); P=0.001]. The median value of 60 mg represents cumulative consumption of rescue analgesia over 24 hours, not a single dose.

The control group experienced a significantly higher incidence of adverse effects than the SPSIPB group: nausea, vomiting, and itching occurred in 18, 9, and 10 patients versus 2, 1, and 2 patients, respectively ($P < 0.005$) (Table 3). Our data show that the control group experienced pain; they received a cumulative rescue meperidine dose equal to twice the standard dose and, because meperidine commonly causes pruritus and vomiting, they experienced these side effects.

Table 3. The Comparison of Opioid (Meperidine) Consumptions, the use of Rescue Analgesia and the Incidence of Side Effects Between Groups			
	Group SPSIPB (n = 30)	**Group control (n = 30)**	***P***
Rescue analgesia (the number of the patients that used rescue analgesia) **(Y/N)**	3/27	26/4	**0.001**
Rescue dose (mg)	0 (0-0)	60 (30-70)	**0.001**
Nausea (Y/N)	2/28	18/12	**0.001**
Vomiting (Y/N)	1/29	9/21	**0.006**
Itching (Y/N)	2/29	10/20	**0.001**

P value is obtained with Pearson's χ^2 test (n), Data are expressed as median

*: *P* value is obtained with Mann-Whitney U test median (percentiles 25-75), *P* values were italicized and values that are written in bold represent statistical significance

Discussion

The results of the research indicate that SPSIPB is a successful and practical approach for managing pain in patients who underwent BCS. Compared to the control group, the SPSIPB group reported lower NRS scores both at rest and during movement throughout the 24-hour postoperative period, as well as reduced opioid consumption, reduced demand for rescue analgesics, and fewer patients requiring additional pain relief. Additionally, the incidence of nausea, vomiting, and itching was lower in the SPSIPB group. The significantly higher incidence of adverse effects, including nausea, vomiting, and pruritus, observed in the control group, appears to be strongly correlated with the increased consumption of rescue opioids. The limited analgesic coverage provided by local infiltration alone likely necessitated increased meperidine use, resulting in these dose-dependent side effects. In contrast, the SPSIPB group demonstrated a clear opioid-sparing benefit, which translated directly into a more favorable adverse effect profile.

Breast surgery is frequently associated with significant acute and chronic postoperative pain, which substantially compromises patient comfort, especially after procedures such as mastectomy and axillary lymph node dissection. Postoperative pain is prevalent, with approximately 50% of patients experiencing severe acute pain that can contribute to chronic pain. This level of discomfort can impede recovery, affecting breathing and delaying mobilization.[1-3] Consequently, regional anaesthesia techniques are frequently employed to optimize postoperative pain management in breast surgery patients.[3] The PROSPECT guidelines propose using regional anaesthetic procedures to provide postoperative analgesia after breast surgery.[2]

Various regional anaesthesia techniques are available for pain management following breast surgery. As plane-block methods have evolved, newer interfascial plane blocks have been introduced to address the limitations of earlier techniques. For instance, the paravertebral block, while effective, carries a high risk of pneumothorax due to its proximity to the pleura.[3] The erector spinae plane block (ESPB), introduced in 2016, is another option for patients undergoing breast surgery.[13,14] However, its mechanism of action remains controversial, with imaging and cadaveric studies demonstrating inconsistent patterns of spread.[14-18] Additionally, dermatome analyses have revealed that ESPB performed at the same level can produce varying sensory block levels among different individuals.[19] Another technique, the rhomboid intercostal block (RIB), has limited axillary spread and may not consistently cover areas beyond the T3 dermatome.[5,20] Given these limitations, SPSIPB offers a promising alternative for patients undergoing breast surgery and axillary dissection.

The SPSIPB technique, first defined by Tulgar et al.[5] in 2023, involves the injection of a local anaesthetic between the SPSM and the third rib. The SPSM is a thin, membranous, periscapular muscle with an oblique course, extending from the C7-T3 vertebral levels to the lateral aspects of the second and fifth ribs. This unique structure allows the anaesthetic to spread widely when injected into the SPSM's deep fascia.[21] Cadaver studies have reported an extensive spread from C7 to T7, involving the intercostal nerves and potentially reaching the dorsal rami of the spinal nerves.[5] In a case series by Ciftci et al.,[9] SPSIPB was applied to three breast surgery patients; all exhibited low pain scores and required no additional analgesics. Dermatomal analysis in these cases demonstrated sensory blockade from C3 to T10, including the axilla. Our study aligns with these findings, with patients showing consistently low pain scores and reduced opioid use compared to the control group. In summary, SPSIPB may offer a practical, safe, and effective pain management option for breast surgery.

A notable advantage of SPSIPB for breast surgery is its distance from the surgical field, meaning that the block's effectiveness is less likely to be compromised by surgical tissue trauma. We performed SPSIPB by positioning the patient in the lateral decubitus position before extubation. Unlike ESPB, which may be challenging to perform in the lateral position due to the depth of the transverse process and difficulties in probe handling, SPSIPB is more straightforward. The rib, being more superficial and lateral, facilitates visualization, and placing the probe medial to the scapula improves grip and control. While case reports suggest that SPSIPB provides effective analgesia in various surgeries, randomized controlled trials remain limited. Avci et al.[22] compared SPSIPB with a control group in thoracoscopic surgery and reported that SPSIPB provided effective analgesia. In another clinical study by Köksal et al.,[23] the authors compared SPSIPB with the control group and reported that SPSIPB provided effective postoperative analgesia in patients who underwent breast cancer surgery. Unlike our study, Köksal et al.[23] reported effective analgesia with 20 mL of local anaesthetic. In our study, we used 30 mL, hypothesizing that a larger volume might improve interfascial spread. While both studies report success, future dose-finding studies are needed to determine the optimal volume-to-efficacy ratio for SPSIPB. Our study is the second clinical investigation of SPSIPB to focus on its application to breast surgery.

Yu et al.[24] compared RIB, serratus anterior plane block (SAPB), and paravertebral block with respect to the quality of recovery after breast cancer surgery. They reported that RIB and the paravertebral block provided similar analgesic effects for breast cancer surgery. However, according to their results, the analgesic effect of the SAPB was inferior to that of the RIB and the paravertebral block. They emphasized that RIB may be one of the best alternatives to the paravertebral

block among fascial plane blocks. Similarly, Altıparmak et al.[25] reported that RIB provided effective analgesic management compared with the control group after breast surgery. However, consistent with our results, SPSIPB, unlike the RIB (which focuses on T2-T9), facilitates cranial spread from C7 to T7, potentially providing superior coverage for the high axillary pain often associated with BCS involving lymph node dissection. Our results using SPSIPB suggest that it may offer a distinct advantage in more consistently targeting the dorsal rami and lateral cutaneous branches than SAPB, which is primarily an anterolateral block. Abdella et al.[26] evaluated the analgesic efficacy and the spread of varying volumes of local anaesthetic in the ESPB. They reported that doubling the injectate volume enhances the craniocaudal spread and may be useful for surgeries involving multiple dermatomes. However, according to their results, larger volume has no effect on analgesic efficacy or patient satisfaction because there is no further spread to the paravertebral, epidural spaces, or spinal nerve rami.

Study Limitations

Our study has some limitations. Although sensory blockade assessments are generally recommended to evaluate the effectiveness of plane blocks, we did not perform a dermatome analysis. We used 30 milliliters of local anaesthetic because plane-block effectiveness varies with volume; different outcomes may therefore occur with other volumes. Furthermore, we had a small sample size. Larger-scale clinical trials are required to demonstrate more conclusively the effectiveness of SPSIPB. Although local infiltration is a standard analgesic method, the control group in our study demonstrated a high requirement for rescue analgesia. This suggests that in BCS with axillary involvement, infiltration alone may be insufficient to address the complex pain mechanisms, or that the specific infiltration technique used may have provided limited coverage compared to the fascial plane spread of SPSIPB. Meperidine was used as the rescue analgesic in accordance with our institution's standard postoperative protocol during the study period, though we acknowledge that other opioids are more commonly used internationally.

Conclusion

SPSIPB offers effective analgesia for patients undergoing BCS with axillary dissection, significantly lowering pain scores and reducing opioid requirements.

Ethics

Ethics Committee Approval: This single-center, prospective, randomized study received approval from the Ethics and Research Committee of the İstanbul Medipol University Clinical Research Ethics Board (approval no.: 365, date: 13.04.2023).

Informed Consent: All participants were informed about the study, and their written consent was obtained.

Footnotes

Authorship Contributions: Surgical and Medical Practices - B.Ç., B.Ö., P.B., T.U.Y.; Concept - B.Ç., B.Ö., B.E.G., S.A., P.B., T.U.Y., B.U.S.; Design - B.Ç., B.E.G., S.A., P.B., T.U.Y., B.U.S.; Data Collection and/or/Processing - B.Ç., B.Ö., P.B., T.U.Y., B.U.S.; Analysis and/or/ Interpretation - B.E.G.; Literature Review - B.Ç., B.Ö., B.E.G., S.A., B.U.S.; Writing - B.Ç., B.E.G., S.A., B.U.S.

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Efficacy of Intranasal Dexmedetomidine Premedication as an Adjunct on Intubation Process in Paediatric Patients: A Randomized, Double-blind, Placebo-controlled Trial

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Abstract

Objective: To evaluate the effect of a single intranasal dose of dexmedetomidine (2 μg kg^{-1}) on intubation efficacy, mask acceptance, sedation quality, intubation duration, and intraoperative fentanyl consumption in children undergoing elective surgery.

Methods: A randomized, double-blind, placebo-controlled trial was conducted in 40 American Society of Anaesthesiologists I-II children aged 1-6 years who were scheduled for elective surgery. Participants were randomized to receive either dexmedetomidine (n = 20) or 0.9% sodium chloride placebo (n = 20). All patients received intravenous midazolam as a routine premedication. Primary outcomes were mean arterial pressure (MAP) and heart rate (HR), measured at baseline and post-intubation; these were compared to assess intubation efficacy. Secondary outcomes included mask acceptance, sedation quality, intubation time, and total fentanyl consumption. Data were analyzed using the independent-samples t-test or the Mann-Whitney U test ($P < 0.05$).

Results: Dexmedetomidine maintained MAP (1.34±19.59%) versus a significant rise with placebo (21.95±26.36%; P=0.008) and limited HR increase (1.6% vs. 22.2%; $P < 0.001$). Mask acceptance and adequate sedation were significantly higher ($P < 0.001$). Intubation duration did not differ (median 39 seconds vs. 44 seconds; P=0.267). Fentanyl consumption was significantly lower (1.10 vs. 2.15 μg kg^{-1}; $P < 0.001$).

Conclusion: A single intranasal dose of dexmedetomidine provides superior intubation efficacy, improves mask acceptance and sedation quality, and yields a significant opioid-sparing effect.

Keywords: Dexmedetomidine, intranasal administration, paediatric intubation, premedication, sedation quality, opioid sparing

Main Points

- A single preoperative intranasal dose of dexmedetomidine (2 μg kg^{-1}) effectively attenuated the hypertensive and tachycardic response to tracheal intubation, maintaining significantly more stable mean arterial pressure and heart rate compared with placebo.
- The dexmedetomidine group demonstrated significantly better mask acceptance and sedation quality prior to anaesthesia induction, facilitating a smoother, more cooperative induction.
- The use of intranasal dexmedetomidine resulted in nearly a 50% reduction in intraoperative fentanyl consumption (median 1.10 μg kg^{-1} vs. 2.15 μg kg^{-1}), highlighting its potent analgesic and adjunctive properties.

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Introduction

Children undergoing tracheal intubation are prone to respiratory and systemic complications because of heightened airway reactivity to mechanical or chemical stimuli, painful laryngoscopy, positive-pressure ventilation, and aspiration. These events are a major source of perioperative morbidity and can precipitate cardiac arrest.[1,2] In addition, intubation-related systemic adverse events range from mild (bronchial or esophageal intubation, dysrhythmias, hypertension, epistaxis) to severe (tooth trauma, pneumothorax, laryngospasm, profound hypotension, aspiration, or cardiac arrest with or without return of spontaneous circulation).[3]

Perioperative anxiety and distress are also highly prevalent in the paediatric population, with up to 75% of children experiencing significant preoperative anxiety that may translate into adverse behavioral and emotional outcomes postoperatively.[4] Effective anxiolysis and sedation before induction can attenuate airway reflexes, improve mask acceptance, and shorten induction time, thereby enhancing intubation conditions and reducing complications.[5,6] Traditional premedication routes—oral and intravenous—are often impractical in children because of poor cooperation, unpredictable absorption, and the discomfort associated with IV cannulation.[7]

The intranasal route is a non-invasive drug administration pathway that produces local, systemic, and central nervous system effects. Intranasal drug delivery offers several advantages, including ease of administration, rapid onset of action, and minimal pain perception.[7,8] Intranasal dexmedetomidine, a highly selective α_2-adrenergic agonist, offers a non-invasive alternative with rapid onset, minimal discomfort, and a favorable safety profile that includes sedation, anxiolysis, and mild analgesia without respiratory depression. It is associated with minimal complications, and nasal irritation is the most commonly reported adverse effect.[8,9]

Recent meta-analyses comparing intranasal dexmedetomidine with intranasal midazolam in paediatric patients have demonstrated superior satisfaction with parental separation, higher mask acceptance rates, and reduced postoperative pain and nasal irritation.[10] Over the past decade, studies have consistently shown that intranasal dexmedetomidine (1-2 μg kg^{-1}) can diminish stress responses during intubation in children.[11] Although previous studies have established the sedative benefits of intranasal dexmedetomidine in children, its direct effects on paediatric intubation have not been investigated.

This study aimed to evaluate the efficacy of adjunct intranasal dexmedetomidine premedication in paediatric intubation, focusing on intubation efficacy, mask acceptance, sedation depth, intubation duration, and opioid consumption-outcomes that directly influence patient safety and procedural efficiency. To our knowledge, this study is the first to evaluate its impact on intubation conditions, providing novel evidence for a potentially safer, non-invasive premedication strategy. We hypothesized that, compared with placebo, intranasal dexmedetomidine would improve intubation efficacy, enhance mask acceptance and sedation quality, stabilize hemodynamic responses, and reduce opioid requirements.

Methods

This randomized, double-blind, placebo-controlled clinical trial evaluated the adjunctive effect of intranasal dexmedetomidine premedication on intubation efficacy and anaesthesia outcomes in paediatric patients. This study was approved by the Ethics Committee of the Indonesia Universty Faculty of Medicine, Dr. Cipto Mangunkusumo National General Hospital (approval no: KET-1568/UN2.F1/ETIK/PPM.00.02/2024, date: 28.10.2024). The study adhered to the Declaration of Helsinki and relevant national regulations and was registered at ClinicalTrials.gov (NCT06991647, date: 18.03.2025). Written informed consent was obtained from the parents or legal guardians of all enrolled children. This manuscript follows the CONSORT reporting guidelines.

The trial was conducted from November to December 2024 in the operating rooms of Cipto Mangunkusumo Hospital, Jakarta, Indonesia. Eligible participants were children aged 1-6 years, with American Society of Anaesthesiologists (ASA) physical status I-II, who were scheduled for elective surgery under general anaesthesia. Exclusion criteria included an anticipated difficult airway, active oral or nasal infection, neurodevelopmental disorders (e.g., cerebral palsy, attention-deficit/hyperactivity disorder), and an inability to obtain intravenous access.

Participants were allocated to the intervention or control arm using simple randomization. Allocation sequences were generated online and placed in opaque, sealed envelopes (SNOSE technique). An independent research assistant prepared the study medication, ensuring blinding of participants, clinicians, and outcome assessors.

The study used a Intranasal Mucosal Atomization Device (MAD) Nasal™ (MAD300, Teleflex Inc., Wayne, PA, USA) coupled with 1 mL syringes to deliver intranasal medication. The investigational drug was dexmedetomidine hydrochloride 100 μg mL^{-1}, which was diluted with 0.9% sodium chloride (NaCl) to a total volume of 1 mL for each dose; the placebo solution consisted of 0.9% NaCl alone, administered in an identical volume. Standard anaesthesia equipment included a sevoflurane vaporizer, fentanyl, and atracurium for induction and muscle relaxation, along with non-invasive blood pressure monitoring, electrocardiogram,

pulse oximetry, and capnography, all integrated into a calibrated anaesthesia workstation. Mask acceptance and sedation quality were assessed throughout the peri-intubation period using the paediatric anaesthesia behaviour (PAB) score and the COMFORT Behaviour Scale, respectively.

Thirty minutes before induction, the intervention group received intranasal dexmedetomidine 2 μg kg^{-1} (diluted to 0.5 mL per nostril), while the control group received an equal volume of intranasal 0.9% NaCl as placebo. All children in both groups received intravenous midazolam 0.05 mg kg^{-1} as routine premedication, immediately after intranasal dexmedetomidine or placebo administration. Baseline mean arterial pressure (MAP) and heart rate (HR) were recorded before drug administration. Upon arrival in the operating theatre, PAB and COMFORT scores were documented. Anaesthesia induction proceeded with sevoflurane 2% inhalation, followed by titrated fentanyl (initial 1 μg kg^{-1}, with additional 1 μg kg^{-1} boluses if MAP or HR increased >20% during intraoperative monitoring). Inhalation induction was preferred because it had minimal effects on MAP and HR compared with IV iSnduction. Atracurium 0.5 mg kg^{-1} was used for muscle relaxation. Direct laryngoscopy was performed, and endotracheal tube size was calculated using the formula: diameter (mm) = 4+ (age in years /4). Intubation duration was measured from laryngoscope insertion to detection of end-tidal carbon dioxide. MAP, HR, and total fentanyl dose required for intubation were recorded immediately after tube placement. Intubation efficacy was defined as the ability to attenuate hemodynamic responses, measured as low variability in MAP and HR across groups. Episodes of bradycardia were treated according to paediatric advanced life support guidelines (atropine 0.02 mg kg^{-1}, maximum 0.5 mg). All adverse events related to intranasal dexmedetomidine administration, anaesthetic induction, or intubation were systematically recorded throughout the perioperative period.

A priori power analysis (α=0.05, power=80%) based on an expected difference in MAP of 10 mmHg and pooled standard deviation (SD) of 7.5 mmHg (from Naushad et al.[12]) indicated a minimum of 36 participants (18 per group). Although the minimum sample size was also estimated using multiple studies assessing various outcomes, this calculation yielded the largest sample size requirement. To compensate for a potential 10% dropout, 40 participants were enrolled consecutively until the target sample size was reached.

The primary outcome was premedication efficacy, measured by MAP and HR at baseline and post-intubation. Secondary outcomes included mask acceptance, sedation quality, intubation duration, and total fentanyl consumption.

Statistical Analysis

Data were entered into a blinded case report form and analyzed using the Statistical Package for the Social Sciences version 20 (IBM, Armonk, NY, USA). Continuous variables were expressed as mean ± SD or median (interquartile range) based on distribution (Kolmogorov-Smirnov test). Between-group comparisons used the independent-samples t test or Mann-Whitney U test, and within-group comparisons used the paired-samples t test or Wilcoxon signed-rank test, as appropriate; categorical variables were analyzed using the χ^2 test or Fisher's exact test. A two-tailed $P < 0.05$ was considered statistically significant.

Results

A total of 40 paediatric patients who met the inclusion criteria and consented to participate were enrolled in the study. The participants were randomly assigned to two groups using a double-blind design: a placebo group and an intranasal dexmedetomidine group, with comparable median ages (2 years for dexmedetomidine vs. 3 years for placebo) and similar gender distribution (Table 1). The majority of patients were ASA II, indicating that they were generally healthy, and fasting durations were similar, with just over half fasting <12 hours. Nutritional status was largely comparable, although the dexmedetomidine group included a higher proportion of underweight children and contained the sole overweight participant, whereas the placebo arm had more normal-weight participants. The distribution of surgical specialties was well-balanced across groups, covering general, paediatric, urologic, plastic, orthopedic, ear, nose and throat, and dental procedures, with comparable numbers in each category. No adverse events related to the intranasal route of administration or to dexmedetomidine side effects were reported during the sampling period. Additionally, no participants dropped out during the course of the study (Figure 1).

Table 2 shows that the baseline MAP was similar between the dexmedetomididine (72.35±15.95 mmHg) and placebo (69.30±17.04 mmHg) groups, indicating comparable initial hemodynamic conditions prior to intervention. Following intubation, the placebo group experienced a marked increase in MAP to 82.60±19.46 mmHg, which was significantly greater than the dexmedetomidine group (71.70±14.00 mmHg). The percentage change from baseline further highlighted this difference, with the placebo group showing a 21.95±26.36% rise compared with only 1.34±19.59% in the dexmedetomidine group (P=0.008). Within-group analyses confirmed a statistically significant elevation in MAP for the placebo group (P=0.002), whereas the dexmedetomidine group showed a non-significant change in MAP (P=0.852).

Regarding HR, the dexmedetomidine group demonstrated a higher baseline HR of 121.35±20.68 beats per minute (bpm) than the placebo group (105.65±14.72 bpm), which may be attributed to the younger average age of patients in the dexmedetomidine arm. After intubation, the placebo

group exhibited a notable increase in HR to 132.00±12.07 bpm, significantly surpassing the post-intubation HR of the dexmedetomidine group (123.80±16.01 bpm). The percentage change in HR from baseline differed significantly between groups; the placebo group showed a median increase of 22.22%, versus a minimal increase of 1.57% in the dexmedetomidine group ($P < 0.001$). Furthermore, within-group comparisons revealed a highly significant elevation in HR in the placebo group ($P < 0.001$), whereas HR changes in the dexmedetomidine group were not statistically significant (P=0.268).

Table 3 shows significantly greater mask acceptance in the dexmedetomidine group than in the placebo group, particularly in the highest acceptance category labeled "Happy." All Patients in the dexmedetomidine group were rated "Happy" (100%), whereas none of the patients in the placebo group were classified at this level. This corresponds to an odds ratio of 168.20 [95% confidence interval (CI) =7.4-3,818.5; $P < 0.001$], indicating that dexmedetomidine was associated with a markedly higher likelihood of achieving the highest mask acceptance. Conversely, the "Sad" and "Mad" categories, indicating poorer mask acceptance, were predominantly observed in the placebo group.

Table 1. Patient Characteristics

Variable	Treatment arm		*P* value
	Dexmedetomidine (n = 20)	Placebo (n = 20)	
Age (years)	2.00 (1.00, 4.00)	3.00 (1.00, 5.00)	0.524[a]
Gender			0.465[b]
Male	14 (46.7)	16 (53.3)	
Female	6 (60.0)	4 (40.0)	
Asa classification			0.723[b]
I	6 (54.5)	5 (45.5)	
II	14 (48.3)	15 (51.7)	
Nutritional status			0.219[b]
Underweight	5 (62.5)	3 (37.5)	
Normal	13 (43.3)	17 (56.7)	
Overweight	2 (100.0)	0 (0)	
Fasting duration			0.548[b]
<12 hours	19 (51.4)	18 (48.6)	
≥12 hours	1 (33.3)	2 (66.7)	
Surgical specialty			0.761[b]
General paediatric	6 (50.0)	6 (50.0)	
Urologic	8 (53.3)	7 (46.7)	
Plastic	3 (60.0)	2 (40.0)	
Orthopedic	2 (66.7)	1 (33.3)	
Ear, nose, and throat	1 (25.0)	3 (75.0)	
Dental	0 (0)	1 (100.0)	

Values are median (1Q, 3Q) or n (%), [a]: Mann-Whitney U test, [b]: Pearson chi-square
ASA, American Society of Anesthesiologists

Sedation quality was also markedly better in the dexmedetomidine group, with significantly greater sedation scores reflecting more effective anxiolysis and sedation-an effect up to 51-fold greater than placebo (95% CI=7.6-343.7; $P < 0.001$). Despite differences in sedation and cooperation, intubation duration did not differ significantly between groups (median time =39 second in the dexmedetomidine group vs. 44 second in the placebo group; P=0.267). Finally, fentanyl consumption was significantly lower in the dexmedetomidine group ($P < 0.001$), with a median of 1.10 µg kg^{-1}, than in the placebo group (median=2.15 µg kg^{-1}).

Discussion

Dexmedetomidine preserves baseline MAP by activating central α2-adrenergic receptors, suppressing norepinephrine release, reducing sympathetic outflow, and enhancing parasympathetic tone. This autonomic modulation and its analgesic effects blunt stress responses during intubation and prevent hypertensive surges in children, who are particularly vulnerable to blood pressure fluctuations.[13-15] Naushad et al.[12] similarly reported that paediatric patients receiving dexmedetomidine maintained more stable MAP

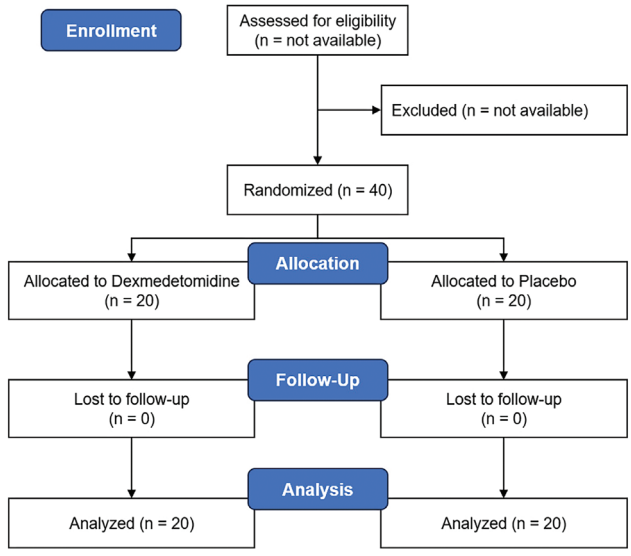

Figure 1. CONSORT flow diagram.

levels than those premedicated with opioids, emphasizing the importance of hemodynamic stability in reducing the risk of end-organ injury during invasive procedures.[12]

Our findings are consistent with the above findings, supporting the utility of dexmedetomidine not only for sedation but also for protection of paediatric patients from harmful blood pressure fluctuations during intubation and other invasive procedures. These advantages position dexmedetomidine as a safer and more effective premedication option in paediatric clinical practice.[12,15]

Dexmedetomidine maintains HR control by activating central α_2-adrenergic receptors, which reduces central sympathetic outflow and augments vagal activity, thereby directly lowering HR.[16] Its analgesic effects indirectly support HR control by minimizing pain-induced sympathetic activation. By blunting autonomic stress responses and reducing adrenergic stimulation through hemodynamic and analgesic mechanisms, dexmedetomidine contributes to the induction of effective bradycardia and the modulation of pain.[13,17]

This study's findings regarding the level of mask acceptance are consistent with those of Zhang et al.,[9] who reported that intranasal dexmedetomidine resulted in higher rates of mask acceptance than midazolam (81.47% vs. 60.92%; $P < 0.01$). Dexmedetomidine's sedative effects promote greater cooperation in paediatric patients during anaesthetic

Table 2. Premedication Efficacy Between Treatment Arms

Variable	Treatment arm		*P* value (between groups)
	Dexmedetomidine (n = 20)	Placebo (n = 20)	
Mean arterial pressure (mmHg)			
Baseline	72.35±15.95	69.30±17.04	0.562[a]
Post-intubation	71.70±14.00	82.60±19.46	**0.049[a]***
Percentage of change	1.34±19.59	21.95±26.36	**0.008[a]***
P value (within groups)	0.852[c]	**0.002[c]***	
Heart rate (beats per minute)			
Baseline	121.35±20.68	105.65±14.72	**0.009[a]***
Post-intubation	123.80±16.01	132.00±12.07	0.075[a]
Percentage of change	1.57 (-4.18, 12.063)	22.22 (14.34, 30.66)	**<0.001[b]***
P value (within groups)	0.268[d]	**<0.001[d]***	

Values are mean ± standard deviation or median (1Q, 3Q), [a]: Independent-samples t test, [b]: Mann-Whitney U test, [c]: Paired-samples t test, [d]: Wilcoxon signed-rank test, *: Statistically significant

Table 3. Secondary Outcomes

Variable	Treatment arms		*P* value and odds ratio
	Dexmedetomidine (n = 20)	Placebo (n = 20)	
Mask acceptance			**<0.001[a]***
Happy	14 (100.0)	0 (0)	168.20 (7.4-3818.5)
Sad	4 (40.0)	6 (60.0)	4.67 (0.7-32.7)
Mad	2 (12.5)	14 (87.5)	1.00
Sedation quality			**<0.001[a]***
Adequate	18 (85.7)	3 (14.3)	51.0 (7.6-343.7)
Inadequate	2 (10.5)	17 (89.5)	1.00
Intubation duration (second)	39 (34, 59)	44 (39, 62)	0.267[b]
Fentanyl consumption (μg kg^{-1})	1.10 (1.10, 1.48)	2.15 (1.83, 2.58)	**<0.001[b]***

Values are n (%) or median (1Q, 3Q), odds ratios for categorical data are presented as odds ratio (95% confidence interval), [a]: Pearson chi-square, [b]: Mann-Whitney U test, *: Statistically significant

mask application and reduce resistance to anaesthesia induction.[9] Our results corroborate these findings, further supporting the use of dexmedetomidine as a premedication that effectively reduces preoperative anxiety in paediatric patients.[10]

A meta-analysis conducted by Lang et al.,[18] comparing dexmedetomidine and midazolam across 34 randomized controlled trials involving 2,281 paediatric patients, found that dexmedetomidine was associated with better sedation outcomes during parent-child separation, with a risk ratio (RR) of 0.78 [95% CI (0.65-0.92)]. Improved sedation quality with dexmedetomidine contributes to reduced preoperative anxiety, a frequent challenge in paediatric anaesthesia. Sedation assessments in these studies used structured tools, such as six-point sedation scales to evaluate aspects including patient cooperation and mask acceptance.

This study's findings align with prior evidence showing that dexmedetomidine provides high-quality sedation without serious adverse effects, such as respiratory depression or postoperative agitation-side effects that are more commonly associated with midazolam. Furthermore, the same meta-analysis found that dexmedetomidine was associated with a significantly lower incidence of postoperative agitation [RR 0.31; 95% CI (0.24-0.41)], underscoring its dual benefit as both an effective sedative and a modulator of postoperative behavior.[18]

Although intranasal dexmedetomidine may facilitate a more favorable sedative state, similar intubation times between the two groups suggest that the duration of intubation is influenced by factors beyond premedication. Variables such as the use of muscle relaxants, operator experience, intubation technique, and the procedural environment also play substantial roles in determining the time required for intubation.

A study by Castle et al.[19] supports this interpretation, in which the use of various sedative premedications and intubation aids did not significantly affect the duration of intubation. Instead, operator experience was identified as a more critical determinant of procedural duration. Their study also emphasized that the primary benefit of premedication lies in improving patient comfort rather than reducing procedural time.[19] Nevertheless, that study highlighted that improving patient comfort during intubation can reduce resistance and procedural difficulty, enhance clinician satisfaction, and potentially lower the risk of complications. Although intubation duration may not be a direct indicator of dexmedetomidine's efficacy, its ability to foster a calm, cooperative patient environment remains a compelling rationale for its use in paediatric anaesthesia protocols. Further studies may be warranted to investigate the combined impact of pharmacologic premedication and operator training on clinical outcomes.[19]

Hu et al.[20] identified an optimal intranasal dose of 2 μg kg^{-1} dexmedetomidine in paediatric patients, demonstrating significant analgesic efficacy and a marked reduction in opioid requirements. Similarly, Kumar et al.[21] found that intranasal dexmedetomidine at doses of 1-2 μg kg^{-1} provided prolonged analgesic effects due to stable plasma concentrations achieved through slow absorption across the nasal mucosa. Both studies support the role of intranasal dexmedetomidine as an effective opioid-sparing analgesic strategy.

In our study, the dexmedetomidine group required significantly lower doses of fentanyl than the control group. This reduction reflects dexmedetomidine's ability to provide additional analgesia, thereby decreasing reliance on opioids such as fentanyl during intubation. This analgesic effect not only reduces pain perception but also suppresses excessive nociceptive responses, thereby making dexmedetomidine a valuable analgesic adjuvant in paediatric anaesthetic procedures.[16]

The baseline characteristics of the two groups were highly similar in terms of age, gender, ASA status, fasting duration, and surgical distribution, suggesting effective randomization and a low risk of confounding from baseline imbalances. This comparability strengthens the validity of any observed differences in outcomes between the groups. The absence of adverse events associated with intranasal dexmedetomidine and the lack of study dropouts indicate a favorable safety and tolerability profile in this paediatric cohort, supporting its potential use in preoperative settings. These findings align with existing literature on the safety of intranasal dexmedetomidine and underscore the feasibility of its administration in young children undergoing elective surgery.

Study Limitations

This study has several limitations. First, intubation was not performed by the same operator for all participants, potentially introducing variability in mechanical manipulation and nociceptive stimulation. The study population was limited to paediatric patients with ASA I-II status, which may limit the generalizability of the findings to children with higher ASA classifications or severe comorbidities. Other variables—such as operator skill, procedural environment, and anaesthetic protocols beyond premedication—were not analyzed. Dexmedetomidine was administered as a fixed weight-based dose, despite possible interindividual pharmacologic variability. The observation period was restricted to the intubation procedure, without assessment of postoperative outcomes or adverse events. Conducting the study at a single center and using 0.9% NaCl as the sole placebo, without comparison with other common

premedications such as ketamine or propofol, further limits the generalizability and comparative interpretation of the findings.

Conclusion

Adjunct intranasal dexmedetomidine premedication (2 μg kg^{-1}) markedly provides superior efficacy in intubation, enhances preintubation sedation quality and mask acceptance, and produces a significant opioid-sparing effect in children undergoing airway instrumentation, while not prolonging intubation duration when compared with placebo. These findings support its use as a safe, non-invasive premedication to facilitate smoother induction of paediatric anaesthesia and to reduce intraoperative fentanyl requirements.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of the Indonesia Universty Faculty of Medicine, Dr. Cipto Mangunkusumo National General Hospital (approval no.: KET-1568/UN2.F1/ETIK/PPM.00.02/2024, date: 28.10.2024).

Informed Consent: Written informed consent was obtained from the parents or legal guardians of all enrolled children.

Footnotes

Authorship Contributions: Concept - O.P.A., R.Z., C.K.; Design - O.P.A., R.Z., C.K., I.M., A.H.M.M., A.H.; Data Collection and/or/Processing - O.P.A., R.Z., C.K.; Analysis and/or/ Interpretation - O.P.A., R.Z., C.K., I.M., A.H.M.M., A.H.; Literature Review - O.P.A., R.Z., C.K.; Writing - O.P.A., R.Z., C.K., I.M., A.H.M.M., A.H.

Declaration of Interests: The authors declare no conflict of interests.

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Comparison of Ultrasound-guided Erector Spinae Plane Block Versus Rhomboid Intercostal Block for Perioperative Analgesia in Breast Cancer Surgery

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Abstract

Objective: Over 75% of women who have post-mastectomy reconstruction feel significant pain right away, and about 50% endure chronic pain. Thus, increasing the efficiency of postoperative pain management is crucial. Our study investigated the effects of ultrasound-guided erector spinae plane blocks (ESPB) and rhomboid intercostal blocks (RIB) on perioperative fentanyl use and pain scores in patients undergoing radical mastectomy surgery.

Methods: This was a double-blind, randomised controlled trial conducted at a tertiary care hospital. Patients with breast cancer aged 18-70 years and American Society of Anaesthesiologists status I-II who were scheduled for unilateral modified radical mastectomy were included. They were randomly assigned to two groups. ESPB was performed in the ESPB group, and RIB was performed in the RIB group, using ultrasound guidance. Total postoperative fentanyl usage in the first 24 hours was the primary outcome indicator of the study. Intraoperative fentanyl requirements and numerical rating scale (NRS) scores at seven distinct time points were used as secondary outcome measures.

Results: The difference between the mean of total postoperative fentanyl consumption in 24 hours in Group ESPB (2.67±0.68 μg kg^{-1}) and Group RIB (3.68±1.22 μg kg^{-1}) was statistically significant (t value: -4.183, df:66, *P* value: < 0.001). There was no difference in intraoperative opioid consumption between the groups (*P*=0.7). However, NRS scores were not significantly different between the ESPB group and the RIB group.

Conclusion: Our study's outcome demonstrates ultrasound-guided ESPB to be more effective than RIB in terms of lower perioperative fentanyl consumption.

Keywords: Modified radical mastectomy, opioids analgesics, interventional ultrasonography, postoperative pain, fentanyl, nerve block

Main Points

- This study investigated the effects of ultrasound-guided erector spinae plane block (ESPB) and rhomboid intercostal block (RIB) on perioperative fentanyl consumption and pain scores in patients undergoing radical mastectomy.
- Total postoperative fentanyl usage in the first 24 hours was the primary outcome indicator of the study.
- The difference in mean total postoperative fentanyl consumption over 24 hours was statistically significant between Group ESPB (2.67±0.68 μg kg^{-1}) and Group RIB (3.68±1.22 μg kg^{-1}) ($P < 0.001$).
- Our findings indicate that ultrasound-guided ESPB is more effective than RIB in reducing perioperative fentanyl requirements in breast cancer surgery.

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Introduction

The primary approach to treating breast cancer typically involves surgical interventions such as mastectomy, often supplemented with chemotherapy and radiotherapy.[1] Due to the dense and complex nerve network in the breast region, inadequate management of acute postoperative pain can result in a transition to chronic pain. Notably, more than 75% of women undergoing post-mastectomy reconstruction experience significant acute pain, and nearly half continue to experience chronic pain.[2-4] This underscores the critical importance of optimising postoperative pain control.

Regional anaesthesia techniques are foundational components of multimodal analgesia in breast cancer surgery.[5] Previously, thoracic epidural was considered the gold standard in this regard. The PROSPECT guidelines for oncological breast surgery recommend paravertebral block (PVB), fascial blocks such as pectoral nerve block, and/or local anaesthetic infiltration for improved analgesia.[6] However, conventional regional techniques such as PVB and thoracic epidural analgesia have notable limitations, including the technical complexity, the risk of hemodynamic instability, and the potential for bleeding or hematoma formation.[7] Pectoral nerve block or local anaesthetic infiltration provides short-term pain relief.

In contrast, newer techniques such as the erector spinae plane block (ESPB) and rhomboid intercostal block (RIB) appear to offer promising alternatives. These blocks prevent entry into the paravertebral space, thereby minimising the risk of affecting the neuroaxis, major plexuses, and blood vessels. There is limited evidence on the analgesic efficacy of newer blocks, such as the ESPB and the RIB.

The ESPB is an interfascial technique for performing regional anaesthesia that is relatively simple to administer and provides effective postoperative analgesia in major thoracic procedures.[8] In ESPB, local anaesthetic is injected deep to the erector spinae muscle at the T5-T6 level of the posterior chest wall. Some studies have reported that ESPB may affect the dorsal as well as ventral rami of multiple spinal nerves, with sensory spread often observed between approximately T3 and T9; however, the extent of spread varies across reports.[9]

The RIB, a more recently developed technique introduced by Elsharkawy et al.[10] It involves injection of local anaesthetic into the fascial plane between the rhomboid major and the intercostal muscles at the T5-T6 level. Previous studies suggest that RIB can block dermatomes from T2 to T9 on the ipsilateral ventral and dorsal hemithorax, providing effective perioperative analgesia and reducing opioid requirements and associated side effects.[11]

Several studies of drug spread in ESPB have shown extension to the paravertebral and epidural spaces.[12,13] Hence, we expected that ESPB might provide more extensive analgesia in breast surgery as compared to RIB, where the spread of the drug is more peripheral. In the present study, we aimed to determine whether ultrasound-guided ESPB provided superior perioperative analgesia compared with RIB in breast cancer surgery.

Methods

Study Design and Ethics Committee Approval

Ethical approval for this study was obtained from the Institutional Ethics Committee of the All India Institute of Medical Sciences in Patna (approval no.: AIIMS/Pat/IEC/PGTh/Jan20/14, date: 25.01.2021). Following approval, it was planned as a randomized controlled trial at the All India Institute of Medical Sciences in Patna. The study was carried out in compliance with the World Medical Association's Declaration of Helsinki after obtaining written informed consent from all patients prior to their enrolment. The trial was registered prospectively at the Clinical Trials Registry of India (CTRI/2021/03/031983). The study comprised patients scheduled for unilateral modified radical mastectomy surgery between 15 March 2021 and 14 March 2022 with American Society of Anaesthesiologists physical status I-II of age group 18-70 years and body mass index 18-24.9 kg m^{2-1}. The exclusion criteria were chronic opioid use, known allergy to local anaesthetics, procedure-site infection, previous mastectomy, and significant spinal or chest wall deformity.

Anaesthetic Technique

All patients underwent a preoperative assessment, including a comprehensive history, physical examination, and relevant investigations. Participants were randomised to two groups: ESPB and RIB. Standard intraoperative monitoring electrocardiogram, non-invasive blood pressure (NIBP), and peripheral oxygen saturation (SpO_2), was initiated upon arrival in the operating room. Baseline parameters, mean arterial pressure (MAP), heart rate (HR), and SpO_2, were recorded as the last measurements just before induction. Intravenous Ringer's lactate was administered at 15 mL kg^{-1} h^{-1}.

Induction of general anaesthesia was performed with 2 µg kg^{-1} fentanyl, 2 mg kg^{-1} propofol, and 0.1 mg kg^{-1} vecuronium, followed by endotracheal intubation. Anaesthesia was maintained with isoflurane (1-2%) in a 50% O_2-air mixture, and end-tidal carbon dioxide was maintained between 30-35 mmHg. Vecuronium (0.02 mg kg^{-1}) was administered every 30 minutes. Bispectral index was maintained between 40 and 60 by titrating the isoflurane concentration. Intraoperatively, 0.5 µg kg^{-1} fentanyl was administered when HR or MAP increased by >20% from baseline. NIBP was measured every 5 minutes. Baseline (preinduction), preincision (after administering the block and before

incision), postincision, and any episode of hypotension were recorded. Hypotension (systolic blood pressure <90 mmHg), respiratory depression, and postoperative nausea and vomiting (PONV) were monitored. A senior anaesthesiologist, experienced in performing more than 20 ultrasound-guided fascial plane blocks, administered the allocated block but did not participate in patient assessment or data collection.

Prophylactically, ondansetron (4 mg), dexamethasone (8 mg), and paracetamol (15 mg kg^{-1}) were administered 30 minutes before surgical closure. Injections of glycopyrrolate (0.01 mg kg^{-1}) and neostigmine (0.05 mg kg^{-1}) were used to reverse neuromuscular blockade.

Group Allocation and Randomisation

Eligible patients were randomised using a computer-generated block randomisation with block sizes of 4 and 6. Allocation cards prepared using a random-number were sealed in opaque envelopes prepared by an independent investigator. Both participants and outcome assessors were blinded to group assignments. The anaesthesiologist performing the block was excluded from all postoperative assessments.

Block Technique

Group ESPB

Following intubation, patients lie in the lateral position with the affected breast uppermost. The spinous processes from C7 to T5 were palpated, and the T5 level was marked. The trapezius, rhomboid major, erector spinae, and transverse processes were identified using a high-frequency linear ultrasound probe (M-Turbo, Fujifilm Sonosite Edge II, USA; 6-13 MHz) (Figure 1A). A 100-mm, 22-gauge needle (Stimuplex® Ultra 360®, B. Braun, Germany) was introduced in-plane 2-3 cm lateral to the midline until it contacted the T5 transverse process (Figure 1B and 1C). Confirming proper placement by injecting 5 mL of normal saline (hydro dissection), 25 mL of bupivacaine (0.25%) was injected in aliquots, visualising its spread deep to the erector spinae muscle (Figure 1D).

Group RIB

Patients were positioned laterally in a similar manner. The arm on the upper side was placed across the chest to expose the triangle of auscultation, which is bordered by the trapezius, latissimus dorsi, and the scapula. Key anatomical landmarks (bounded by the trapezius, rhomboid major, intercostal muscles, rib, pleura, and lung) were identified using a 6-13 MHz linear ultrasound probe placed along the inferior scapular border (Figure 2A). A 100-mm, 22-gauge needle was introduced in-plane between the rhomboid major and the intercostal muscles. Following hydrodissection with 5 mL of saline, 25 mL of 0.25% bupivacaine was injected after negative aspiration (Figure 2B). Ultrasound was used to confirm appropriate spread. Patients were repositioned to the supine position for further surgical management. All other perioperative care followed the institutional protocols at All India Institute of Medical Sciences, Patna.

Evaluation of Pain

Postoperative pain was assessed using the 11-point numerical rating scale (NRS), with 0 indicating no pain and 10 indicating the worst possible pain. NRS scores at 0, 1, 2, 4, 6, 12, and 24 hours were recorded postoperatively.

Analgesia and Rescue Protocol

All patients received intravenous patient-controlled analgesia (PCA) on arrival in the post-anaesthesia care unit. The PCA was programmed to deliver 30 µg fentanyl boluses, with a 20 minute lockout and no background infusion. Time to first rescue analgesia and total fentanyl consumed over 24 hours were recorded. Intravenous paracetamol (15 mg kg^{-1}) was administered every 8 hours. If NRS was >4 despite PCA fentanyl, intravenous tramadol (100 mg) was administered, and the dose was converted to fentanyl-equivalent doses for analysis.

Outcome Measures

The primary outcome was total postoperative fentanyl consumption during the first 24 hours. Secondary outcome measures were: intraoperative fentanyl requirement; time to first rescue analgesia; NRS pain scores at defined intervals; intraoperative hemodynamic stability; and additional rescue analgesic requirements.

Sample Size Calculation

Based on findings by Kumar et al.[14] where postoperative fentanyl consumption following RIB was 1.45±0.65 µg kg^{-1}, a 30% reduction was deemed clinically significant for ESPB. With an alpha error of 5%, a power of 80%, and a 95% confidence interval, the sample size was estimated to be 68 (34 patients per group).

Statistical Analysis

Data were initially recorded on a structured data-capture sheet , then compiled and analysed using IBM SPSS Statistics (version 25.0, student edition). Continuous variables with a normal distribution (e.g., age) were presented as mean ± standard deviation, whereas non-normally distributed continuous data were expressed as medians. Binary (categorical) variables were reported as absolute numbers and percentages.

Between-group comparisons of normally distributed continuous variables were performed using the unpaired Student's t-test. To compare non-normally distributed continuous data or ordinal data between groups, the Mann-Whitney U test was applied. Repeated measures ANOVA was used for within-group analysis of changes across multiple time points.

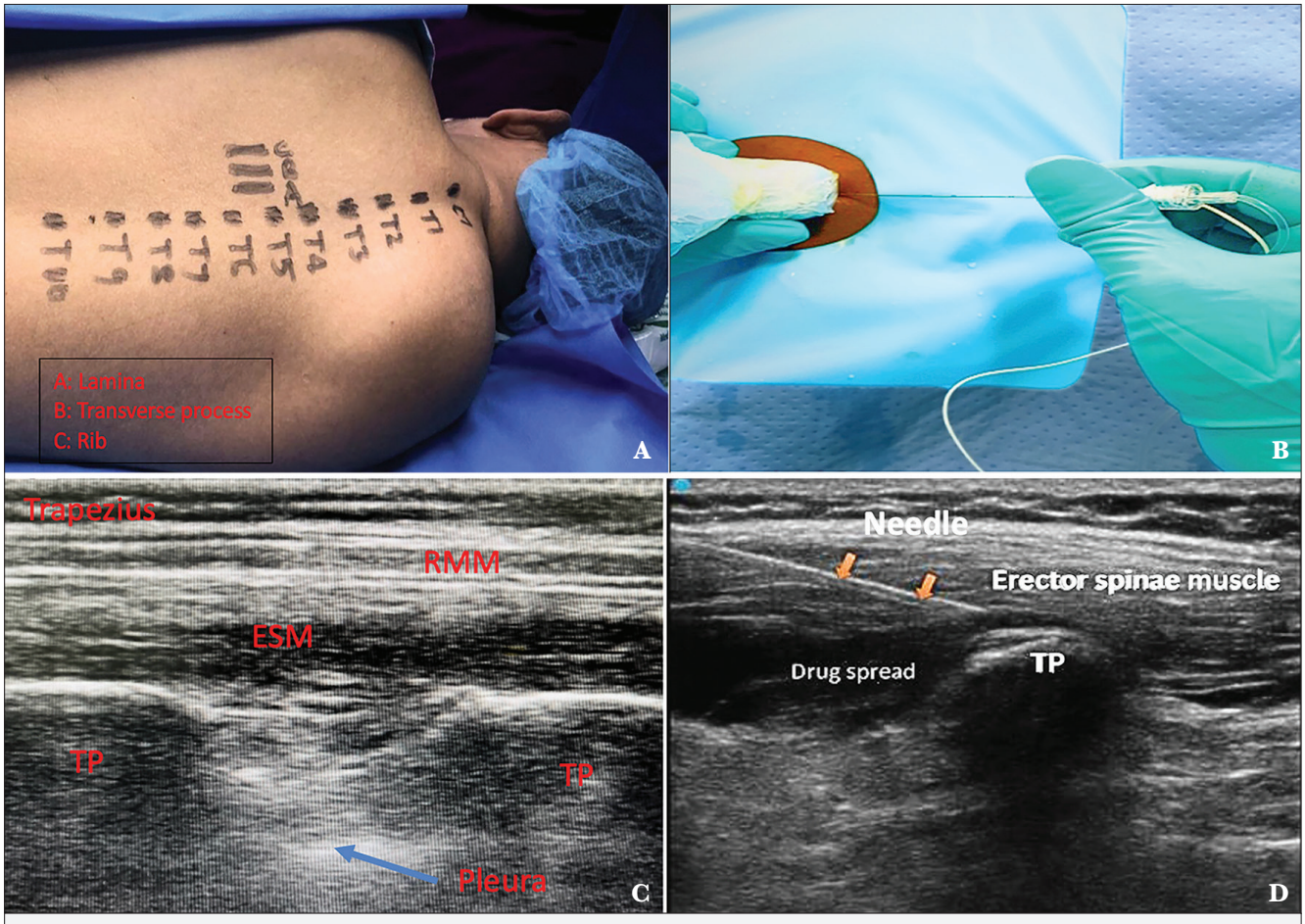

Figure 1. Erector spine plane block.

A: Patient position and surface marking; B: Probe position and in-plane needling; C: Landmarks of ESPB from superficial to deep: Trapezius muscles, Rhomboid major, Erector spinae and T5 Transverse process; D: Placement of needle under ultrasound and spread of local anaesthetic drug.

RMM, rhomboid major muscle; ESM, erector spinae muscle; TP, transverse process; ESPB, erector spinae plane block.

Results

Overall, 84 patients were assessed for eligibility. Fourteen of them did not fulfill the inclusion criteria, and two refused to participate. The remaining 68 patients were randomised and evenly allocated to two groups (Figure 3). Demographic characteristics of the two study groups were comparable, as shown in Table 1.

Postoperative total fentanyl consumption over 24 hours was normally distributed across groups, as verified through visual inspection of Q-Q plots. An independent t-test revealed that patients belonging to the ESPB group consumed significantly less fentanyl than those in the RIB group (mean difference, t=-4.183, df=66, $P < 0.001$). The calculated effect size (Cohen's d=1.023) indicates a large clinical effect (Table 2).

In contrast, intraoperative fentanyl consumption did not follow a normal distribution across the groups. As shown in Table 2, there was no statistically significant difference in intraoperative fentanyl use between the ESPB and RIB groups.

Similarly, the time to first rescue analgesia was not normally distributed. Visual inspection of boxplots revealed no significant outliers. A Mann-Whitney U test showed no statistically significant difference in the time to first rescue analgesia between groups (U=508.5, z=-0.880, P=0.379) (Table 2). However, the frequency of rescue analgesic supplementation was significantly lower in the ESPB group than in the RIB group (U=895.0, z=4.203, $P < 0.001$).

The mean NRS pain scores did not differ significantly between the ESPB and RIB groups when analyzed using the Mann-Whitney U test, both at rest and during movement, as detailed in Tables 3A and 3B.

Repeated-measures ANOVA demonstrated that mean HR varied significantly across time points (F=96.870, $P < 0.001$). A significant decrease in HR between

preinduction and preincision (after administration of blocks and before incision) and between preinduction and postincision was observed in Bonferroni-adjusted post-hoc pairwise comparisons ($P < 0.001$ for both comparisons). Preincision and postincision HR values did not differ significantly ($P=1.000$) (Table 4A). Similar changes were seen in MAP (Table 4B).

In our study, none of the patients reported adverse effects or complications, except for two patients in group EPSP and three patients in group RIB, all of whom experienced PONV.

Discussion

This study compared the analgesic efficacy of the ESPB and the RIB in reducing perioperative opioid requirements in patients undergoing breast cancer surgery. Both blocks were administered safely under ultrasound guidance, with no observed procedural complications. ESPB produced greater opioid-sparing effects than RIB, as demonstrated by significantly lower 24-hour postoperative fentanyl consumption. This difference likely stems from their distinct anatomical spread patterns: ESPB facilitates paravertebral diffusion and, potentially, epidural diffusion, thereby offering broader dermatomal coverage, whereas RIB primarily targets the lateral cutaneous branches of intercostal nerves, resulting in more localised analgesia.[12,13,15] However, the spread to the epidural and paravertebral spaces is less reliable and has not been found in all cases.[13] Notably, intraoperative fentanyl requirements were similar between groups, indicating that the blocks provided comparable analgesia. An insignificant difference in intraoperative opioid requirement and in NRS scores could be related to other causes, such as different local anaesthetic absorption kinetics, rather than to a difference in anatomical spread between the two blocks.

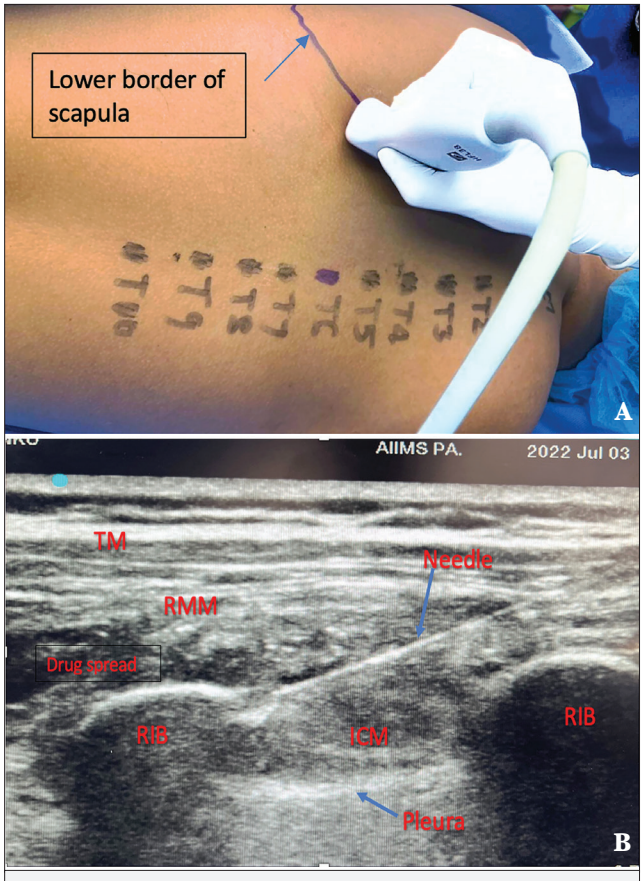

Figure 2. Rhomboid intercostal block.

A: Placement of ultrasound probe for administration of rhomboid intercostal block; B: The Landmarks of rhomboid intercostal block and local anaesthetic injection under ultrasound view.

TM, Trapezius muscle; RMM, Rhomboid major muscle; ICM, Intercostal muscle; RIB, rhomboid intercostal blocks.

The efficacy of ESPB has been well established in previous literature. Singh et al.[16] reported enhanced analgesia with ESPB compared to controls. Altiparmak et al.,[18] observed a 35-40% reduction in tramadol use, while Kendall et al.,[18] in a meta-analysis, reported an 8.84 mg reduction in intravenous morphine equivalents. ElHawary et al.,[19] in a systematic review, further confirmed the effectiveness of ESPB for pain control following mastectomy. Although Gürkan et al.[20] did not report any significant difference in NRS scores between ESPB and the control group, ESPB was associated with significantly lower morphine consumption compared with the control group in a study conducted by them. Most evidence—including randomised controlled trials, systematic reviews and meta-analyses—supports ESPB's analgesic superiority in thoracic and breast surgeries.

In line with these findings, our results reinforce ESPB's reliability in providing broad dermatomal coverage, producing significant reductions in postoperative opioid use, and delivering consistent analgesic efficacy across patient populations. These advantages validate ESPB as a potent regional anaesthetic technique for breast surgery.

RIB, although a relatively recent technique, has also demonstrated promising results. A meta-analysis by Chen et al.,[21] including four randomised controlled trials with a total of 216 participants, showed that RIB significantly reduced acute postoperative pain and 24-hour opioid consumption compared to systemic analgesia. Cadaveric studies have confirmed RIB's ability to achieve extensive craniocaudal and anteroposterior spread of dye, supporting its potential to effectively block intercostal nerves.[22] Similarly, our study showed reduced pain scores, although the postoperative analgesic consumption and frequency of rescue analgesia were significantly higher with RIB than with ESPB (Tables 2 and 3).

In our comparative analysis, ESPB demonstrated better opioid-sparing effects. However, both blocks yielded effective analgesia in the first 24 hours postoperatively, as reflected in low NRS scores both at rest and during movement. Thus, both blocks achieved clinically meaningful pain control throughout the postoperative period.

Zhang et al.[23] compared the analgesic efficacy of ESPB, RIB, and serratus plane block (SPB) for video-assisted thoracic surgery. They found ESPB and RIB to be equally effective regarding postoperative sufentanil consumption and NRS scores, but both were superior to SPB. We found ESPB to have lower compared with RIB, although there was no significant difference in pain scores. The reason could be

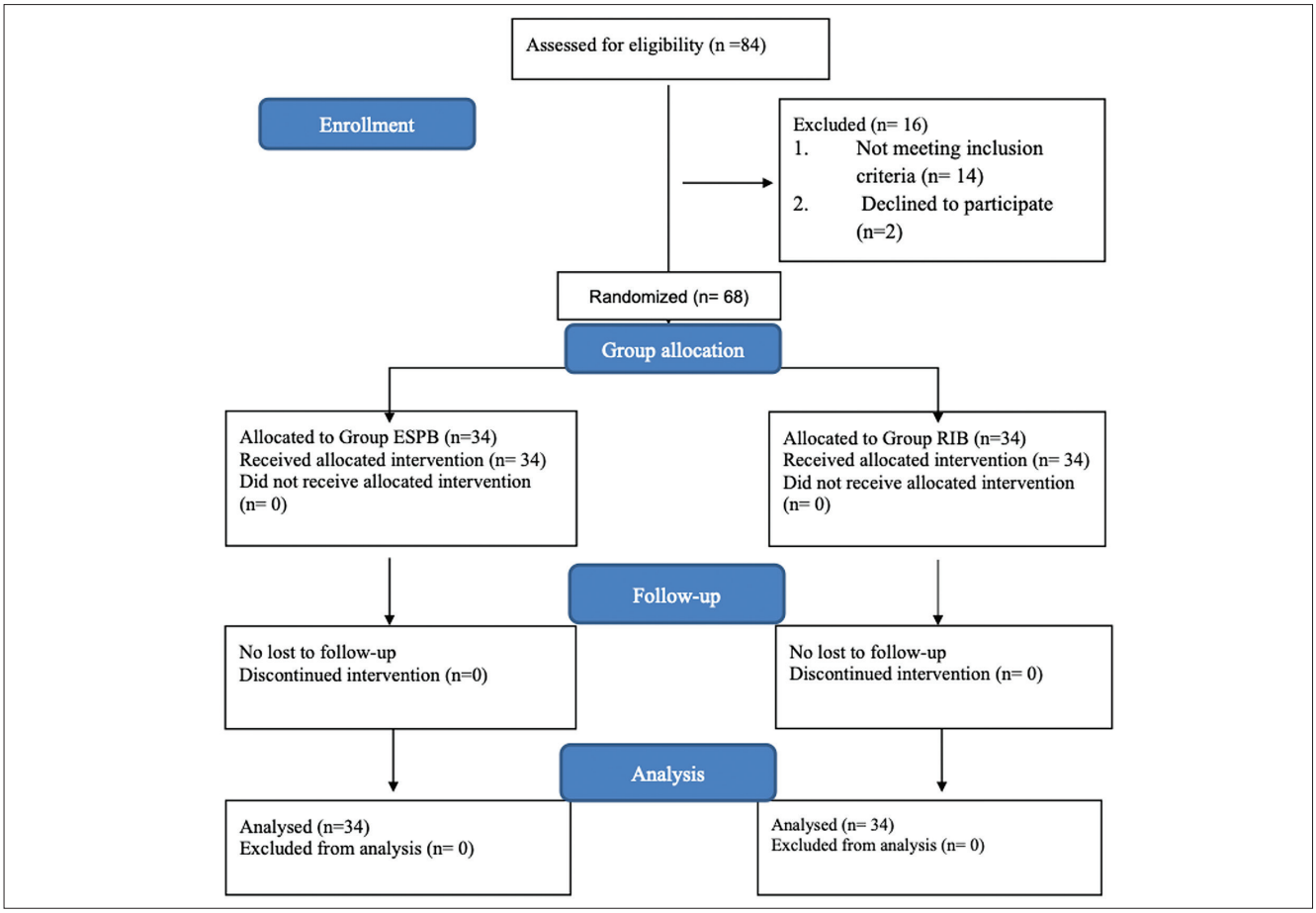

Figure 3. Consort chart.

CONSORT flow diagram showing inclusion, randomization and exclusion of participants.

ESPB, erector spinae plane block; RIB, rhomboid intercostal blocks.

Table. 1 Comparison of Demographic Variables Between the Groups (Group ESPB vs. Group RIB)

	Group ESPB n = 34	Group RIB n = 34	*P* value
Age (years)	54.32±9.58#	54.09±9.634#	0.920*
Weight (kg)	51.21±4.73#	53.27±6.02#	0.121*
Height (cm)	151.32±2.77#	152.15±2.94#	0.239*
BMI (kg m^{2-1})	22.33±1.90#	22.81±2.04#	0.312*
ASA I:II	14:20	16:18	0.625**
Duration of surgery (min)	140.0 (110-180) ##	140.0 (110-160) ##	0.475***

#: mean ± SD; ##: median (IQR); *: unpaired t-test; **: chi-square test; ***: Mann Whitney U test

EPSP, erector spinae plane block; RIB, rhomboid intercostal block; ASA, American Society of Anaesthesiologists; BMI, body mass index; IQR, interquartile range

Table 2. Total Fentanyl used Perioperatively among the Groups

	Group ESPB n = 34	Group RIB n = 34	*P* value
Total fentanyl used intraoperatively (μg kg^{-1})	2.07[#]	2.15[#]	0.716*
Postoperative fentanyl consumption in 24 hours (μg kg^{-1})	2.67±0.68[$]	3.68±1.22[$]	<0.001**
Time to first rescue analgesia (hours)	6 (3-8)[#]	5 (2-8)[#]	0.379*
Frequency of rescue analgesia required	3 (2-4)	4 (2-5)	<0.001*

[#]: median; *: Mann-Whitney U test; [$]: mean ± SD: **: unpaired t-test
EPSP, erector spinae plane block; RIB, rhomboid intercostal block; SD, standard deviation

Table 3A. NRS at Rest Score among the Groups

	Group ESPB	Group RIB	
Time intervals (hours)	**Median (IQR)**	**Median (IQR)**	***P* value[#]**
T0	1 (1.00)	1 (1.00)	0.579
T1	2 (0.00)	2 (0.00)	0.449
T2	2 (1.00)	1 (1.00)	0.229
T4	1 (1.00)	2 (1.00)	0.510
T6	1 (1.00)	1 (1.00)	0.498
T12	1 (1.00)	1 (1.00)	0.883
T24	1 (0.00)	1 (0.00)	0.832

[#]: Mann-Whitney U test
EPSP, erector spinae plane block; RIB, rhomboid intercostal block; IQR, interquartile range; NRS, numerical rating scale

Table 3B. NRS Score at Movement among the Groups

	Group ESPB	Group RIB	*P* value[#]
Time intervals (hours)	**Median (IQR)**	**Median (IQR)**	
T0	2 (0.00)	2 (1.00)	0.742
T1	2 (1.00)	2 (1.00)	0.675
T2	2 (1.00)	2 (0.00)	0.071
T4	2 (0.00)	2 (1.00)	0.322
T6	2 (1.00)	2 (1.00)	0.765
T12	1 (0.00)	1 (1.00)	0.353
T24	1 (1.00)	1 (1.00)	0.239

[#]: Mann-Whitney U test
NRS, numerical rating scale; EPSP, erector spinae plane block; RIB, rhomboid intercostal block; IQR, interquartile range

differences in the types of surgery. Both blocks could provide adequate analgesia in video-assisted surgery.

Jiang et al.[24] compared ESPB, RIB, and SPB for pain management in modified radical mastectomy using 20 ml of 0.5% ropivacaine. They found RIB and ESPB to be equally effective, but both were superior to SPB in terms of opioid consumption. Çiftçi et al.[25] found equal levels of pain relief with ESPB and RIB in breast-conserving surgery. They used 30 ml of 0.25% bupivacaine. These results could differ from our study, in which ESPB was found to be superior to RIB with respect to analgesic consumption, because different local anaesthetics, volumes, or concentrations were used in that study.

Hemodynamic outcomes were comparable between groups. Both ESPB and RIB maintained stable intraoperative cardiovascular parameters, with significant reductions in HR and MAP from baseline following block administration ($P < 0.05$); intergroup analysis revealed no significant differences (Table 4). This indicates that both blocks were effective. Importantly, neither technique resulted in clinically significant hypotension, underscoring its cardiovascular safety profile.

Beyond analgesia, neither group exhibited opioid-related side effects such as constipation and pruritus, suggesting potential for enhanced postoperative recovery. No patient experienced respiratory depression or splinting due to pain, which further supports the utility of regional blocks in preserving respiratory function. The incidence of PONV was similar in both groups. Prior research by Chen et al.[21] also reported a 20% absolute risk reduction in respiratory complications with RIB compared to systemic analgesia.

Table 4A. Post-hoc Pairwise Comparisons for Intraoperative Heart Rate

(I) time	(J) time	Mean difference (I-J)	*P* value*
HR1	HR2	16.191*	<0.001
	HR3	16.868*	<0.001
HR2	HR3	0.676	1.000

*: Repeat measure analysis of variance; I, Column 1; J, Column 2; HR1, preinduction heart rate; HR2, preincision heart rate; HR3, postincision heart rate

Table 4B. Post-hoc Pairwise Comparisons for Intraoperative Mean Arterial pressure

(I) time	(J) time	Mean difference (I-J)	*P* value*
MAP1	MAP2	15.462*	<0.001
	MAP3	18.809*	<0.001
MAP2	MAP3	3.382	0.223

*: Repeat measure analysis of variance; I, Column 1; J, Column 2; MAP1, preinduction mean arterial pressure; HR2, preincision mean arterial pressure; HR3, postincision mean arterial pressure

Crucially, no procedural complications such as pneumothorax, infection, or local anaesthetic systemic toxicity were encountered in our study. This outcome likely reflects the use of ultrasound guidance, adherence to strict aseptic technique, and the procedural expertise of the anaesthesiologist performing the block.

Study Limitations

Despite these strengths, the study is not without limitations. A primary limitation of the study was that hemodynamic parameters were the sole trigger for analgesia, and no objective nociception monitoring, such as the Surgical Plethysmographic Index or Analgesia Nociception Index, was used. A fixed concentration of bupivacaine (0.25%) was used in all patients, precluding exploration of dose-response relationships at other doses. The study population was relatively homogeneous and limited to a single centre, which may limit the generalizability of the findings to broader age groups and different body mass index categories. Additionally, alternative local anaesthetic agents and combinations of volumes were not evaluated, thereby limiting the pharmacologic scope. We could not assess the dermatomal level of sensory block achieved by these two blocks because the patients were under general anaesthesia when the blocks were performed; this is another limitation of this study. We did not collect data on subjects receiving HR-lowering drugs, such as beta-blockers. We did not compare the comorbidities or patients taking antihypertensive medications between the groups. These also add to the limitations of this study. A limitation of the study is that we did not include a control group that received no block or a sham block.

Conclusion

Our study demonstrates that ultrasound-guided ESPB results in significantly lower perioperative fentanyl consumption and less frequent analgesic supplementation than RIB. While both regional blocks effectively reduce pain in patients undergoing breast cancer surgery, ESPB provides better postoperative analgesia with a modest reduction in opioid consumption. These findings support the preferential use of ESPB to optimise postoperative analgesia in this surgical population.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Institutional Ethics Committee of the All India Institute of Medical Sciences in Patna (approval no.: AIIMS/Pat/IEC/PGTh/Jan20/14, date: 25.01.2021).

Informed Consent: All patients provided written informed consent prior to enrollment.

Footnotes

Authorship Contributions: Surgical and Medical Practices - S.K., S.N., N.S., S.A., C.K.J., A.V., G.P.; Concept - S.N.; Design - S.N.; Data Collection and/or/Processing - S.K., S.N., S.A., A.V., G.P.; Analysis and/or/Interpretation - S.K., S.N., N.S.; Literature Review - S.K., S.N., N.S., S.A., G.P.; Writing - S.K., S.N., N.S., S.A., C.K.J., A.V.

Declaration of Interests: The authors declare no conflict of interests.

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The Association Between Systemic Inflammatory and Metabolic Indices and Early Adverse Clinical Outcomes in Adult Patients Admitted to the Post-anaesthesia Care Unit: A Retrospective Observational Study

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Abstract

Objective: This study aimed to investigate the association of systemic inflammatory and metabolic indices with short-term adverse clinical outcomes in adult patients admitted to the post-anaesthesia care unit (PACU).

Methods: In this retrospective single-center observational study, adults admitted to the PACU following surgical procedures were analysed. The association between systemic inflammatory and metabolic indices, calculated from routine laboratory data, and short-term clinical outcomes was evaluated. Missing data were handled using multiple imputation. Associated risk factors were examined using multiple statistical analyses, and ridge regression was performed to assess model stability and potential multicollinearity. Receiver operating characteristic (ROC) analysis was performed to assess the discriminative ability of the investigated markers.

Results: A total of 860 patients were included in the analysis. In multiple analyses, use of inotropic agents on arrival at the PACU, higher monocyte-to-lymphocyte ratio (MLR), and higher blood urea nitrogen-to-albumin ratio were associated with poor short-term clinical outcomes. ROC analysis demonstrated limited discriminative performance, with area under the curve values of 0.545 for the MLR and 0.582 for the blood urea nitrogen-to-albumin ratio in predicting poor short-term clinical outcomes.

Conclusion: Higher monocyte-to-lymphocyte and blood urea nitrogen-to-albumin ratios were associated with poor short-term clinical outcomes in adult patients admitted to the PACU. However, the low discriminative performance observed in ROC analyses suggests that these indices should not be interpreted as strong standalone predictors. Instead, they may provide supporting information within multiparametric clinical risk assessment models.

Keywords: Blood urea nitrogen to albumin ratio, monocyte to lymphocyte ratio, inflammation, post-anaesthesia care unit, postoperative care

Main Points

- Systemic inflammatory and metabolic indices derived from routine laboratory data were evaluated in adult patients admitted to the post-anaesthesia care unit after surgery.
- Higher monocyte-to-lymphocyte and blood urea nitrogen-to-albumin ratios were associated with poor short-term clinical outcomes.
- Receiver operating characteristic analyses showed limited discriminative performance for these indices.
- These markers may reflect aspects of postoperative physiological stress and should be interpreted cautiously within the broader clinical context.

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Introduction

The postoperative period is a phase during which physiological changes related to surgery and anaesthesia subside, and patients' clinical stability is reassessed, making close monitoring essential.[1] Post-anaesthesia care units (PACUs) are specialised care areas designed to closely monitor fundamental physiological parameters such as respiratory, cardiovascular, and neurological status in postoperative patients and to enable the early detection of potential complications.[1] In the PACU, early detection and proper management of postoperative complications are essential for improving clinical outcomes and optimising perioperative care.[2]

The increasing volume of surgical procedures has led to a higher proportion of high-risk patients who require advanced monitoring in the postoperative period. Consequently, the efficient use of limited intensive care resources has become increasingly important. In this context, high-dependency units (HDUs), also referred to as intermediate or step-down care units, play a critical role between general wards and intensive care units in many healthcare systems.[3]

At our centre, to address this need, a PACU with characteristics consistent with those of an HDU, as described in the literature, is available. This unit admits patients identified as high risk during preoperative assessment and allows for close postoperative haemodynamic monitoring, short- to medium-term mechanical ventilation, inotropic support, and advanced monitoring.

In recent years, the surgical stress response has been shown to influence the clinical course through systemic inflammatory and metabolic changes. Accordingly, ratios and indices derived from routine laboratory parameters have attracted increasing interest in postoperative risk assessment.[4-8] The ease of calculation and low cost of these indicators provide practical advantages for their use in the early postoperative period, particularly in time-critical settings such as the PACU. Although studies have investigated risk factors for adverse short-term clinical outcomes in postoperative intensive care unit and PACU populations, data specifically evaluating these risks in PACU populations with HDU characteristics remain limited.

Accordingly, the present study sought to investigate the relationship between systemic inflammatory and metabolic indices and short-term adverse clinical outcomes and to determine their predictive performance among adults receiving care in the PACU.

Methods

Study Design and Ethical Approval

The study protocol was approved by the Scientific Research Ethics Committee of University of Health Sciences Türkiye, Kocaeli City Hospital (approval no.: 2025-181, date: 08.01.2026). Owing to the retrospective design, the requirement for written informed consent was waived. All procedures were carried out in accordance with the principles of the Declaration of Helsinki. This single-center, retrospective observational study was prepared in line with the STROBE guidelines.[9]

Study Population

This study was conducted at University of Health Sciences Türkiye, Kocaeli City Hospital, a tertiary care teaching and research hospital located in Kocaeli, Türkiye. Adults (≥18 years) admitted to the PACU after surgical procedures between 1 March 2025 and 30 June 2025 were retrospectively identified through the hospital's electronic records and were enrolled in the study.

Patients who were admitted to the PACU more than once for repeat postoperative surgical procedures, as well as individuals younger than 18 years, were excluded.

Data Collection

The data analysed in this study were obtained retrospectively from the hospital's electronic medical record system. The collected data were evaluated across five main categories: demographic characteristics, clinical and surgical variables, laboratory findings, inflammatory and metabolic indices, and postoperative outcomes. Demographic data included age, sex, American Society of Anesthesiologists (ASA) physical status score, blood group, and comorbidities, including cardiovascular, pulmonary, renal, neurological, and endocrine-metabolic diseases, malignancy, and other conditions. Clinical and surgical variables included the following: surgical specialty performing the operation; urgency of surgery (elective or emergency); duration of surgery; type of anaesthesia administered; intraoperative use of erythrocyte suspension (ES), fresh frozen plasma (FFP), and colloids; airway status on arrival at the PACU (extubated, intubated, or tracheostomised); and the need for inotropic support at PACU admission.

Laboratory parameters were obtained from blood samples collected at the time of the first admission to the PACU. Arterial blood gas analysis included the following parameters: pH, partial pressure of carbon dioxide (PCO_2, mmHg), partial pressure of oxygen (PO_2, mmHg), oxygen saturation (SO_2, %), lactate (mmol L^{-1}), bicarbonate (HCO_3-, mmol L^{-1}), and base excess (mmol L^{-1}).

Haematological parameters included platelet count (PLT, $\times 10^3/\mu L$), mean platelet volume (MPV, fL), plateletcrit (%), platelet distribution width (PDW, %), white blood cell count (WBC, $\times 10^3/\mu L$), haemoglobin (Hb, g dL^{-1}), haematocrit (Htc, %), mean corpuscular haemoglobin (MCH, pg), mean corpuscular volume (MCV, fL), mean corpuscular haemoglobin concentration (MCHC, g dL^{-1}), and absolute

neutrophil, lymphocyte, monocyte, eosinophil, and basophil counts ($\times 10^3/\mu L$).

Biochemical parameters included glucose (mg dL^{-1}), creatinine (mg dL^{-1}), estimated glomerular filtration rate (eGFR, mL min^{-1} 1.73 m^2), blood urea nitrogen (BUN, mg dL^{-1}), C-reactive protein (CRP, mg L^{-1}), aspartate aminotransferase (AST, U L^{-1}), alanine aminotransferase (ALT, U L^{-1}), lactate dehydrogenase (LDH, U L^{-1}), albumin (g dL^{-1}), total protein (g dL^{-1}), total bilirubin (mg dL^{-1}), direct bilirubin (mg dL^{-1}), calcium (mg dL^{-1}), magnesium (mg dL^{-1}), sodium (mmol L^{-1}), potassium (mmol L^{-1}), and amylase (U L^{-1}).

Coagulation parameters included prothrombin time (PT, second), activated partial thromboplastin time (aPTT, second), and international normalised ratio (INR).

Inflammatory and metabolic indices were calculated from laboratory data obtained at first admission to the PACU. These indices included: the monocyte-to-lymphocyte ratio (MLR) (MLR=monocytes/lymphocytes), PLT-to-lymphocyte ratio [platelet-to-lymphocyte ratio (PLR)=PLTs/lymphocytes], neutrophil-to-lymphocyte ratio (NLR) (NLR=neutrophils/lymphocytes), lymphocyte-to-monocyte ratio (LMR) (LMR=lymphocytes/monocytes), neutrophil-lymphocyte-PLT ratio (NLPR) [NLPR=(neutrophils/lymphocytes) ×PLTs], mean PLT volume-to-PLT ratio (MPR) (MPR=MPV/PLTs), systemic immune-inflammation index [SII=(neutrophils×PLTs]/lymphocytes), pan-immune-inflammation value [pan-immune-inflammation value=(neutrophils×monocytes ×PLTs)/lymphocytes], CRP-to-lymphocyte ratio (CLR) (CLR=CRP/lymphocytes), CRP-to-albumin ratio (CAR) (CAR=CRP/albumin), neutrophil-to-albumin ratio (NAR) (NAR=neutrophils/albumin), albumin-to-creatinine ratio (ACR=albumin/creatinine), and BUN-to-albumin ratio (BAR) (BAR=BUN/albumin).

Bias and Sample Size Considerations

Because of the retrospective design, the study may be subject to selection and information bias. To reduce this potential bias, all consecutive patients meeting the predefined eligibility criteria were enrolled. Cases with missing data were not excluded; instead, missing values were handled using multiple imputation and included in the analysis, with the aim of reducing bias related to missing data.[10]

An a priori sample size calculation was not conducted because of the study's retrospective design. The study population included all patients who fulfilled the eligibility criteria during the predefined time frame.

Definition of Clinical Outcomes

In routine PACU practice, patients were initially monitored during the early postoperative period and subsequently transferred to the general ward or an advanced intensive care unit, according to their clinical status. Taking into account both the routine clinical workflow of the PACU and the recommendations of current post-anaesthesia care guidelines, patients who remained in the PACU for ≥24 hours were classified as having a prolonged PACU stay.[1]

Accordingly, in this study, a PACU length of stay of ≥24 hours was defined as a prolonged PACU stay. Clinical outcomes were classified as binary variables. Patients with a prolonged PACU stay, those transferred to an advanced intensive care unit, and those who died within the first 7 postoperative days were classified as having a poor short-term clinical outcome. In contrast, the good short-term clinical outcome group consisted of patients without a prolonged PACU stay, patients discharged directly to the general ward, and patients who did not experience death within the first 7 postoperative days.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as mean ± standard deviation, median (minimum-maximum), or frequency and percentage (n, %). The distribution of variables was assessed using the Kolmogorov-Smirnov test. Independent continuous variables with a normal distribution were analysed using the Student's t test and reported as mean ± standard deviation, whereas those without normal distribution were analysed using the Mann-Whitney U test and reported as median (minimum-maximum). Independent categorical variables were analysed using the Pearson chi-square test (with Yates' continuity correction when appropriate) or Fisher's exact test, as appropriate. Categorical data were presented as frequencies and percentages. A P value of <0.05 was considered statistically significant.

Missing data were initially evaluated using missing- data analysis. Little's missing completely at random test was applied to assess the randomness of missing values for comorbidities, pH, pCO_2, pO_2, SO_2, HCO_3^-, base excess (mmol L^{-1}), lactate, MPV, plateletcrit, PDW, AST, ALT, LDH, potassium, direct bilirubin, aPTT, duration of surgery, ES, FFP, and colloid replacement. The test result (P=0.763) confirmed that the data were missing completely at random. Multiple imputation (m=5) was applied to these variables.

Primary statistical analyses were performed using the observed (original) dataset. Multiple imputation analysis was conducted as a sensitivity analysis to evaluate the potential impact of missing data on the results. Post-imputation results were pooled according to Rubin's rules, and only findings identified as sensitive to imputation were explicitly reported in the text.

Inflammatory and metabolic indices identified with $P < 0.20$ in univariable analyses[11,12] were evaluated for

multicollinearity using the variance inflation factor (VIF). Indices with a VIF value >5 [NLR and natural logarithm of NLR multiplied by PLT count (lnNLRP)] were excluded from the multiple logistic regression model because of multicollinearity. The remaining indices [PLR, MLR, CAR, CLR, BAR, ACR, and ln(MPR)] were included in the multivariable model.

During univariable analyses, NLPR and MPR demonstrated overdispersion and wide confidence intervals (CIs). Therefore, to reduce the influence of extreme values and improve model stability, these indices were subjected to natural logarithmic transformation and evaluated as ln(NLPR) and ln(MPR) in regression analyses.

In addition to the indices, variables with $P < 0.20$ in univariable analyses—age, ASA score, inotropic use on arrival, administration of ES and FFP, and airway status on arrival to the PACU—were included in the model as potential confounders. The final model was obtained using the backward likelihood ratio approach to achieve a more parsimonious structure. In this final model, inotropic use on arrival to the PACU and the MLR and BAR indices remained independently significant.

To assess the stability of the final multiple model and to evaluate potential residual multicollinearity, ridge regression was performed as a supplementary analysis using the same independent variables in NCSS statistical software, version 11 (NCSS, LLC, Kaysville, Utah, USA). Ridge regression analysis (k=0.005) demonstrated that the model was statistically significant (F=4.033; $P < 0.001$) and that multicollinearity was effectively controlled.

Receiver operating characteristic (ROC) analysis was conducted to examine the discriminative capacity of MLR and BAR, which were found to be independently related to poor short-term clinical outcomes. The area under the curve (AUC) was estimated together with its 95% CI. Optimal cut-off values were identified at the point where the difference between sensitivity and specificity was smallest. For these cut-off points, sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy were also calculated.

Because the primary outcome was defined as a composite endpoint including prolonged PACU stay, transfer to the intensive care unit, and 7-day mortality, additional sensitivity analyses were performed by evaluating the individual components of this composite outcome separately. In this context, prolonged PACU stay, transfer to the intensive care unit, and 7-day mortality were each analyzed using multivariable logistic regression models.

Furthermore, ROC analysis was conducted to evaluate the ability of the BAR to predict 7-day mortality. The optimal cut-off value was determined based on the point at which the difference between sensitivity and specificity was minimized. In this analysis, sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy were calculated, together with their corresponding 95% CIs.

Results

Participants and Flow Diagram

Of the 884 patients screened for eligibility, those younger than 18 years (n = 7) and those readmitted to the PACU for repeat surgical procedures in the postoperative period (n = 17) were excluded. After applying the exclusion criteria, 860 patients were included in the final analysis (Figure 1).

Baseline Characteristics

Among the 860 patients included in the study, the median age was 68 years (range, 18-98). No statistically significant differences in age or sex distribution were observed between patients with and without poor short-term clinical outcomes (all $P > 0.05$).

At least one comorbidity was present in 90.2% of the patients. No significant differences were observed between the groups regarding the presence of overall comorbidity or specific comorbid conditions, including cardiovascular, pulmonary, malignant, neurological, endocrine-metabolic, and other diseases (all $P > 0.05$). In contrast, the prevalence of renal disease was significantly higher in the poor short-term clinical outcome group (P=0.002).

No significant differences between groups were observed in blood group or surgical specialty distribution ($P > 0.05$). However, ASA scores differed significantly between the groups ($P < 0.001$).

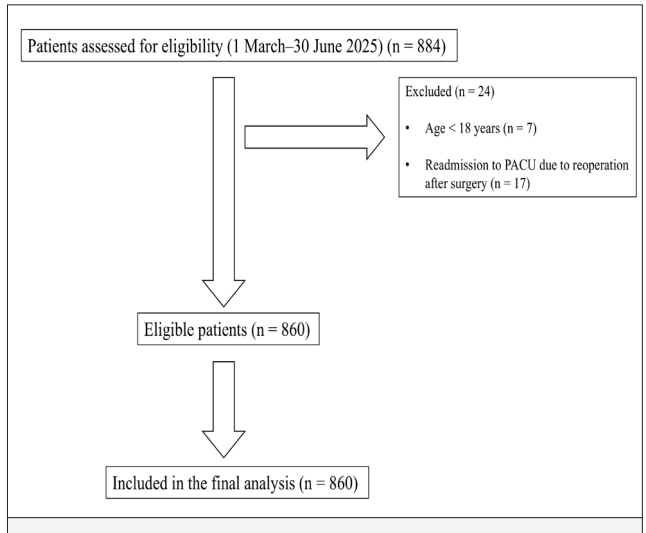

Figure 1. Flow chart.

PACU, post-anaesthesia care unit.

Among the baseline characteristics presented in Table 1, missing data on comorbidities were identified for 23 patients. Variables related to comorbidities were therefore considered sensitive to the missing data structure.

Perioperative and Postoperative Characteristics

No statistically significant differences were observed between groups in surgical urgency, anaesthesia type, duration of surgery, or colloid use (all $P > 0.05$).

Table 1. Baseline Characteristics of the Study Population According to Short-term Clinical Outcomes

Variables	All patients (n = 860)	Good outcome (n = 327)	Poor outcome (n = 533)	*P value
Age (years)	68 (18-98)	67 (21-92)	69 (18-98)	0.204[m]
Sex				
Female	388 (45.1)	144 (44)	244 (45.8)	0.618[x]
Male	472 (54.9)	183 (56)	289 (54.2)	
Comorbidities	755 (90.2) [23]	274 (89) [19]	481 (90.2) [4]	0.356[x,ƒ]
Cardiovascular diseases	539 (64.4) [23]	293 (65.9) [19]	336 (63.5) [4]	0.486[x]
Neurological diseases	102 (12.2) [23]	29 (9.4) [19]	73 (13.8) [4]	0.062[x,ƒ]
Pulmonary diseases	146 (17.4) [23]	50 (16.2) [19]	96 (18.1) [4]	0.482[x]
Endocrine and metabolic disorders	325 (38.8) [23]	117 (38) [19]	208 (39.3) [4]	0.703[x]
Renal diseases	62 (7.4) [23]	11 (3.6) [19]	51 (9.6) [4]	**0.002*[y,ƒ]**
Malignancy	142 (17) [23]	44 (14.3) [19]	98 (18.5) [4]	0.115[x]
Other comorbidities	65 (7.8) [23]	24 (7.8) [19]	41 (7.8) [4]	1.000[y,ƒ]
Blood types				
O Rh^-	44 (5.1)	18 (5.5)	26 (4.9)	0.896[x]
O Rh^+	233 (27.1)	87 (26.6)	146 (27.4)	
A Rh^-	58 (6.7)	22 (6.7)	36 (6.8)	
A Rh^+	350 (40.7)	129 (39.4)	221 (41.5)	
B Rh^-	14 (1.6)	4 (1.2)	10 (1.9)	
B Rh^+	116 (13.5)	46 (14.1)	70 (13.1)	
AB Rh^-	7 (0.8)	4 (1.2)	3 (0.6)	
AB Rh^+	38 (4.4)	17 (5.2)	21 (3.9)	
ASA physical Status				
ASA I	10 (1.2)	5 (1.5)	5 (0.9)	**<0.001*[z]**
ASA II	204 (23.7)	90 (27.5)	114 (21.4)	
ASA III	544 (63.3)	213 (65.1)	331 (62.1)	
ASA IV	92 (10.7)	18 (5.5)	74 (13.9)	
ASA V	10 (1.2)	1 (0.3)	9 (1.7)	
Surgical specialties				
Neurosurgery	97 (11.3)	37 (11.3)	60 (11.3)	0.207[x]
General surgery	350 (40.7)	118 (36.1)	232 (43.5)	
Thoracic surgery	47 (5.5)	20 (6.1)	27 (5.1)	
Obstetrics and gynecology	54 (6.3)	21 (6.4)	33 (6.2)	
Orthopedics	148 (17.2)	55 (16.8)	93 (17.4)	
Urology	106 (12.3)	51 (15.6)	55 (10.3)	
Other specialties	58 (6.7)	25 (7.6)	33 (6.2)	

Data are presented as number (%) or median (minimum-maximum). [x]: Pearson's chi-squared test; [y]: Pearson's chi-squared test with Yates' continuity correction; [z]: Fisher's exact test; [m]: Mann-Whitney U test, ƒ: variable sensitive to missing data. *: P value <0.05 was considered statistically significant; ASA, American Society of Anesthesiologists

In contrast, airway status at PACU admission differed significantly between the groups, with a higher proportion of patients in the poor short-term clinical outcome group admitted while intubated (*P*=0.002). Inotropic use was also significantly more frequent in this group (*P* < 0.001). Additionally, ES and FFP replacements were significantly higher in the poor short-term clinical outcome group (*P*=0.023 and *P*=0.014, respectively).

Missing data were present for duration of surgery (min) (n = 1), ES replacement (n = 8), FFP replacement (n = 8), and colloid use (n = 8). Multiple imputation analyses applied to these variables did not identify any inconsistent parameters that would indicate sensitivity to the missing-data structure. Perioperative and postoperative characteristics are summarised in Table 2.

Laboratory Findings

Among blood gas parameters, PCO_2 levels differed significantly between the groups (*P*=0.026). Hb and Htc values differed significantly between the groups (*P*=0.035 and *P*=0.029, respectively).

When leukocyte subgroups were examined, lymphocyte and eosinophil counts differed significantly between the groups (*P*=0.009 and *P*=0.049, respectively), whereas no significant differences were observed for the other leukocyte subgroups (*P* > 0.05).

Among renal function parameters, levels of creatinine, GFR, and BUN differed significantly between the groups (*P*=0.004, *P*=0.004, and *P* < 0.001, respectively). In addition, CRP and albumin levels differed significantly between the groups (*P*=0.044 and *P*=0.031, respectively).

Table 2. Perioperative and Postoperative Characteristics of the Study Population According to Short-term Clinical Outcomes

Variables	All patients (n = 860)	Good outcome (n = 327)	Poor outcome (n = 533)	*P value
Surgical Urgency				
Elective	612 (71.2)	239 (73.1)	373 (70)	0.329[x]
Emergency	248 (28.8)	88 (26.9)	160 (30)	
Type of anaesthesia				
General anaesthesia (TIVA)	17 (2)	9 (2.8)	8 (1.5)	0.624[z]
General anaesthesia (inhalational)	778 (90.5)	293 (89.6)	485 (91)	
Regional anaesthesia	57 (6.6)	22 (6.7)	35 (6.6)	
Sedoanalgesia	8 (0.9)	3 (0.9)	5 (0.9)	
Airway status on PACU admission				
Extubated	690 (80.2)	281 (85.9)	409 (76.7)	**0.002*[x]**
Intubated	148 (17.2)	37 (11.3)	111 (20.8)	
Tracheostomized	22 (2.6)	9 (2.8)	13 (2.4)	
Inotrope requirement at PACU admission	68 (7.9)	9 (2.8)	59 (11.1)	**<0.001*[x]**
Duration of surgery (minute)	120 (15-630) [11]	120 (20-570) [5]	120 (15-630) [6]	0.322[m¥]
Erythrocyte suspension transfusion	128 (15) [8]	37 (11.5) [4]	91 (17.2) [4]	**0.023*[x¥]**
Fresh frozen plasma transfusion	67 (7.9) [8]	16 (5) [4]	51 (9.6) [4]	**0.014*[x¥]**
Colloid administration	117 (13.9) [18]	48 (15.2) [12]	69 (13.1) [6]	0.384[x¥]
Discharge destination				
Ward	796 (92.6)	327 (100)	469 (88)	N/A
Level 2-3 ICU	37 (4.3)	0 (0)	37 (6.9)	
Mortality				
Death in the PACU	27 (3.1)	0 (0)	27 (5.1)	N/A
7 day mortality	41 (4.8)	0 (0)	41 (7.7)	N/A

Data are presented as number (%) or median (minimum-maximum). Missing data are indicated as [n], [x]: Pearson's chi-squared test; [z]: Fisher's exact test; [m]: Mann-Whitney U test, *: *P* value <0.05 was considered statistically significant. [¥]: Not sensitive to missing data, N/A, not applicable; ICU, intensive care unit; TIVA, total intravenous anaesthesia; PACU, post-anaesthesia care unit

Among coagulation parameters, PT and INR values differed significantly between the groups (P=0.016 and $P < 0.001$, respectively), whereas no significant differences were observed in the remaining coagulation parameters ($P > 0.05$).

Missing data were present for the following variables: pH, PCO_2, HCO_3, and base excess (63 patients); PO_2 (80 patients); SO_2 (73 patients); lactate (70 patients); MPV, plateletcrit, and PDW (14 patients); AST (14 patients); ALT (22 patients); LDH (8 patients); direct bilirubin (6 patients); potassium (5 patients); and aPTT (38 patients). In the multiple imputation assessment, the findings for PCO_2, base excess, and aPTT were identified as sensitive to the structure of the missing data. All laboratory findings are summarised in Table 3.

Systemic Inflammatory and Metabolic Indices

PLR and MLR values differed significantly between the groups (P=0.033 and P=0.028, respectively). CAR and CLR were significantly higher in the poor short-term clinical outcome group (P=0.033 and P=0.022, respectively). Similarly, LMR values differed significantly between the groups (P=0.033).

Table 3. Laboratory Findings and Systemic Inflammatory and Metabolic Indices According to Short-term Clinical Outcomes

Variables	All patients (n = 860)	Good outcome (n = 327)	Poor outcome (n = 533)	*P value
pH	7.4 (6.8-7.7) [63]	7.4 (7.1-7.6) [25]	7.4 (6.8-7.7) [38]	0.258[m]
PCO_2 (mmHg)	36 (16.5-70.7) [63]	36.6 (16.5-55.2) [25]	35.7 (19-70.7) [38]	**0.026*[mƒ]**
PO_2 (mmHg)	102.4 (30.8-545.9) [80]	101.9 (42.2-450.4) [27]	102.7 (30.8-545.9) [53]	0.918[m]
SO_2 (%)	96.9 (47-99.9) [73]	96.9 (76.6-99.9) [25]	96.9 (47-99.9) [48]	0.569[m]
Lactate (mmol L^{-1})	1.6 (0.5-20.8) [70]	1.7 (0.7-9.3) [26]	1.6 (0.5-20.8) [44]	0.401[m]
HCO_3^- (mmol L^{-1})	20.8 (6.5-32.4) [63]	20.7 (9.3-29.7) [25]	20.8 (6.5-32.4) [38]	0.849[m]
Base excess (mmol L^{-1})	-4 (-26.1-8.1) [63]	-4.3 (-19.7-5.9) [25]	-3.8 (-26.1-8.1) [38]	0.060[mƒ]
White blood cell count ($\times10^3$/µL)	10.7 (0.5-33.6)	10.7 (0.5-33.5)	10.7 (1.2-33.6)	0.419[m]
Haemoglobin (g dL^{-1})	11.3 (4.7-17.7)	11.5 (7.2-16.6)	11.3 (4.7-17.7)	**0.035*[m]**
Haematocrit (%)	35±5.5	35±5.3	34.7±5.5	**0.029*[t]**
Mean corpuscular volume (fL)	88.6 (59.4-106.9)	88.7 (61.2-105.1)	88.3 (59.4-106.9)	0.319[m]
Mean corpuscular haemoglobin (pg)	29 (0-38.1)	28.8 (18.9-35.6)	29.1 (0-38.1)	0.496[m]
Mean corpuscular haemoglobin concentration (g dL^{-1})	32.5 (27.6-36.2)	32.6±1.3	32.5±1.3	0.178[t]
Platelet count ($\times10^3$/µL)	230 (13-977)	231 (39-977)	229 (13-565)	0.417[m]
Mean platelet volume (fL)	10.3 (8.3-111) [14]	10.2 (8.3-81) [5]	10.3 (8.3-111) [9]	0.474[m]
Plateletcrit (%)	0.2 (0-1.2) [14]	0.2 (0.1-1.2) [5]	0.2 (0-1.2) [9]	0.666[m]
Neutrophil count ($\times10^3$/µL)	8.3 (0.2-30)	8.5 (0.2-26.6)	8.2 (0.7-30)	0.429[m]
Lymphocyte count ($\times10^3$/µL)	1.4 (0.2-18.1)	1.5 (0.2-5.1)	1.4 (0.2-18.1)	**0.009*[t]**
Monocyte count ($\times10^3$/µL)	0.6 (0-3.7)	0.6 (0-2.4)	0.6 (0-3.7)	0.642[m]
Eosinophil count ($\times10^3$/µL)	0 (0-6.5)	0.1 (0-1)	0 (0-6.5)	**0.049*[m]**
Basophil count ($\times10^3$/µL)	0 (0-1.1)	0 (0-1.1)	0 (0-0.3)	0.207[m]
Platelet distribution width (%)	11.4 (0.1-98) [14]	11.4 (0.1-98) [5]	11.4 (7.5-22.1) [9]	0.970[m]
Glucose (mg dL^{-1})	144 (66-568)	145 (68-568)	144 (66-519)	0.691[m]
Creatinine (mg dL^{-1})	0.8 (0.1-7.7)	0.7 (0.3-7.7)	0.8 (0.1-6.8)	**0.004*[m]**
Estimated glomerular filtration rate (mL min^{-1} 1.73 m^2)	90 (7-201)	92 (8-151)	87 (7-201)	**0.004*[m]**
Blood urea nitrogen (mg dL^{-1})	15 (1.1-137)	14 (4-64)	16 (1.1-137)	**<0.001*[m]**
C-reactive protein (mg L^{-1})	8 (0-510)	7.8 (0.2-341)	8.4 (0-510)	**0.044*[m]**

Table 3. Continued

Variables	All patients (n = 860)	Good outcome (n = 327)	Poor outcome (n = 533)	*P value
Aspartate aminotransferase (U L^{-1})	23 (7.6-2360) [14]	22.8 (8-974) [6]	23 (7.6-2360) [8]	0.671[m]
Alanine aminotransferase (U L^{-1})	16 (5-1164) [22]	16 (5-329) [6]	15 (5-1164) [16]	0.692[m]
Lactate dehydrogenase (U L^{-1})	220.5 (98-3237) [8]	215 (98-3237) [5]	222 (102-2949) [3]	0.119[m]
Albumin (g dL^{-1})	3.4 (1.2-5)	3.5 (1.6-4.7)	3.4 (1.2-5)	**0.031*[m]**
Total protein (g dL^{-1})	5.7 (2.3-8.8)	5.8 (2.6-8.8)	5.7 (2.3-8.8)	0.116[m]
Total bilirubin (mg dL^{-1})	0.5 (0.1-8.7)	0.6 (0.1-2.9)	0.5 (0.1-8.7)	0.259[m]
Direct bilirubin (mg dL^{-1})	0.2 (0-4.4) [6]	0.2 (0-1.6) [2]	0.2 (0-4.4) [4]	0.829[m]
Calcium (mg dL^{-1})	8.3 (5.7-10.9)	8.4 (6.4-10.9)	8.3 (5.7-10.7)	0.097[m]
Magnesium (mg dL^{-1})	1.9 (0.1-3.3)	1.9 (1-3.3)	1.9 (0.1-3.2)	0.553[m]
Sodium (mmol L^{-1})	139 (123-167)	139 (124-155)	139 (123-167)	0.612[m]
Potassium (mmol L^{-1})	4.2 (2.5-6.8) [5]	4.2 (2.5-5.9) [2]	4.2 (2.7-6.8) [3]	0.512[m]
Amylase (U L^{-1})	55 (3.7-960)	55.5 (13-417)	54.6 (3.7-960)	0.999[m]
Prothrombin time (s)	9.8 (7.6-78.3)	9.7 (7.6-18.2)	9.8 (8.3-78.3)	**0.016*[m]**
Activated partial thromboplastin time (s)	26.4 (16.4-117) [38]	25.9 (16.4-81.2) [9]	26.6 (17.1-117) [29]	0.070[m]
International normalised ratio (unitless)	1.1 (0.8-8.2)	1.1 (0.8-5.1)	1.1 (0.9-8.2)	**<0.001*[m]**
Systemic inflammatory and metabolic indices				
Neutrophil-to-lymphocyte ratio	5.9 (0.4-69.3)	5.5 (0.9-39.8)	6.2 (0.4-69.3)	0.155[m]
Platelet-to-lymphocyte ratio	161.5 (9.3-1844.4)	148.4 (33.9-1644)	174.1 (9.3-1844.4)	**0.033*[m]**
Monocyte-to-lymphocyte ratio	0.4 (0-4)	0.4 (0-2)	0.4 (0-4)	**0.028*[m]**
Systemic immune-inflammation index	1348 (52-30500)	1228 (235-13270)	1384 (52-30500)	0.364[m]
Pan-immune-inflammation value	736.2 (0-22569.6)	703.6 (0-17196.6)	749.1 (0-22569.6)	0.351[m]
C-reactive protein-to-albumin ratio	2.4 (0-188.9)	2.4 (0.1-126.3)	2.5 (0-188.9)	**0.033*[m]**
C-reactive protein-to-lymphocyte ratio	5.8 (0-1642.3)	4.8 (0.1-1075.3)	6.4 (0-1642.3)	**0.022*[m]**
Mean platelet volume-to-platelet ratio	0 (0-0.8)	0 (0-0.2)	0.1 (0-0.8)	0.232[m]
Neutrophil-lymphocyte-platelet ratio	0 (0-1.2)	0 (0-0.3)	0 (0-1.2)	0.147[m]
Lymphocyte-to-monocyte ratio	2.6 (0-46.8)	2.8 (0-22)	2.5 (0-46.8)	**0.033*[m]**
Blood urea nitrogen-to-albumin ratio	4.7 (0.3-76.1)	4.3 (1.1-21.2)	5 (0.3-76.1)	**<0.001*[m]**
Neutrophil-to-albumin ratio	2.5 (0.1-14.9)	2.6 (0.1-9.2)	2.5 (0.3- 14.9)	0.928[m]
Albumin-to-creatinine ratio	4.2 (0.4-23.6)	4.5 (0.6-10.3)	4.1 (0.4-23.6)	**0.001*[m]**

Data are presented as mean ± standard deviation or median (minimum-maximum). Missing data are indicated as [n]. [t]: Student's t test, [m]: Mann-Whitney U test. *: *P* value <0.05 was considered statistically significant, *f*: Variable sensitive to missing data

Among metabolic indices, BAR was markedly higher in the poor short-term clinical outcome group, and this difference was statistically significant ($P < 0.001$). A significant difference in ACR was observed between the groups ($P=0.001$).

No statistically significant differences were observed between the groups with respect to NLR, SII, PIV, MPR, NLPR, or NAR (all $P > 0.05$). Systemic inflammatory and metabolic indices are summarised in Table 3.

Risk Factors for Poor Short-term Clinical Outcomes

The results of the univariable and multiple analyses are presented in Table 4.

In univariable analysis, an ASA IV score was associated with a significantly increased risk of poor short-term clinical outcomes [Odds ratio (OR)=4.111, 95% CI: 1.074-15.737; $P=0.039$]. Similarly, the use of inotropic agents on arrival at the PACU was associated with a marked increase in risk of poor short-term clinical outcomes (OR=4.398, 95% CI: 2.150-8.996; $P < 0.001$).

Perioperative administration of ES (OR=1.606, 95% CI: 1.066-2.420; $P=0.024$) and perioperative administration of FFP (OR=2.047, 95% CI: 1.147-3.655; $P=0.015$) were also identified as factors associated with an increased risk of poor short-term clinical outcomes, and the findings for these two parameters were not sensitive to the missing data structure.

Table 4. Univariable and Multiple Analyses of Factors Associated with Short-term Poor Outcomes in PACU Patients

	Groups		Total (n = 860)	Univariable		Multiple	
	Good outcome (n = 327)	Poor outcome (n = 533)		OR (95% CI)	*P value	OR (95% CI)	*P value
Age (years)	67 (21-92)	69 (18-98)	68 (18-98)	1.006 (0.997-1.016)	0.186		
ASA scores							
ASA I	5 (1.5)	5 (0.9)	10 (1.2)	Reference			
ASA II	90 (27.5)	114 (21.4)	204 (23.7)	1.267 (0.356-4.511)	0.715		
ASA III	213 (65.1)	331 (62.1)	544 (63.3)	1.554 (0.445-5.432)	0.490		
ASA IV	18 (5.5)	74 (13.9)	92 (10.7)	4.111 (1.074-15.737)	**0.039***		
ASA V	1 (0.3)	9 (1.7)	10 (1.2)	9.000 (0.809-100.139)	0.074		
Inotrope requirement at PACU admission	9 (2.8)	59 (11.1)	68 (7.9)	4.398 (2.15-8.996)	**<0.001***	2.785 (1.320- 5.875)	**0.007***
Erythrocyte suspension transfusion	37 (11.5) [4]	91 (17.2) [4]	128 (15) [8]	1.606 (1.066-2.42)	**0.024***		
Fresh frozen plasma transfusion	16 (5) [4]	51 (9.6) [4]	67 (7.9) [8]	2.047 (1.147-3.655)	**0.015***		
Airway status on PACU admission							
Extubated	281 (85.9)	409 (76.7)	690 (80.2)	Reference			
Intubated	37 (11.3)	111 (20.8)	148 (17.2)	2.061 (1.379-3.081)	**<0.001***		
Tracheostomized	9 (2.8)	13 (2.4)	22 (2.6)	0.992 (0.419-2.353)	0.986		
Laboratory parameters and systemic inflammatory-metabolic indices							
Haemoglobin (g dL^{-1})	11.6±1.8	11.3±1.9	11.4±1.9	0.913 (0.847-0.984)	**0.017***		
Haematocrit (%)	35.5±5.3	34.7±5.5	35±5.5	0.972 (0.948-0.997)	**0.029***		
Mean corpuscular volume (fL)	87.7±6.3	88.3±6.4	88.1±6.3	1.014 (0.993-1.037)	0.199		
Mean corpuscular haemoglobin concentration (g dL^{-1})	32.6±1.3	32.5±1.3	32.5±1.3	0.931 (0.838-1.033)	0.178		
Creatinine (mg dL^{-1})	0.8±0.5	1±0.7	0.9±0.7	1.665 (1.237-2.242)	**0.001***		
Estimated glomerular filtration rate (mL min^{-1} 1.73 m^2)	88.1±24.5	81.7±29.6	84.1±27.9	0.992 (0.987-0.997)	**0.001***		
Blood urea nitrogen (mg dL^{-1})	16.1±8	20.4±14.3	18.8±12.5	1.036 (1.021-1.052)	**<0.001***		
C-reactive protein (mg L^{-1})	26.9±46.1	42.5±69.4	36.6±62	1.005 (1.002-1.008)	**0.001***		
Albumin (g dL^{-1})	3.4±0.6	3.2±0.7	3.3±0.6	0.719 (0.576-0.899)	**0.004***		
Total protein (g dL^{-1})	5.6±0.9	5.5±1	5.6±1	0.861 (0.748-0.991)	**0.037***		
Total bilirubin (mg dL^{-1})	0.7±0.4	0.8±0.8	0.7±0.7	1.212 (0.964-1.523)	0.100		
Direct bilirubin (mg dL^{-1})	0.3±0.2 [2]	0.3±0.4 [4]	0.3±0.3 [6]	1.615 (0.969-2.692)	0.066¥		
Calcium (mg dL^{-1})	8.3±0.6	8.2±0.7	8.2±0.7	0.808 (0.659-0.99)	**0.040***		
Amylase (U L^{-1})	67±46.7	72.9±71.4	70.7±63.2	1.002 (0.999-1.004)	0.184		
PCO_2 (mmHg)	36.7±5.7 [54]	36.1±6.6 [13]	36.3±6.2 [67]	0.985 (0.962-1.007)	0.183¥		
SO_2 (%)	96.1±2.8 [54]	95.7±4.6 [14]	95.8±4 [68]	0.971 (0.933-1.011)	0.154¥		
Base excess (mmol L^{-1})	-4.4±3.5 [67]	-3.9±4.9 [23]	-4.1±4.5 [90]	1.026 (0.993-1.059)	0.125¥		
Activated partial thromboplastin time (s)	27±5.6 [9]	28±8.1 [29]	27.6±7.2 [38]	1.024 (1.000-1.049)	**0.046***		
Prothrombin time (s)	9.9±1.1	10.5±3.6	10.2±2.9	1.198 (1.076-1.334)	**0.001***		

Table 4. Continued

	Groups		Total (n = 860)	Univariable		Multiple	
	Good outcome (n = 327)	Poor outcome (n = 533)		OR (95% CI)	*P value	OR (95% CI)	*P value
International normalised ratio (unitless)	1.1±0.3	1.2±0.4	1.2±0.4	8.938 (3.873-20.631)	**<0.001***		
Neutrophil-to-lymphocyte ratio	7.4±6.1	8.5±8.1	8.1±7.4	1.021 (1.000-1.042)	**0.045***		
Platelet-to-lymphocyte ratio	197.2±158.1	225.7±194.8	214.9±182.2	1.001 (1.000-1.002)	**0.028***		
Monocyte-to-lymphocyte ratio	0.5±0.5	0.5±0.5	0.5±0.5	1.836 (1.263-2.671)	**0.001***	1.668 (1.118-2.488)	**0.002***
C-reactive protein-to-albumin ratio	9±16.2	16.8±30.6	13.8±26.4	1.015 (1.007-1.022)	**<0.001***		
C-reactive protein-to-lymphocyte ratio	29.9±79.8	61±140.8	49.1±122.2	1.003 (1.001-1.005)	**<0.001***		
Blood urea nitrogen-to-albumin ratio	4.9±2.6	7±6.5	6.2±5.5	1.121 (1.075-1.169)	**<0.001***	1.100 (1.052-1.150)	**<0.001***
Albumin-to-creatinine ratio	4.7±1.7	4.2±2.1	4.4±2	0.896 (0.833-0.963)	**0.003***		
ln (mean platelet volume/ platelet)	-3.1±0.4	-3.1±0.5	-3.1±0.5	1.305 (0.958-1.777)	0.092		
ln (neutrophil to lymphocyte, platelet ratio)	-3.7±0.8	-3.5±0.9	-3.6±0.8	1.199 (1.009-1.425)	**0.039***		
Constant	-	-		-	-	1.164 (0-0)	0.544

Cox & Snell R square=0.063; Nagelkerke R square=0.085; Accuracy=0.622. Data are presented as number (%) and mean ± standard deviation. Missing data are indicated as [n], *: *P* value <0.05 was considered statistically significant, : Variable sensitive to missing data, ¥: Not sensitive to missing data, PACU, post-anaesthesia care unit; ASA, American Society of Anesthesiologists; OR, odds ratio; CI, confidence intervals

Among patients admitted to the PACU while intubated, the risk of poor short-term clinical outcomes was significantly higher than in extubated patients (OR=2.061, 95% CI: 1.379-3.081; $P < 0.001$).

When laboratory parameters were evaluated, higher Hb (OR=0.913, 95% CI: 0.847-0.984; $P=0.017$) and Htc (OR=0.972, 95% CI: 0.948-0.997; $P=0.029$) levels were associated with a reduced risk of poor short-term clinical outcomes, indicating a protective effect. In contrast, increased levels of creatinine (OR=1.665, 95% CI: 1.237-2.242; $P=0.001$), BUN (OR=1.036, 95% CI: 1.021-1.052; $P < 0.001$), and CRP (OR=1.005, 95% CI: 1.002-1.008; $P=0.001$) were associated with an increased risk of poor short-term clinical outcomes.

GFR (OR=0.992, 95% CI: 0.987-0.997; $P=0.001$), albumin (OR=0.719, 95% CI: 0.576-0.899; $P=0.004$), and total protein (OR=0.861, 95% CI: 0.748-0.991; $P=0.037$) levels were protective against poor short-term clinical outcomes. Calcium levels similarly showed a significant protective association (OR=0.808, 95% CI: 0.659-0.990; $P=0.040$).

Among coagulation parameters, increases in aPTT (OR=1.024, 95% CI: 1.000-1.049; $P=0.046$), PT (OR=1.198, 95% CI: 1.076-1.334; $P=0.001$), and, particularly INR (OR=8.938, 95% CI: 3.873-20.631; $P < 0.001$) were associated with markedly increased risk of poor short-term clinical outcomes. The findings for aPTT were sensitive to the structure of missing data.

When systemic inflammatory and metabolic indices were examined, increases in NLR, PLR, MLR, CAR, CLR, BAR, and lnNLPR were associated with an increased risk of poor short-term clinical outcomes (all $P < 0.05$). In contrast, increasing ACR values were associated with a reduced risk of poor short-term clinical outcomes, indicating a protective effect (OR=0.896, 95% CI: 0.833-0.963; $P=0.003$).

In multiple logistic regression analysis, after adjustment for potential confounding variables, the use of inotropic agents on arrival at the PACU remained an independent risk factor for poor short-term clinical outcomes (OR=2.785, 95% CI: 1.320-5.875; $P=0.007$).

Among systemic inflammatory and metabolic indices, an increase in MLR was independently associated with an increased risk of poor short-term clinical outcomes (OR=1.668, 95% CI: 1.118-2.488; $P=0.002$). Similarly, higher BAR values were independently associated with poor

short-term clinical outcomes (OR=1.100, 95% CI: 1.052-1.150; $P < 0.001$).

To validate the stability of the multiple logistic regression model and to assess potential residual multicollinearity, ridge regression analysis was performed using the same independent variables. In ridge regression analysis, VIF values for all variables included in the model ranged from 1.19 to 3.57. Examination of standardised regression coefficients showed that BAR had the strongest effect on the dependent variable (β=0.107), followed by ASA score (β=0.078), MLR (β=0.075), and inotropic use on arrival at the PACU (β=0.067). All of these variables demonstrated a positive effect on the dependent variable. In addition, the direction and relative magnitude of the coefficients were consistent with those obtained from the logistic regression model (Supplementary Table 1).

Sensitivity Analyses of Individual Outcome Components

Because the composite outcome consisted of components with different clinical weights, additional sensitivity analyses were performed. In the multivariable analysis conducted for prolonged PACU stay, the BAR (OR=1.097, 95% CI: 1.058-1.137; $P < 0.001$), the MLR (OR=1.822, 95% CI: 1.266-2.622; $P=0.001$), and the requirement for inotropic support at PACU admission (OR=3.489, 95% CI: 1.967-6.188; $P < 0.001$) were independently associated with the outcome (Supplementary Table 2).

In the analysis of 7-day mortality, BAR (OR=1.121, 95% CI: 1.063-1.183; $P < 0.001$) and the need for inotropic support (OR=17.2, 95% CI: 7.798-37.935; $P < 0.001$) remained significant, whereas MLR was not statistically significant ($P=0.645$) (Supplementary Table 3). In the intensive care unit (ICU) transfer analysis, MLR was independently associated with the outcome (OR=1.471, 95% CI: 1.043-2.075; $P=0.028$), whereas BAR was not statistically significant ($P=0.645$) (Supplementary Table 4).

Additionally, an exploratory ROC analysis was performed to evaluate BAR's ability to predict 7-day mortality (Supplementary Figure 1, Supplementary Table 5). In this analysis, BAR demonstrated good discriminative performance for predicting mortality (AUC=0.850, 95% CI: 0.780-0.919; $P < 0.001$). The optimal cut-off value was determined as ≥6.715. At this threshold, sensitivity was 75.6% (95% CI: 59.7-87.6), specificity was 76.0% (95% CI: 73-79), positive predictive value was 13.7% (95% CI: 11.3-16.4), negative predictive value was 98.4% (95% CI: 97.3-99.1), and overall accuracy was 76.1% (95% CI: 73.1-78.9).

ROC Analysis of MLR for Predicting Poor Short-term Clinical Outcomes

ROC analysis of MLR showed an AUC of 0.545 for predicting poor short-term clinical outcomes (95% CI: 0.506-0.584; $P=0.028$) (Figure 2). The optimal cut-off value, defined as the point with the smallest difference between sensitivity and specificity, was ≥0.375. At this cut-off value, sensitivity was 53.3% (95% CI: 49-57.6) and specificity was 53.5% (95% CI: 48-59). The positive predictive value was 65.1% (95% CI: 61.9-68.3), the negative predictive value was 41.3% (95% CI: 38-44.6), and the overall accuracy was 53.4% (95% CI: 50-56.8) (Table 5).

ROC Analysis of BAR for Predicting Poor Short-term Clinical Outcomes

ROC analysis of BAR yielded an AUC of 0.582 for predicting poor short-term clinical outcomes (95% CI: 0.544-0.619; $P < 0.001$) (Figure 3). The optimal cut-off value, defined using the same criterion, was ≥4.605. At this cut-off value, sensitivity was 54.4% (95% CI: 50.1-58.7) and specificity was 54.1% (95% CI: 48.6-59.6). The positive predictive value was 65.9% (95% CI: 62.7-69); the negative predictive value was 42.1% (95% CI: 38.9-45.5); and the overall accuracy was 54.3% (95% CI: 50.9-57.7) (Table 5).

Discussion

This retrospective observational study investigated the potential association between systemic inflammatory and metabolic indices and short-term adverse clinical outcomes in adult patients admitted to the PACU. In multiple logistic regression analysis, after adjustment for potential clinical and biochemical confounders, MLR and BAR were associated with short-term adverse clinical outcomes.

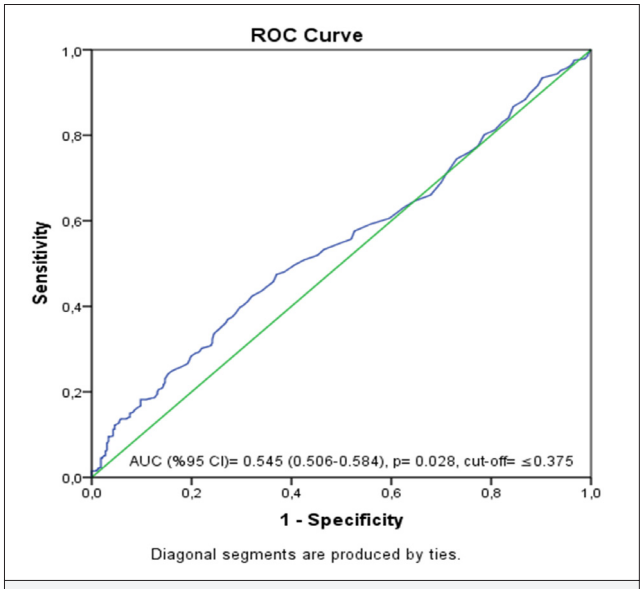

Figure 2. ROC curve of the monocyte-to-lymphocyte ratio for predicting short-term poor clinical outcomes.

ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval.

Table 5. Receiver Operating Characteristic Analysis of MLR and BAR for Predicting Poor Short-term Clinical Outcomes

	MLR	BAR
Cut-off value	≥0.375	≥4.605
AUC (95% CI)	0.545 (0.506-0.584)*	0.582 (0.544-0.619)¥
Sensitivity (95% CI)	53.3 (49-57.6)	54.4 (50.1-58.7)
Specificity (95% CI)	53.5 (48-59)	54.1 (48.6-59.6)
Positive predictive value (95% CI)	65.1 (61.9-68.3)	65.9 (62.7-69)
Negative predictive value (95% CI)	41.3 (38-44.6)	42.1 (38.9-45.5)
Accuracy (95% CI)	53.4 (50-56.8)	54.3 (50.9-57.7)

Data are presented as estimates with 95% confidence intervals. The optimal cut-off value was determined based on the threshold that minimised the absolute difference between sensitivity and specificity

*: $P < 0.001$. ¥: $P < 0.001$, AUC, area under the curve; CI, confidence interval; MLR, monocyte-to-lymphocyte ratio; BAR, blood urea nitrogen-to-albumin ratio

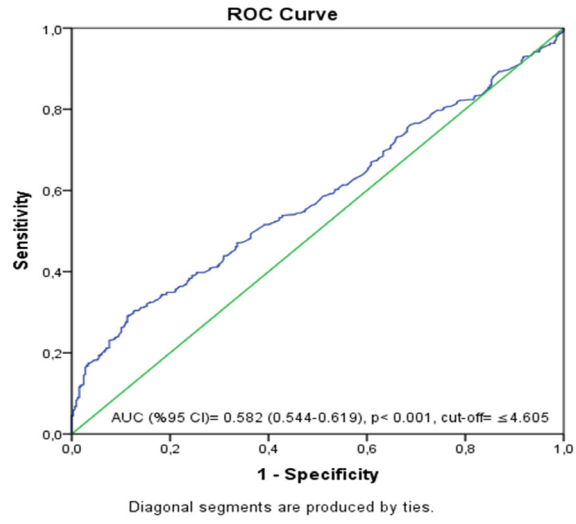

Figure 3. ROC curve of the blood urea nitrogen-to-albumin ratio for predicting short-term poor clinical outcomes.

ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval.

However, the AUC values for both indices in ROC analyses were close to 0.5, indicating that these parameters have limited discriminative ability in predicting clinical outcomes. Although the findings suggest a statistical association of BAR and MLR with adverse clinical outcomes, they do not indicate that these indices can be used as strong predictors on their own. In addition, this study did not evaluate whether adding these indices to standard clinical risk models, including the ASA physical status classification or other perioperative clinical variables, would improve predictive performance. Accordingly, when considering the clinical use of these indices, it should be noted that the findings may primarily reflect a biological association and that their predictive performance appears limited.

Because the primary outcome in our study was defined as a composite including prolonged PACU stay, ICU transfer, and 7-day mortality, additional sensitivity analyses were performed to determine whether the findings differed according to the individual components. In these analyses, the multivariable analysis for prolonged PACU stay showed that BAR, MLR, and the requirement for inotropic agents at PACU admission remained significant. In contrast, in the mortality analysis, only BAR and the requirement for inotropic agents remained significant, whereas MLR lost statistical significance. In the ICU transfer analysis, MLR was independently associated with the outcome, whereas BAR was not significant. These findings suggest that inflammatory and metabolic indices may reflect different aspects of postoperative clinical deterioration. In the additional ROC analysis for mortality, the discriminative performance of BAR was markedly higher (AUC=0.850, 95% CI: 0.780-0.919). Moreover, the high negative predictive value (98.4%) suggests that low BAR levels may be useful in identifying patients at low risk of short-term mortality. This observation suggests that composite outcomes that combine results with different clinical weights may attenuate the predictive performance of certain biomarkers.

Surgical procedures may affect host defence mechanisms through local tissue injury and disruption of physiological barriers; this process can increase susceptibility to infectious agents and trigger both local and systemic inflammatory responses.[4] The magnitude and duration of the inflammatory response may vary depending on the type of surgical procedure, the extent of surgical trauma, and patient-related clinical characteristics.[4] During the postoperative period, this inflammatory response is modulated by the dynamic interplay between pro-inflammatory and anti-inflammatory components of the immune system.[4] Disruption of this balance may lead to uncontrolled systemic inflammation, potentially predisposing patients to organ dysfunction and being associated with increased morbidity and mortality.[4]

In recent years, inflammatory markers have gained attention as potential prognostic indicators of mortality and adverse clinical outcomes in postoperative patients.[13] Incorporation of these markers into risk assessment processes has been reported to contribute to the development of personalised treatment strategies and to improvement in postoperative patient outcomes.[13] The existing literature comprises studies evaluating various inflammatory and metabolic markers across different surgical procedures; however, these studies exhibit considerable heterogeneity in terms of patient populations and surgical characteristics.[14-16] Indeed, Kilinc et al.[13] reported that postoperative inflammation and nutritional condition were linked to mortality in patients undergoing surgery for femoral fracture.

In this study, the association of inflammatory and metabolic markers with poor short-term clinical outcomes was evaluated in adult patients from a heterogeneous surgical population monitored in the PACU. In contrast to most studies, which primarily focus on specific surgical subgroups, the inclusion of patients requiring PACU monitoring after diverse surgical procedures allows for assessment of the potential utility of these indices in real-world clinical practice. The finding that BAR and MLR remained associated with poor clinical outcomes after adjustment for other variables reflecting clinical severity in multiple analyses suggests that these indices may contribute to risk stratification within the PACU population.

BAR is an index that reflects the combined effects of multiple pathophysiological processes, including renal perfusion and clearance, hepatic synthetic capacity, nutritional status, and endothelial integrity.[17] Because BUN reflects renal function and metabolic status, while albumin plays a critical role in maintaining fluid balance and oncotic pressure, the combined assessment of these two parameters has been emphasised for its clinical relevance.[17,18] Evidence from earlier studies suggests a relationship between BAR and mortality or morbidity in different patient groups.[15,17,19-22] In a study by Chen et al.,[15] BAR was linked to long-term mortality in patients treated surgically for hip fracture and was proposed as a practical indicator for early risk evaluation. However, differences between the patient populations and outcome measures reported in the literature and those in the present study limit direct comparisons of findings regarding the prognostic value of BAR. Heterogeneity in patient populations and clinical contexts may also contribute to variability in the discriminative performance reported in ROC analyses. This observation suggests that, rather than functioning as a strong standalone predictor, BAR may be more appropriately considered as a complementary marker within multiparametric risk assessment models.

In the present study, MLR was found to be independently associated with poor short-term clinical outcomes in adult patients monitored in the PACU. As a marker of systemic immune response, the prognostic value of MLR has been explored in various clinical settings and has been linked to adverse outcomes, particularly among patients with malignancies and surgical populations.[23-25] In addition, studies involving elderly patients with hip fractures have reported associations between MLR and both mortality and intensive care unit admission.[14,16,26] However, the moderate discriminative performance of MLR observed in our ROC analysis suggests that, rather than serving as a strong standalone predictor, this index—similar to BAR—may be more appropriately considered as a complementary marker within multiparametric risk assessment models.

In this study, the use of inotropic agents upon admission to the PACU was independently associated with poor short-term clinical outcomes. This finding suggests that haemodynamic instability in the early postoperative period may indicate a more complicated clinical trajectory and a greater need for close monitoring. The potential for haemodynamic instability to increase the risk of organ dysfunction and the need for higher levels of care may plausibly explain the observed association between inotropic support on PACU admission and poor short-term clinical outcomes.

Study Limitations

This study has several limitations. Owing to its retrospective and single-center design, causal relationships cannot be established, and the generalisability of the findings to other centres is limited. In addition, the heterogeneous nature of the study population—encompassing multiple surgical specialties, variable anaesthetic techniques, and a broad spectrum of comorbidities—may have complicated the interpretation of the associations between inflammatory and metabolic indices and poor short-term clinical outcomes.

The use of electronic medical records as the primary data source may have precluded detailed evaluation of certain potential confounding variables, such as analgesic regimens, sedative dosages, neurological assessments, and preoperative anticoagulant therapy. Furthermore, as laboratory parameters reflect only the initial postoperative values obtained at PACU admission, it remains unclear to what extent these measurements distinguish chronic physiological status from the acute surgical stress response. Outcome assessment was also limited to the early postoperative period, and data on longer-term outcomes, including 30-day mortality, were not available. Accordingly, the findings should be interpreted as reflecting short-term clinical outcomes.

Another limitation is the use of a composite primary outcome that combines prolonged PACU stay, ICU transfer, and 7-day mortality. As these components differ in their clinical significance, the use of a composite endpoint may have influenced the observed predictive performance of the investigated indices. Although additional sensitivity

analyses examining individual outcome components were performed, future studies may benefit from evaluating these outcomes separately.

Decisions regarding PACU admission and escalation to higher levels of care during the postoperative period were partly based on clinicians' judgement, suggesting that unmeasured clinical factors may have influenced outcomes. Despite the use of multiple imputation to handle missing data, the potential impact of this approach on the results cannot be entirely excluded. Finally, our institution's PACU has characteristics similar to those of an HDU, which may restrict the generalisability of these findings to PACU settings intended primarily for brief postoperative recovery.

Conclusion

In this retrospective observational study, metabolic and inflammatory indices derived from routine laboratory data were evaluated among adult patients admitted to the PACU; BAR and MLR were associated with short-term adverse clinical outcomes. However, the AUC values obtained in the ROC analyses were close to 0.5, indicating that the discriminative performance of these indices is limited. Although a statistical association was observed between these indices and adverse clinical outcomes, these findings do not support the use of these parameters as strong predictive tools on their own. These indices may instead reflect certain aspects of postoperative physiological stress and should be interpreted cautiously within the broader clinical context. Further prospective, multicentre studies are needed to clarify the potential role of metabolic and inflammatory indices in postoperative risk assessment.

Ethics

Ethics Committee Approval: The study protocol was approved by the Scientific Research Ethics Committee of University of Health Sciences Türkiye, Kocaeli City Hospital (approval no.: 2025-181, date: 08.01.2026).

Informed Consent: Owing to the retrospective design, the requirement for written informed consent was waived.

Footnotes

Authorship Contributions: Concept - B.G., A.Z.T.C.; Design - B.G., A.Z.T.C.; Data Collection and/or/Processing - F.Z., C.A., E.R.K., B.E.; Analysis and/or/Interpretation - B.G.; Literature Search - B.G., A.Ş., Z.Y.T.; Writing - B.G., A.Ş., Z.Y.T., F.Z., C.A., E.R.K., B.E., A.Z.T.C.

Declaration of Interests: The authors declare no conflicts of interest.

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Declaration Regarding the Use of AI and AI-Assisted Technologies: During the preparation of this article, the authors used artificial intelligence for language correction and text editing. The authors are fully responsible for the accuracy, completeness, and scientific content of the final article.

Supplementary Tables 1-5: https://d2v96fxpocvxx.cloudfront.net/beb8919b-f013-4ea1-b1c8-40332e840fe1/content-images/ba0a05d8-be93-427b-bc9e-eb766e80b7c1.pdf

Supplementary Figure 1: https://d2v96fxpocvxx.cloudfront.net/beb8919b-f013-4ea1-b1c8-40332e840fe1/content-images/fcaef28c-1cd3-45cd-a935-f16098c4b88f.pdf

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Original Article
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Relationship Between Patient State Index and Richmond Agitation Sedation Scale for Sedation in Critically Ill Patients: An Observational Analytical Study

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Abstract

Objective: The objective of this study was to find the relationship between Patient State Index (PSI) and Richmond Agitation Sedation Scale (RASS) for sedation in critically ill patients.

Methods: This was a prospective, observational study. Thirty-five patients were recruited to assess the correlation between PSI and RASS scores of 0 to -3 for sedation in mechanically ventilated, critically ill patients. Paired observations (RASS and PSI) were made for each patient every 4 hours for at least 72 hours or until discontinuation of monitoring, whichever occurred earlier. Appropriate statistical analyses were applied; a $P < 0.05$ was considered significant.

Results: Out of the expected 665 pairs of observations, only 608 pairs were observed. The median PSI value with all sedation regimen was 72 with an interquartile range of 60 and 86 (1st and 3rd quartile) respectively. There was significant and strong correlation between PSI and RASS 0 to -3 with Spearman correlation coefficient of 0.822; R^2=0.675 ($P < 0.001$) which dropped to 0.786 with repeated measures correlation. The sensitivity and specificity were 88.66% and 88.57%, respectively, with an area under the receiver operating characteristic curve of 0.947; these improved to 100% and an area under the curve of 1 when analysed per patient. To maintain RASS between 0 and -3, the PSI cutoff was found to be 50-52.

Conclusion: PSI correlates well with RASS across sedation regimens in critically ill patients and assists in monitoring of sedation. Adequate sedation to reach an RASS of 0 to -3 may be achieved at a PSI of 50-52. However, these findings are preliminary and require validation in larger cohorts.

Keywords: Deep sedation, fentanyl, intensive care unit, midazolam, morphine, receiver operating curve

Main Points

- Patient State Index (PSI) can be used to monitor sedation continuously in the intensive care unit.
- There is a strong and statistically significant correlation between PSI and Richmond Agitation Sedation Scale (RASS) scores from 0 to -3, with a Spearman correlation coefficient of 0.822.
- PSI correlates well with RASS across all sedation regimens in critically ill patients.
- Adequate sedation to achieve a RASS of 0 to -3 may be achieved at a PSI 50-52.

Introduction

Critically ill patients or those undergoing major surgery frequently require mechanical ventilation as part of their care. Appropriate administration of analgesia and sedation is important for patient comfort, safety, and synchrony with mechanical ventilation. The level of sedation should be titrated to each individual's requirements to allow a shorter duration of mechanical ventilation, a shorter hospital stay, and reduced mortality.[1] Off-target sedation results in excessive pain, anxiety, and agitation; self-removal of tubes and catheters; violence toward caregivers; myocardial ischemia; and hypoxemia. In contrast, excessive

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or prolonged sedation can lead to skin breakdown, nerve compression, delirium, long-term cognitive dysfunction, ventilator-associated pneumonia, posttraumatic stress disorder, and other complications. Different scoring systems are used for the assessment of sedation, such as Sedation Agitation Score (SAS), Glasgow Coma Scale (GCS), Ramsay Sedation Score (RSS), and Richmond Agitation Sedation Scale (RASS). Sedation scales are used to assess depth of sedation, wakefulness, arousal in response to stimuli, and cognition.[2]

RASS is the most commonly used tool for assessing level of sedation in intensive care unit (ICU) patients. It is a subjective 10-point scale with four levels indicating anxiety or agitation, one level denoting a calm and alert state, and 5 levels indicating sedation (-5 to +5); it has been validated for interrater reliability in the ICU. A RASS score between -3 and 0 should be maintained in the ICU.[3] However, as with others, it depends on the user's interpretation and is not continuous. Electroencephalogram (EEG)-based depth of anaesthesia monitors, such as bispectral index (BIS), Narcotrend, CONOX, Entropy, and PSI, on the other hand, provide a continuous measurement of the depth of sedation.

The PSI is a dimensionless number ranging from 100 (fully awake) to 0 (deeply anaesthetised), based on the analysis of four-channel EEG, and inversely reflects the level of sedation and hypnosis. PSI has been used extensively in operating theatres to measure depth of anaesthesia and can be utilised in the ICU to measure the level of sedation continuously without applying arousal stimuli, and hence may allow the maintenance of a more constant level of sedation with continuous rather than intermittent monitoring.[4] The PSI is used to assess sedation, but there is no defined PSI value for sedation in critically ill patients. Currently, few studies have examined the use of PSI to evaluate depth of sedation in the ICU and to compare its performance with established sedation scores. Although PSI values during anaesthesia have been defined as between 25 and 50 to ensure adequate depth, no such values have been defined for ICU sedation. The range of PSI corresponding to RASS scores of 0 to -3 remains unknown. PSI may better reflect depth of sedation, as it aggregates 4 waveforms (2 each bilaterally) and thereby reflects both the dominant and non-dominant hemispheres compared with the BIS or entropy, which are unilateral and should ideally be applied contralaterally to the dominant hand. Therefore, this study was planned to investigate the relationship between PSI and RASS and to determine the PSI corresponding to RASS 0 to -3 in critically ill patients.

Methods

This prospective observational study was approved by the Institutional Ethics Committee of Lady Hardinge Medical College and Affiliated Hospitals, Shahid Bhagat Singh Marg, New Delhi, India (approval no.: LHMC/IEC/2023/PG Thesis/4/R, date: 06.05.2023). The study was pre-registered in the Indian Clinical Trials Registry (CTRI registration number CTRI/2023/06/053988) on June 16, 2023. All procedures were carried out in accordance with the standards of the institutional ethical committee on human experimentation and with the Declaration of Helsinki (1975) and its 2013 revision. Patients of either sex aged more than 18 years who were admitted to the ICU were included in the study. Patients receiving muscle relaxants, those with head injury, focal brain disease, or abnormal electrical brain activity were excluded from the study. A written, informed, voluntary consent for participation in the study was obtained from the patient, next of kin, or authorized signatory after carefully explaining the procedure and the need for the study in their own language. A careful and detailed history and physical examination were performed, including the patient's current treatment and medication history. Patients were sedated according to the regimen advised by the treating physician. The drugs used for sedation were recorded.

Table 1. Richmond Agitation-sedation Scale

Score	Term	Description
+4	**Combative**	Overtly combative or violent; immediate danger to staff
+3	**Very agitated**	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
+2	**Agitated**	Frequent non-purposeful movement or patient-ventilator dyssynchrony
+1	**Restless**	Anxious or apprehensive but movements not aggressive or vigorous
0	**Alert and calm**	Spontaneously pays attention to caregiver
-1	**Drowsy**	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
-2	**Light sedation**	Briefly (less than 10 seconds) awakens with eye contact to voice
-3	**Moderate sedation**	Any movement (but no eye contact) to voice
-4	**Deep sedation**	No response to voice, but any movement to physical stimulation
-5	**Unarousable**	No response to voice or physical stimulation

After skin preparation with alcohol, PSI electrodes were attached to specified locations on the forehead. Adequate electrode contact, as depicted on the monitor, was maintained throughout the study. The PSI value was recorded on a Root model Masimo SET monitor every 4 hours after confirming adequate contact, signal quality, and artifact <10%. The value of PSI was recorded either before any stimulus to the patient or after the stimulus-at least 15 minutes later or when the PSI value had stabilized; stimuli included tube suction, change of dressing or bed linen, or a recent bolus of sedative. The trained attending ICU resident on duty recorded the PSI values before noting the RASS. RASS was observed and rated as described in Table 1. Both readings were noted every 4 hours for at least 72 hours or until discontinuation of monitoring, whichever occurred earlier.

Based on a study by Abouelela and Abdelazim,[1] with a correlation coefficient of 0.686 between BIS and RASS in ICU patients, with an α=0.05 and β=0.01, sample size was calculated to be 29 patients. Assuming a 20% dropout rate, 35 patients were recruited for the study.

Statistical Analysis

The data obtained were entered into a Microsoft Excel worksheet and analysed using IBM Statistical Package for Social Sciences (SPSS), USA, version 29. The Spearman correlation coefficient was calculated to assess the relationship between PSI and RASS. As a secondary analysis to account for repeated measures within patients, a repeated-measures Spearman correlation was performed using Jamovi version 2.7.17 (retrieved from https://www.jamovi.org). Correlation values between 0 and 0.20 were considered negligible; values between 0.21 and 0.40 were considered weak; values between 0.41 and 0.60 were considered moderate; values between 0.61 and 0.80 were considered strong; and values between 0.81 and 1 were considered very strong. The value of PSI corresponding to RASS 0 to -3 was obtained using receiver operating characteristic (ROC) curve analysis. Further sub-analysis was performed by categorising the data based on the sedation regimen used. Individual relationships between PSI and RASS and cut-offs of PSI with respect to the sedation regimen were also calculated. To account for repeated measures within patients, the PSI was averaged for RASS 0 to -3 and for values beyond this range. ROC was recalculated using the patient as a unit rather than the total number of observations.

Results

Forty patients were screened for the study; five were excluded: the relatives of three patients did not consent to the study, and for two patients the device was not functioning due to a technical problem. A total of 35 patients were recruited. Based on the observation interval, 19 paired observations were to be made for each patient. Out of the expected 665 pairs of observations, only 608 pairs (n = 608) were observed because two patients were discontinued from mechanical ventilation within 72 hours; for these patients only 10 and 11 observations, respectively, could be recorded. In two other patients, only 4 observations per patient could be noted due

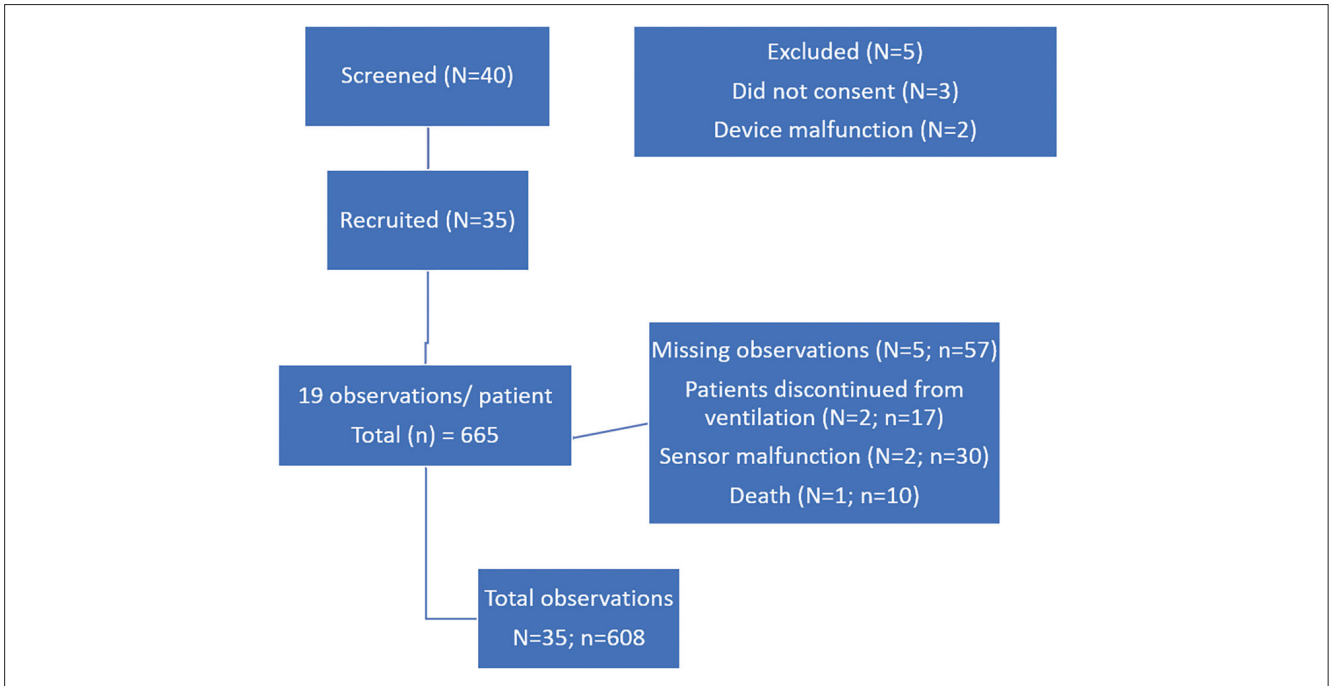


Figure 1. Flow of patients.

to sensor malfunction. In one patient, only 9 observations could be noted, as the patient expired before the completion of our study (Figure 1). The patient characteristics are described in Table 2.

Of the 608 observed pairs, only 538 were within RASS 0 to -3, indicating that the patients were oversedated at 70 time points (Table 3).

The Spearman correlation (ρ) between PSI and RASS with all sedation regimen was found to be 0.822 with an R^2 of 0.675 (Table 4).

Table 2. Patient Characteristics

Age (years)	**Median (IQR)**	46 (30, 60)
	Mean ± SD	46.49±16.55
Gender N (%)	**Male**	13 (37%)
	Female	22 (63%)
Daignosis N (%)	**Liver abscess**	3 (12%)
	Acute appendicitis	1 (2.8%)
	Buccal mucosal carcinoma	1 (2.8%)
	Colon cancer	1 (2.8%)
	Gall bladder cancer	1 (2.8%)
	Acute cholecystitis	1 (2.8%)
	Choledocholithiasis	1 (2.8%)
	Duodenal stricture	1 (2.8%)
	Morbid obesity	2 (5.7%)
	Multinodular goitre	1 (2.8%)
	Intestinal obstruction	2 (5.7%)
	Whipple's procedure	1 (2.8%)
	Perforation peritonitis	10 (28.5%)
	Hemorrhagic changes and anemia in pregnancy	9 (25.7%)
Comorbidities N (%)	**Hypertension**	9 (22%)
	Diabetes mellitus	7 (17%)
	Hypothyroidism	3 (7%)
	Obesity	1 (3%)
	CVS/CLD/renal	3 (2%)
	No- comorbidities	19 (45%)

IQR, interquartile range; SD, standard deviation; CVS, cardiovascular system; CLD, chronic liver disease

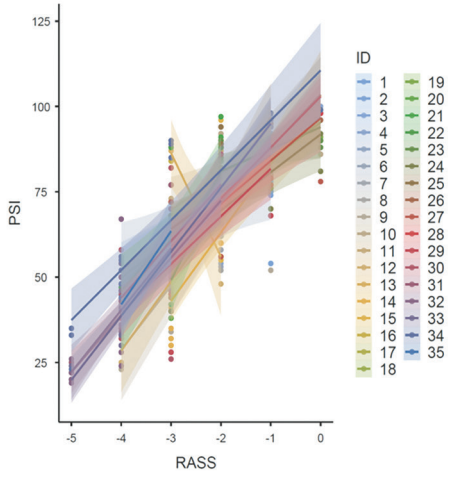
Table 3. Distribution table: RASS 0 to -5

RASS	**-5**	**-4**	**-3**	**-2**	**-1**	**0**
n	13	57	188	230	103	17
Total	**70 (oversedation)**		**538 (desired sedation)**			

RASS, Richmond Agitation Sedation Scale

To account for within-patient clustering, a repeated-measures Spearman correlation was performed with each patient treated as a cluster. The Spearman correlation (ρ) between PSI and RASS was 0.786 (95% CI: 0.753, 0.816; $P < 0.001$), indicating a strong correlation (Figure 2).

ROC analyses were carried out to identify the cutoff PSI value corresponding to RASS scores 0 to -3, with an AUC of 0.94 sq units (Table 5). The cutoff PSI value was 50.5 for all sedation regimens, suggesting that at a PSI of 50.5, the RASS would be between 0 and -3, and the patient would be adequately sedated with any of the regimens. Similar ROC curves were also plotted to determine PSI cutoffs for predicting RASS between 0 and -3 for each sedation regimen (Table 5). However, accounting for repeated measures for the same patient, PSI was averaged for RASS groups and ROC reperformed. A PSI of 51.4 corresponds to RASS scores 0 to -3, with an AUC of 1. Table 5 describes



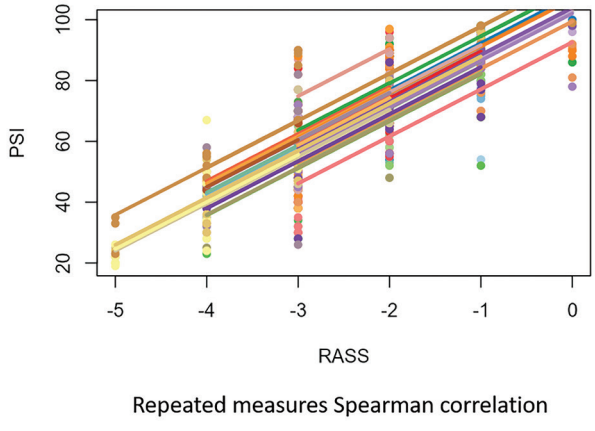


Figure 2. Repeated measures correlation.

PSI, Patient State Index; RASS, Richmond Agitation Sedation Scale.

Table 4. Relationship Between PSI and RASS

Sedation regimen	Observations						
Total (all sedation) (N = 35/ n = 608)	**Spearman's rho**		**R^2**	**Trend (X=RASS)**			***P* value**
	0.822		0.675	15.23x+103.38			**<0.001**
	RASS	**-5**	**-4**	**-3**	**-2**	**-1**	**0**
	n	13	57	188	230	103	17
	Median	22	41	56	75	90	92
	Q1	20	35	48	68	84	89
	Q3	26	48	66	84	94	98
Midazolam (N = 16/n = 257)	**Spearman's rho**		**R^2**	**Trend (X=RASS)**			***P* value**
	0.806		0.604	15.71x+105.71			**<0.001**
	RASS	**-5**	**-4**	**-3**	**-2**	**-1**	**0**
	n	0	8	84	114	42	9
	Median		43	56	76.5	90.5	96
	Q1		40	47	68	89	87
	Q3		53	66	87.25	95	98
Midazolam + morphine (N = 6/n = 104)	**Spearman's rho**		**R^2**	**Trend (X=RASS)**			***P* value**
	0.823		0.674	13.39x+100.77			**<0.001**
	RASS	**-5**	**-4**	**-3**	**-2**	**-1**	**0**
	n	3	23	28	37	9	4
	Median	33	45	62	75	88	90.5
	Q1	23	40	56	68	78	90
	Q3		50	70	80	94	97
Midazolam + fentanyl (N = 2/n = 38)	**Spearman's rho**		**R^2**	**Trend (X=RASS)**			***P* value**
	0.71		0.538	11.82x+92.897			**<0.001**
	RASS	**-5**	**-4**	**-3**	**-2**	**-1**	**0**
	n	0	0	16	15	5	2
	Median			53.5	68	88	86.5
	Q1			48.5	66	73	81
	Q3			67	75	89	-
Morphine (N = 8/n = 152)	**Spearman's rho**		**R^2**	**Trend (X=RASS)**			***P* value**
	0.872		0.768	16.55x+105.28			**<0.001**
	RASS	**-5**	**-4**	**-3**	**-2**	**-1**	**0**
	n	10	24	51	45	21	1
	Median	22	38	56	75	86	99
	Q1	20	33	48	66	80	99
	Q3	24.25	45.25	62	83	94	99
Fentanyl (N = 3/n = 57)	**Spearman's rho**		**R^2**	**Trend (X=RASS)**			***P* value**
	0.774		0.651	17.15x+102.70			**<0.001**
	RASS	**-5**	**-4**	**-3**	**-2**	**-1**	**0**
	n	0	2	9	19	26	1
	Median		32	45	72	90	98
	Q1		23	38	65	79.5	98
	Q3		-	60	78	92	98

PSI, Patient State Index; RASS, Richmond Agitation Sedation Scale

Table 5. ROC Analysis: PSI with Respect to RASS 0 to -3

Regimen		Median PSI	IQR		PSI cut -off	Sensitivity	Specificity	PPV	NPV	AUC	95% CI AUC		*P* value
			1st Quartile	3rd Quartile							Lower bound	Upper bound	
Total	**(n = 538)**	72	60	86	50.5	88.66	88.57	98.35	50.41	0.94	0.92	0.96	**<0.001**
	(N = 35)				51.4	100	100	-	100	1	0.83	1	**<0.001**
Midazolam	**(n = 249)**	73	59	88	57	78.31	100	100	12.9	0.92	0.87	0.97	**<0.001**
	(N = 16)				55	100	100	-	100	1	0.83	1	**<0.001**
Midazolam + morphine	**(n = 78)**	73.5	66	82	55.5	92.31	92.31	97.3	80	0.96	0.92	1	**<0.001**
	(N = 6)				57.4	100	100	-	100	1	0.69	1	**<0.001**
Midazolam+fentanyl	**(n = 38)**	67	56.5	76.25	All 38 observations were between 0 to -3 and no observations were noted in other group hence, analysis could not be performed.								
	(N = 2)												
Morphine	**(n = 118)**	66	56	80	57	88.98	91.18	97.22	70.45	0.95	0.91	0.98	**<0.001**
	(N = 8)				45.4	100	100	-	100	1	0.73	1	**<0.001**
Fentanyl	**(n = 55)**	78	65	90	41.5	96.36	100	100	50	0.98	0.94	1	**<0.001**
	(N = 3)				56	100	100	-	100	1	.48	1	**<0.001**

*: n represents total number of observations; N represents averaged values per patient

**: Given the small sample size in subgroup analyses, this result may reflect overfitting or statistical instability, rather than truly perfect predictive performance

PSI, Patient State Index; RASS, Richmond Agitation Sedation Scale; ROC, receiver operating characteristic; IQR, interquartile range; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve; CI, confidence interval

ROC characteristics for data points treated as independent observations (n) and for averaged data per patient (N).

Discussion

This prospective observational study (n = 608) aimed to determine the relationship between PSI and RASS during sedation in critically ill patients. Our study suggests a very strong correlation (ρ-0.822, R^2=0.67; $P < 0.001$) between PSI and RASS. Of the 608 observations, patients were oversedated at 70 time points (RASS<-3). A PSI >50.5 corresponds to RASS scores of 0 to -3, with both sensitivity and specificity of 88.6%. However, in repeated-measures analysis, the correlation remained strong (ρ-0.786; $P < 0.001$). The corresponding PSI for RASS scores of 0 to -3 was 51.4, with both sensitivity and specificity at 100%. Since the sample size for subgroup analyses was small, the root-mean-square differences between the estimated and true metrics may be considerable, with weak correlation and poor regression fit between the estimated and true metrics.

Sedation during mechanical ventilation is important not only to relieve stress, anxiety, pain, and suffering, but also to facilitate patient-ventilator interaction and synchrony and to minimize potential adverse effects related to mechanical ventilation. Excessive or prolonged sedation can lead to skin breakdown, nerve compression, delirium, long-term cognitive dysfunction, ventilator-associated pneumonia, post-traumatic stress disorder, and other complications. Inadequate sedation may result in excessive pain, anxiety, agitation, self-removal of tubes and catheters, violence towards caregivers, myocardial ischemia, and hypoxemia.[2]

Conventionally, sedation has been assessed using clinical signs, such as patient response to a stimulus (which may be masked if paralysis has been achieved), hemodynamic parameters (heart rate, non-invasive blood pressure), and subjective scales such as the RSS, Sedation Agitation Scoring System, RASS. A RASS score of 0 to -3 is considered adequate for sedation and to prevent recall. However, they are not continuous, and inter-user variability exists. A RASS value between -3 and 0 indicates light to moderate sedation; -4 and -5 indicate oversedation, while a RASS value >0 indicates insufficient sedation. RASS is the first sedation scale validated for its ability to detect changes in sedation status in ICU patients.[3]

Since most sedative agents elicit a neurohormonal response in the cerebral cortex, changes from wakefulness to sleep and unconsciousness can be monitored using EEG. During relaxation with the eyes closed, a predominance of alpha waves (7.5-12.50 Hz) is observed. Light sedation causes a decrease in alpha power and an increase in beta power (12.530 Hz). With deepening of sedation, slow-wave activity—specifically delta (1.5-3.5 Hz) and theta (3.5-7.5 Hz) waves—increases and becomes more prominent, accompanied by a spontaneous decrease in alpha and beta activity in all regions. This represents a decrease in cortical generators of alpha and beta activity, with a shift towards control by thalamo-hippocampal-septal generators of delta and theta activity.[5] The EEG requires placement of 32 electrodes across the skull, but its interpretation is difficult, and continuous monitoring is not possible.

To simplify the interpretation of EEG waves, processed EEG was developed to study the effects of various drugs on the brain. The transition from awake to unconscious state is accompanied by changes in the brain's spontaneous electrical activity, which can be recorded by electrodes placed on the forehead, analyzed, and converted into a number. This has led to the development of monitors, such as PSI, to measure the depth of sedation and anaesthesia. PSI is a composite EEG measure that correlates with behavioral assessments of sedation and hypnosis. The PSI was developed using an algorithm; values range from 0 to 100, with 25-50 signifying surgical anaesthesia and a low incidence of recall.[4] However, no such value has been defined for assessing sedation in critically ill patients.

All the drugs used for sedation in the ICU affect cognitive function and memory, with resultant characteristic changes on EEG. Benzodiazepines such as midazolam bind to gamma-aminobutyric acid (GABA) A receptors and enhance the ability of endogenous GABA to open the channel by inducing a rotational conformational change that increases chloride conductance through the receptor. This results in neuronal hyperpolarization and reduced neuronal excitability.[6] The most important effects are sedative-hypnotic and amnestic properties. Midazolam increases delta and beta power, whereas alpha power is significantly decreased. However, midazolam decreases cerebral blood flow, and the resultant changes are reflected in a shift of EEG power toward lower frequencies. It acts on the GABA-A receptor to reduce the excitability of neurons, resulting in impairment of multidomain cognitive functions: it impairs the encoding of new information, has no deleterious effect on either retention or retrieval of information acquired before drug administration, and leads to a dose-dependent decrease in PSI.[7]

Opioids, such as morphine and fentanyl, on the other hand, produce their main pharmacologic effects by interacting with opioid receptors, which are G protein-coupled. Binding of opioid agonists to these receptors leads to activation of the G protein, producing primarily inhibitory effects at the neuronal level. These effects ultimately lead to reduced presynaptic neurotransmi tter release and postsynaptic hyperpolarization of neurons.[8] The relief of pain is the primary therapeutic effect of opioids. Opioids mediate their effects via opioid receptors: mu, delta, and kappa. They act on spinal and brain mu receptors and provide analgesia by attenuating the nociceptive fibres and altering the affective response to painful stimulation. However, as the dose increases, mu agonism produces drowsiness and sleep by inducing changes in subcortical brain areas. They produce delta wave activity that, on the EEG, resembles the pattern observed during natural sleep. Opioids at their analgesic doses produce minimal electrophysiological changes in the cerebral cortex and subcortical areas, whereas higher concentrations of opioids are required to induce EEG changes. They produce significant pain relief at doses that do not induce sleep.[9]

Fentanyl induces frontal theta-wave activity, which leads to deep relaxation and consequently to the lowest PSI values, since the major EEG signal is obtained from the frontal cortex. A small dose of fentanyl (2-5 μg kg^{-1}) produces minimal EEG changes, whereas a high dose (30-70 μg kg^{-1}) produces high-voltage slow waves (δ), resulting in sedation.[8] Although we used a low dose of fentanyl (2 μg kg^{-1}), the resultant median PSI was the highest, while the cutoff (41.5) corresponding to RASS 0 to -3 was the lowest among the sedation regimens used, indicating increased suppression of the EEG, which is contrary to known theories. This may be due to patients included in this regimen being sicker; a larger heterogeneous sample may be required to prove or disprove these findings.

Morphine reduces high frequency β_1 and β_2 EEG powers and decrease coherence between frontal and occipital activity indicating that morphine induces a deep state of sedation, which is reflected by the lowest median values, strong correlation and association and a resultant PSI cutoff of >57, similar to that of midazolam.[8] In the critically ill, active metabolite and decreased renal clearance can be additional factors leading to enhanced drug effects.

Deogaonkar et al.[10] compared BIS with three commonly used SAS (RASS/SAS/GCS) in brain injury patients. The study showed a strong correlation between the BIS and RASS (R^2=0.810; $P < 0.0001$), SAS score (R^2=0.725; $P < 0.0001$), and GCS score (R^2=0.655; $P < 0.0001$). This correlation was present regardless of whether the patients received any sedative medications. Thus, processed EEG may accurately mimic the established scales and provide continuous monitoring of underlying consciousness.

However, little difference was observed when midazolam and morphine were administered together. The cut-off

value for PSI to maintain RASS 0 to -3 was >55 versus >50.5 for midazolam alone. This further augurs the fact that suppression of consciousness at analgesic doses is not a property that can be attributed to opioids.

Although studies have compared BIS and entropy with other sedation scales, we found no literature regarding the use of PSI and RASS for sedation in ICU patients. The relationship between continuous monitors and objective scales has been observed to be poor or, at best, moderate.

When SAS was compared with BIS in critically ill patients receiving lorazepam infusions, the two showed a poor correlation (r^2=0.006). Moreover, the plasma concentrations of lorazepam also did not correlate with BIS (r^2=0.30).[11] Similarly, state entropy showed a poor correlation (r=0.33) with RASS when propofol and fentanyl were used for sedation in critically ill patients.[12]

However, Arbour et al.[13] found a moderately positive correlation between BIS and SAS (r=0.50 and R^2=0.252) suggesting that the BIS explained only 25.2% of the variance in SAS score. This suggests that, when clinical assessment is equivocal, BIS may have an adjunctive role in assessing sedation.

Contrary to the above the studies, our results were similar to that by Abouelela and Abdelazim,[1] who reported a consistent and strong correlation of RASS with BIS (r=0.611-0.699) using midazolam for sedation and fentanyl infusion for analgesia in the critically ill. This was not replicated using dexmedetomidine as a sedative (r=0.011 to 0.514).

We found a very strong correlation between RASS scores from 0 to -3 and PSI, indicating that the two measures mirror each other. PSI has the added advantage of providing continuous monitoring, which helps prevent oversedation, detect acute changes in consciousness, and identify EEG alterations due to spike activity (e.g., absence or focal seizures) that may otherwise go unnoticed.

The strengths of our studies are that, at present few studies have compared PSI and sedation scales in ICU patients. Although other continuous monitors have been used, none specifies the processed EEG value that should be maintained for appropriate sedation in critically ill patients.

Study Limitations

Our study is not without limitations. Although a strong correlation and association were observed between RASS and PSI, this could be confounded by patients' underlying conditions and different sedation regimens. Small subgroup sizes limit the reliability of subgroup analyses and may produce unstable statistical estimates; hence, these analyses should be interpreted with caution. This was addressed by excluding patients with expected neurological deficits or muscle relaxation, and by performing a further sub-analysis of the sedation regimens, which yielded the same results.

Conclusion

PSI correlates well with RASS across sedation regimens in critically ill patients and assist in monitoring of sedation. Adequate sedation to achieve a RASS of 0 to -3 may be achieved at a PSI 50-52. However, these findings are preliminary and require validation in larger cohorts.

Ethics

Ethics Committee Approval: This prospective observational study was approved by the Institutional Ethics Committee of Lady Hardinge Medical College and Affiliated Hospitals, Shahid Bhagat Singh Marg, New Delhi, India (approval no.: LHMC/IEC/2023/PG Thesis/4/R, date: 06.05.2023).

Informed Consent: A written, informed, voluntary consent for participation in the study was obtained from the patient, next of kin, or authorized signatory after carefully explaining the procedure and the need for the study in their own language.

Footnotes

Authorship Contributions: Surgical and Medical Practices - N.K., K.T.; Concept - N.K., K.T., M.P.; Design - N.K., M.P.; Data Collection and/or/Processing - N.K., K.T.; Analysis and/or/Interpretation - N.K., K.T., M.P.; Literature Review - N.K., K.T.; Writing - N.K., K.T., M.P.

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Oropharyngeal Packing in Nasal Surgery: Effects on Gastric Fullness and Perioperative Safety

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Abstract

Objective: To investigate whether drinking-water-moistened oropharyngeal packing during nasal surgery is associated with ultrasound-assessed gastric fullness and postoperative nausea and vomiting (PONV), compared with no packing.

Methods: This single-center, retrospective before-after cohort study included 118 adults undergoing nasal surgery, following an institutional protocol change on December 1, 2024. Sixty patients received oropharyngeal packing moistened with drinking water, and 58 received no packing. All patients received standardized anaesthesia and PONV prophylaxis with dexamethasone 4 mg IV administered after intubation. Packing was placed before surgery and removed before extubation. PONV and throat-related symptoms were recorded at 30 minutes, 2 hours, and 24 hours postoperatively. Gastric fullness was assessed ultrasonographically by measuring gastric antral cross-sectional area (GCSA) and gastric volume before and after extubation.

Results: At 30 minutes, PONV was more frequent in the no-packing group (58.6% vs. 18.3%, $P < 0.001$), as was sore throat (41.4% vs. 26.7%, $P=0.035$). At 2 hours, PONV remained more frequent in the no-packing group (31.0% vs. 13.3%, $P=0.026$), but there was no difference at 24 hours. GCSA and gastric volume decreased in the packing group but increased in the no-packing group (GCSA: -14.14% vs. 20.86%; gastric volume: -15.67% vs. 22.00%; both $P < 0.001$). Demographics, surgical variables, dysphagia, hoarseness, and analgesic/rescue antiemetic use were similar.

Conclusion: Drinking-water-moistened oropharyngeal packing was associated with lower postoperative gastric fullness and a lower incidence of early PONV, without increased throat-related symptoms or rescue medication use. These findings indicate associations, not causal effects, and require confirmation in randomized trials.

Keywords: Nasal surgical procedures, gastric ultrasonography, oropharyngeal packing, postoperative nausea and vomiting, perioperative care

Main Points

- Drinking-water-moistened oropharyngeal packing during nasal surgery was associated with a lower incidence of early postoperative nausea and vomiting compared with no packing.
- Gastric ultrasonography enabled an objective bedside assessment of postoperative gastric fullness using the gastric antral cross-sectional area and estimated gastric volume.
- Postoperative throat-related symptoms were assessed as safety outcomes, which support the technique moistened with drinking water compared with no oropharyngeal packing.

Introduction

Nasal procedures, including septoplasty, rhinoplasty, and functional endoscopic sinus surgery (FESS), are frequently performed.[1] Because the nasal cavity and paranasal sinuses are highly vascular, perioperative bleeding and irrigating fluids may be swallowed and thereby reach the stomach.[2] Blood ingestion is a recognized contributor to postoperative nausea and vomiting (PONV) in this setting, and published series report a wide range of PONV rates after nasal surgery (34-60%).[3,4]

PONV can negatively affect patient comfort, delay recovery, and lead to serious complications, including electrolyte imbalance, epistaxis, and aspiration. It also increases healthcare costs by prolonging postoperative stays and elevating readmission rates.[2,5]

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Therefore, effective prevention and management of PONV remain a priority in current anaesthesia practice.[6,7]

Strategies to prevent PONV include pharmacological and non-pharmacological approaches. Pharmacological prophylaxis typically involves the combined administration of agents with different mechanisms of action, such as antagonists of 5-hydroxytryptamine type 3, dopamine D_2, histamine H_1, muscarinic cholinergic, and neurokinin-1 receptors, and corticosteroids, with multi-agent protocols recommended based on individual patient risk.[5,7] However, pharmacological interventions alone are often insufficient; non-pharmacological approaches that limit the swallowing of blood, particularly in nasal surgery, continue to play an important role.

Oropharyngeal packing is one of the most commonly used non-pharmacological interventions for managing PONV. Oropharyngeal packing, by creating a physical barrier in the oropharynx, is intended to reduce the passage of blood and irrigation fluids into the stomach, thereby potentially limiting gastric volume expansion and reducing the risk of PONV.[2,3,8,9] Despite these potential benefits, oropharyngeal packing is not without its complications. Dry oropharyngeal packing is associated with postoperative sore throat, edema, and mucosal ulceration, which result from compression and dryness.[2] The present study evaluated oropharyngeal packing moistened with drinking water versus no oropharyngeal packing.

The effects of oropharyngeal packing on PONV are inconsistent in the literature. While Jin et al.[2] reported that oropharyngeal packing did not significantly reduce PONV, a recent randomized controlled trial by Altun et al.[9] demonstrated that oropharyngeal packing significantly reduced the gastric antral cross-sectional area (GCSA). However, the method of moistening the pack (physiological saline, drinking water, or other solutions) and its effect on mucosal irritation have not been sufficiently clarified.

Gastric ultrasonography is a non-invasive method for assessing gastric fullness.[10] By measuring the cross-sectional area of the gastric antrum, ultrasonography provides an objective estimate of gastric volume and helps contextualize aspiration risk. Accordingly, changes in gastric volume are appropriate parameters for evaluating the association between oropharyngeal packing and gastric fullness. In this study, we examined the association of drinking-water-moistened oropharyngeal packing with PONV (primary outcome, assessed within 24 hours), ultrasound-derived gastric fullness metrics, and throat-related symptoms (secondary outcomes).

Methods

This single-center, retrospective, before-after cohort study, conducted at a tertiary care center, was based on an institutional protocol change implemented on December 1, 2024, whereby drinking-water-moistened oropharyngeal packing replaced no packing as routine practice during nasal surgery. Patients who underwent surgery before this date constituted the no-packing (control) group, and those who underwent surgery on or after this date constituted the packing group. No other changes were made to the perioperative protocols, including anaesthesia induction and maintenance, antiemetic prophylaxis, or postoperative analgesia. Ethical approval was obtained from the Kütahya University of Health Sciences Non-Interventional Clinical Research Ethics Committee (approval no.: 2025/08-50, date: 19.06.2025). The requirement for informed consent was waived due to the retrospective nature of the study. The study was conducted in accordance with the Declaration of Helsinki and was reported according to the STROBE guidelines.

Records of patients who underwent septoplasty, rhinoplasty, or FESS between April 1, 2024, and April 15, 2025, were reviewed. Patients aged 18-67 years who were classified as American Society of Anesthesiologists (ASA) physical status I-II, had a body mass index (BMI) <35 $kg \times m^{-2}$, and underwent the standardized anaesthesia protocol were included. The exclusion criteria were pregnancy, active smoking, uncontrolled diabetes mellitus, a history of gastroesophageal reflux disease, and incomplete records. The final study population consisted of 118 patients: 60 in the packing group and 58 in the no-packing group.

Anaesthesia and Packing Protocol

All patients received the same standardized anaesthesia protocol. Premedication consisted of intravenous midazolam (0.03 mg kg^{-1}). Anaesthesia was induced with fentanyl (1 µg kg^{-1}), propofol (2 mg kg^{-1}), and rocuronium (0.6 mg kg^{-1}). Immediately after endotracheal intubation, all patients received intravenous dexamethasone 4 mg as standard PONV prophylaxis, in accordance with institutional practice; no additional prophylactic antiemetics were administered. Anaesthesia was maintained with 2% sevoflurane in a 50% O_2/air mixture using a cuffed endotracheal tube (7.5-8.0 mm internal diameter). At the end of the surgery, neuromuscular blockade was reversed, and the patients were extubated. Postoperative analgesia consisted of intravenous administration of paracetamol (1 g) and tramadol hydrochloride (100 mg).

In the packing group, oropharyngeal packing was performed under sterile conditions using sterile gauze pads moistened with drinking water at room temperature. With the patient supine and the head in a neutral position, the pack was placed in the oropharynx without excessive pressure before the start of surgery and was removed before extubation. All intraoperative procedures were performed by experienced anaesthesiologists following a standardized institutional protocol.

Gastric Ultrasonography

Gastric ultrasonography is routinely performed in all surgical patients at our institution as part of the standard perioperative assessment and anaesthesiology resident training; it was not introduced specifically for this study. Gastric ultrasound was performed using an Affiniti 50 system (Philips, USA) equipped with a 4-12 MHz linear probe, while the patient was in the right lateral decubitus position. The gastric antrum was identified in the sagittal view using adjacent anatomical landmarks (left liver lobe, abdominal aorta, and superior mesenteric artery). The anteroposterior (D1) and craniocaudal (D2) antral diameters were measured serosa-to-serosa, and the GCSA was calculated using the standard ellipse-based approach (GCSA=π×D1×D2/4). GCSA was recorded preoperatively and 30 minutes after extubation by a single experienced anaesthesiologist who was not involved in the intraoperative care. This approach ensured measurement consistency but precluded the assessment of inter-observer reliability. The estimated gastric volume was derived from the Perlas model [mL=27.0+14.6×GCSA (cm^2)-1.28×age] and expressed as mL kg^{-1}.[11,12] The percentage change was calculated as follows: (postoperative-preoperative)/preoperative)×100. Due to the non-normal distribution of these variables, the results are reported as the median with interquartile range (IQR).

Data Collection and Outcome Definitions

Data were retrospectively extracted from the anaesthesia records, postoperative nursing charts, and physician notes. The following parameters were collected: demographics (age, sex, BMI, ASA classification); surgery type and duration; early post-extubation findings (blood in the endotracheal tube, nausea, vomiting, gag reflex, cough, hoarseness, laryngospasm, and other complications); PONV, sore throat, dysphagia, and hoarseness assessed at 30 minutes, 2 hours, and 24 hours postoperatively; use of rescue antiemetics and analgesics within 24 hours; preoperative and postoperative GCSA; and patient satisfaction at 24 hours.

PONV was defined as any episode of postoperative nausea or vomiting documented in the medical records at predefined time points (30 minutes, 2 hours, and 24 hours). In our institutional protocol, all patients received identical PONV prophylaxis (dexamethasone 4 mg IV after intubation), and no other prophylactic antiemetic was administered. Rescue antiemetic medication was administered exclusively to patients who developed postoperative nausea or vomiting. Accordingly, rescue antiemetic administration served as a corroborating marker of symptomatic PONV rather than an independent diagnostic criterion, and no patient was classified as having PONV based on rescue antiemetic use alone. This definition was consistently applied across all postoperative time points.

Patient satisfaction was assessed 24 hours postoperatively using a simple ordinal Likert scale documented in routine clinical records. Patients selected the option that best represented their level of satisfaction: "good," "very good," "moderate," or "poor". Because this assessment was part of routine clinical documentation, a formally validated satisfaction questionnaire was not prospectively applied, and the responses were recorded as ordinal categories and analyzed accordingly.

Sample Size

The sample size was calculated using G*Power (v3.1), based on the postoperative GCSA. Using the values reported by Altun et al.[9] (control: 999.4±202.1 mm^2; packing: 701.1±82.2 mm^2), Cohen's d was 1.93. A two-sided t-test with $\alpha=0.01$ and power $(1-\beta)=0.90$ required 12 patients per group; therefore, the 118 patients in the present study provided >99% statistical power. A post-hoc power analysis for the 30-minute PONV incidence using Fisher's exact test, based on the observed group proportions and the actual sample size, suggested high achieved power (99.8%); however, post-hoc power analyses do not substitute for prospective sample size planning and should be interpreted cautiously.

Statistical Analysis

Statistical analyses were performed using SPSS version 21.0 (IBM, Armonk, NY, USA). Distributional assumptions were assessed using the Shapiro-Wilk test. Continuous data are summarized as mean (SD) or median (IQR), as appropriate; categorical data are summarized as n (%). Between-group comparisons used the χ^2 test or Fisher's exact test for categorical variables, and the Independent Samples t-test or the Mann-Whitney U test for continuous variables. Within-group pre/post comparisons were performed using the Wilcoxon signed-rank test. A two-sided P value <0.05 was considered statistically significant.

Multivariable logistic regression analysis was performed to evaluate the association between oropharyngeal packing and PONV at the 30-minute and 2-hour time points, for which event frequency was sufficient. Age, sex, BMI, and group (packing vs. no-packing) were entered as independent variables. Multicollinearity was assessed using the variance inflation factor (VIF) and tolerance statistics (acceptance thresholds: VIF <5, tolerance >0.1). Model fit was assessed using the Hosmer-Lemeshow test, and overall model significance was assessed using the Omnibus test of model coefficients. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) are reported. At the 24-hour time point, regression analysis was not performed because event frequency was very low. Analysis of covariance (ANCOVA) was used to compare postoperative GCSA and gastric volume between groups, with oropharyngeal packing as the fixed factor and the respective preoperative values entered

as covariates. Adjusted means, 95% CI, and effect sizes (partial η^2) are reported.

Results

Baseline Characteristics

A total of 118 patients were analyzed: 60 in the packing group and 58 in the no-packing group. Age, sex, height, weight, BMI, and surgical time were comparable between the groups (all $P > 0.05$; Table 1). The median age was 28 years (range, 18-67) in the packing group and 25.5 years (range, 18-66) in the no-packing group. The median surgical duration was 152.5 minutes in the packing group and 135 minutes in the no-packing group. Septoplasty was the most frequently performed procedure in both groups (packing group: 25%; no-packing group: 31%), and the distribution of FESS, submucosal resection, and other nasal procedures between groups was similar (P=0.391).

Early Post-extubation Findings

The early post-extubation parameters are summarized in Table 2. Nausea was significantly more frequent in the no-packing group than in the packing group (20.7% vs. 5.0%, $P < 0.01$), whereas vomiting frequency did not differ significantly between groups (P=0.717). Although the presence of blood in the endotracheal tube did not reach statistical significance (28.3% vs. 39.7%, P=0.133), its frequency was lower in the packing group, suggesting a possible trend toward reduced blood contamination. The incidence of cough, hoarseness, laryngospasm, and other adverse events was similar between the groups.

Table 1. Demographic Characteristics of the Patients

	Group 1 (n = 60)	Group 2 (n = 58)	*P* value
Age (years), med, (min-max)	28 (18-67)	25.5 (18-66)	0.287*
Male sex, n (%)	46 (76.7)	42 (72.4)	0.674**
Female sex, n (%)	14 (23.3)	16 (27.6)	
Height (cm), mean ± SD	171.48±9.01	173.79±9.55	0.179***
Weight (kg), mean ± SD	72.37±13.94	77.14±14.90	0.075***
BMI ($kg \times m^{-2}$), mean ± SD	24.58±4.28	25.57±4.90	0.245***
Duration of surgery (min), med, (min-max)	152.50 (70-480)	135 (60-385)	0.162*

*: Mann-Whitney U test; **: Chi-square test; ***: Independent Samples t-test
Group 1, packing group; Group 2, no-packing group; BMI, body mass index; SD, standard deviation; min-max, minimum-maximum

Postoperative Symptoms at 30 Minutes, 2 Hours, and 24 Hours

Sore throat, PONV, dysphagia, and hoarseness are presented at the three postoperative time points in Table 3. No significant differences were observed between the groups in terms of dysphagia or hoarseness at any time point (all $P > 0.05$). At 30 minutes, sore throat occurred significantly less frequently in the packing group than in the no-packing group (26.7% vs. 41.4%, P=0.035). PONV was significantly less frequent in the packing group at 30 minutes (18.3% vs. 58.6%, $P < 0.001$) and at 2 hours (13.3% vs. 31.0%, P=0.026); however, the difference was no longer apparent at 24 hours ($P > 0.05$). Nausea-vomiting NRS scores at 30 minutes were also significantly lower in the packing group (0.97±1.15 vs. 4.65±1.73; Z=-8.44, $P < 0.001$; effect size r=0.81). No significant differences were observed between the groups in terms of rescue antiemetic or analgesic requirements during the first 24 hours ($P > 0.05$).

Multivariable Analysis of PONV

Multivariable logistic regression, adjusted for age, sex, and BMI, was performed for the 30-minute and 2-hour time points. At 30 minutes, 45 patients presented with PONV (11 in the packing group and 34 in the no-packing group); the model was statistically significant [$\chi^2(4)=27.551$, $P < 0.001$; Nagelkerke $R^2=0.301$; Hosmer-Lemeshow P=0.671]. Oropharyngeal packing was independently associated with lower odds of PONV (OR: 0.12, 95% CI: 0.05-0.28, $P < 0.001$). At 2 hours, 26 patients had PONV (8 vs. 18). The model was also significant [$\chi^2(4)=9.693$, P=0.046; Hosmer-Lemeshow P=0.469], and oropharyngeal packing remained independently associated with lower odds of PONV (OR: 0.32, 95% CI: 0.12-0.84, P=0.021). No significant independent association was found between age, sex, BMI, and PONV (all $P > 0.05$). At 24 hours, only one PONV event was observed in the entire cohort; therefore, multivariable regression was not performed. The unadjusted comparison showed no between-group differences (P=1.000). The magnitude of the adjusted OR should be interpreted in the context of the retrospective before-after design, in which residual confounding may influence effect size estimates.

Patient Satisfaction

As an exploratory outcome, distributions of patient satisfaction differed between groups at 24 hours ($P < 0.001$). In the packing group, 70.7% reported "good," 13.8% "very good," and 15.5% "moderate," with no "poor" responses. In the no-packing group, 80.4% reported "moderate," 13.7% "poor," 5.9% "good," and none reported "very good". As the assessment used a simple non-validated ordinal scale documented in routine charts, these data are only hypothesis-generating.

Table 2. Initial Clinical Findings in the Early Post-extubation Period

	Group 1 (n = 60)		Group 2 (n = 58)		
	Present (n, %)	Absent (n, %)	Present (n, %)	Absent (n, %)	*P* value*
Blood in the endotracheal tube	17 (28.3%)	43 (71.7%)	23 (39.7%)	35 (60.3%)	0.133
Nausea	3 (5.0%)	57 (95.0%)	12 (20.7%)	46 (79.3%)	**<0.01**
Vomit	5 (8.3%)	55 (91.7%)	3 (5.2%)	55 (94.8%)	0.717
Gagging	10 (16.7%)	50 (83.3%)	10 (17.2%)	48 (82.8%)	1.000
Cough	11 (18.3%)	49 (81.7%)	16 (27.6%)	42 (72.4%)	0.276
Hoarseness	2 (3.3%)	58 (96.7%)	0 (0.0%)	58 (100.0%)	0.496
Laryngospasm	2 (3.3%)	58 (96.7%)	1 (1.7%)	57 (98.3%)	1.000
Additional complication	1 (1.7%)	59 (98.3%)	1 (1.7%)	57 (98.3%)	1.000

Group 1, packing group; Group 2, no-packing group
*: Fisher's exact test

Table 3. Postoperative Assessments at 30 Minutes, 2 Hours, and 24 Hours

		Group 1 (n = 60)		Group 2 (n = 58)		*P* value*
		Present (n, %)	Absent (n, %)	Present (n, %)	Absent (n, %)	
30 min	Throat pain	16 (26.7%)	44 (73.3%)	24 (41.4%)	34 (58.6%)	**0.035**
	Nausea/vomit	11 (18.3%)	49 (81.7%)	34 (58.6%)	24 (41.4%)	**<0.001**
	Dysphagia	4 (6.7%)	56 (93.3%)	3 (5.2%)	55 (94.8%)	1.000
	Hoarseness	2 (3.3%)	58 (96.7%)	2 (3.4%)	56 (96.6%)	1.000
2 hour	Throat pain	17 (28.3%)	43 (71.7%)	18 (31.0%)	40 (69.0%)	0.841
	Nausea/vomit	8 (13.3%)	52 (86.7%)	18 (31.0%)	40 (69.0%)	**0.026**
	Dysphagia	5 (8.3%)	55 (91.7%)	3 (5.2%)	55 (94.8%)	0.717
	Hoarseness	2 (3.3%)	58 (96.7%)	1 (1.7%)	57 (98.3%)	1.000
24 hour	Throat pain	2 (3.3%)	58 (96.7%)	1 (1.7%)	57 (98.3%)	1.000
	Nausea/vomit	1 (1.7%)	59 (98.3%)	0 (0.0%)	58 (100.0%)	1.000
	Dysphagia	0 (0.0%)	60 (100.0%)	0 (0.0%)	58 (100.0%)	1.000
	Hoarseness	2 (3.3%)	58 (96.7%)	0 (0.0%)	58 (100.0%)	0.496

Group 1, packing group; Group 2, no-packing group
*: Fisher's exact test

Gastric Ultrasonography Findings

The preoperative and postoperative GCSA and gastric volumes are presented in Tables 4 and 5, respectively. Within-group analysis showed a significant postoperative decrease in GCSA and gastric volume in the packing group, whereas these parameters increased significantly in the no-packing group. Between-group comparisons showed that the median percentage change in GCSA was -14.14% in the packing group and +20.86% in the no-packing group, and that the median percentage change in gastric volume was -15.67% in the packing group and +22.00% in the no-packing group (both $P < 0.001$).

ANCOVA was performed to evaluate the independent association of oropharyngeal packing with postoperative GCSA and gastric volume, adjusting for the respective preoperative values. The assumption of homogeneity of variance was satisfied for both outcomes [Levene's tests: F (1,116)=0.456, P=0.501 for GCSA; F (1,116)=0.025, P=0.875 for gastric volume]. Preoperative values were significant covariates for postoperative GCSA F (1,115)=47.683, $P < 0.001$, partial η^2=0.310) and postoperative gastric volume F (1,115)=84.158, $P < 0.001$, partial η^2=0.443). The adjusted postoperative mean GCSA was lower in the packing group than in the no-packing group (4.39 vs. 6.23 cm^2; adjusted mean difference -1.84, 95% CI: -2.44 to -1.24; F (1,115)=36.663, $P < 0.001$, partial η^2=0.257). Similarly, the adjusted mean postoperative gastric volume was lower in the packing group [50.22 vs. 80.12 mL; adjusted mean difference -29.90, 95% CI: -39.06 to -20.74;

Table 4. Intragroup Comparison of Preoperative and Postoperative GCSA (cm^2) and Gastric Volume Measurements (mL)

	Group 1 (n = 60)				Group 2 (n = 58)			
	Preop median (IQR)	Postop median (IQR)	Median difference	*P* value*	Preop median (IQR)	Postop median (IQR)	Median difference	*P* value*
GCSA (cm^2)	4.82 (2.80)	4.32 (2.19)	-0.50	**<0.001**	4.50 (2.47)	5.80 (2.38)	1.30	**<0.001**
Gastric Volume (mL)	60.20 (33.75)	50.61 (42.63)	-9.59	**<0.001**	56.86 (43.08)	71.86 (32.12)	15.00	**<0.001**
Gastric Volume kg^{-1} ($mL\ kg^{-1}$)	0.81 (0.61)	0.66 (0.69)	-0.15	**<0.001**	0.74 (0.53)	1.06 (0.47)	0.32	**<0.001**

Group 1, packing group; Group 2, no-packing group. GCSA, gastric antral cross-sectional area; IQR, interquartile range. *: Wilcoxon signed-rank test

Table 5. Intergroup Comparison of Preoperative and Postoperative GCSA (cm^2) and Gastric Volume Measurements (mL)

	Group 1 (n = 60) median (IQR)	Group 2 (n = 58) median (IQR)	Z value	*P* value*
Preop GCSA (cm^2)	4.82 (2.80)	4.50 (2.47)	-2.201	**0.028**
Postop GCSA (cm^2)	4.32 (2.19)	5.80 (2.38)	-3.662	**<0.001**
Preop gastric volume (mL)	60.20 (33.75)	56.86 (43.08)	-1.251	0.211
Postop gastric volume (mL)	50.61 (42.63)	71.86 (32.12)	-3.416	**0.001**
Preop gastric volume kg^{-1} ($mL\ kg^{-1}$)	0.81 (0.61)	0.74 (0.53)	-1.634	0.101
Postop gastric volume kg^{-1} ($mL\ kg^{-1}$)	0.66 (0.69)	1.06 (0.47)	-2.815	**<0.01**
ΔGCSA (%)	-14.14 (22.22)	20.86 (44.57)	-7.169	**<0.001**
ΔGastric volume (%)	-15.67 (32.73)	22.00 (53.84)	-7.173	**<0.001**

Group 1, packing group; Group 2, no-packing group; GCSA, gastric antral cross-sectional area; IQR, interquartile range; ΔGCSA, percentage change in GCSA; ΔGastric volume, percentage change in gastric volume

*: Mann-Whitney U test

F (1,115)=41.875, $P < 0.001$, partial $\eta^2=0.283$]. The overall models explained 38.9% of the variance in postoperative GCSA (adjusted $R^2=0.378$) and 50.4% of the variance in postoperative gastric volume (adjusted $R^2=0.495$). These findings are consistent with the independent association between oropharyngeal packing and lower postoperative gastric fullness, possibly reflecting reduced ingestion of blood and irrigation fluids during surgery. A lower gastric volume may theoretically be associated with a reduced aspiration risk; however, aspiration events were not directly evaluated in this study, and this link should therefore be regarded as hypothetical.

Discussion

This retrospective before-and-after cohort study evaluated the association between oropharyngeal packing moistened with drinking water and perioperative outcomes in patients who underwent nasal surgery. The baseline characteristics were comparable between the groups. The packing group had lower rates of early postoperative nausea, vomiting, and sore throat, which were accompanied by objective reductions in GCSA and estimated gastric volume, consistent with possible attenuation of perioperative blood ingestion. Both groups received identical standard PONV prophylaxis (dexamethasone 4 mg IV after intubation), which reduces but does not eliminate the likelihood that the observed differences in PONV were attributable to differential antiemetic management.

Previous studies have reported that conventional (dry) oropharyngeal packs may increase postoperative throat discomfort by causing mucosal compression, friction, and drying.[2,3,13,14] Evidence regarding moistening techniques is limited; however, some studies suggest that pack hydration may improve mucosal tolerability.[3,9,15] In our cohort, early postoperative sore throat was less frequent among patients who received oropharyngeal packing moistened with drinking water. This observation is consistent with reports suggesting improved comfort when moisture reduces frictional injury. However, because our study did not include a saline-moistened comparison arm, the specific

contribution of moistening with water remains uncertain.

The role of oropharyngeal packing in preventing PONV remains controversial. Multiple randomized trials and meta-analyses have reported that oropharyngeal packing, particularly when dry or saline-moistened, does not consistently reduce PONV and may exacerbate early postoperative throat discomfort.[2,16] Conversely, other studies have shown reductions in antral cross-sectional area and postoperative gastric volume in patients undergoing packing, suggesting that decreased blood ingestion may mediate these effects.[3,9] Meta-analytic findings indicate that the timing of evaluation may contribute to these discrepancies: some studies report higher early PONV in patients with packing, whereas others report higher late PONV in patients without packing.[16] Furthermore, gastric blood is frequently detected regardless of packing, with variability attributable to material, moisture, and placement technique.[15,17]

Within this context, the lower early PONV rates and reduced postoperative gastric volumes observed in the packing group align with the findings of studies supporting the role of packing in limiting intraoperative blood ingestion. The disappearance of between-group differences in PONV at 24 hours underscores the multifactorial and time-dependent nature of PONV after nasal surgery. ANCOVA confirmed that postoperative GCSA and gastric volume were lower in the packing group after adjustment for preoperative values. Although the adjusted OR for early PONV was substantial, its magnitude warrants particular caution. The adjusted OR at 30 minutes of 0.12 (95% CI: 0.05-0.28) is unusually large in magnitude for a retrospective before-after design. This estimate likely overestimates the true effect, reflecting inherent design limitations and residual confounding from unmeasured variables, both of which multivariable adjustment cannot fully address. It should therefore be interpreted as an association rather than a causal effect, and the magnitude itself should not be taken at face value.

Although not statistically significant, The trend toward reduced visible blood contamination of endotracheal tubes in the packing group may reflect lower airway exposure. No increase in dysphagia or hoarseness was observed, indicating that the moistened technique did not appear to introduce an additional mucosal burden-a finding consistent with prior reports describing variable tolerability across packing materials and hydration techniques.

Gastric ultrasonography is a useful, non-invasive bedside tool for estimating gastric fullness.[10] In our study, consistent with previous reports,[3,9] postoperative gastric volume increased in patients without packing, whereas moistened oropharyngeal packing was associated with measurable reduction. These objective findings support the plausibility of a packing-related reduction in perioperative blood ingestion, although the observational design precludes causal conclusions.

Patient satisfaction scores were higher in the packing group, possibly reflecting reduced early symptom burden. However, as this was an exploratory finding based on a non-validated ordinal scale, it should not be interpreted as a primary outcome and should be evaluated prospectively with a validated instrument.

Study Limitations

This study has several limitations inherent in its single-center, retrospective, before-after cohort design. Because group allocation was based on a time-dependent institutional protocol change rather than randomization, temporal confounding cannot be fully excluded. Learning curve effects, staffing changes, secular modifications in perioperative care, and seasonal or case-mix variations may have influenced outcomes independently of oropharyngeal packing. The use of a uniform anaesthesia and antiemetic protocol in both groups reduces the likelihood that differential prophylaxis accounts for the observed PONV differences, but does not eliminate the possibility of other unmeasured confounders.

PONV assessment relied on retrospective chart review rather than on a prospectively applied, validated scale, which may have resulted in underreporting or misclassification of mild symptoms. Similarly, patient satisfaction was evaluated using a simple, non-validated ordinal Likert scale documented in routine charts rather than with a validated questionnaire; thus, these results should be interpreted with caution.

All gastric ultrasound measurements were performed by a single, experienced anaesthesiologist who was not involved in the intraoperative care. Although a standardized scanning protocol and consistent anatomical landmarks were used, complete blinding to group allocation could not be guaranteed given the retrospective design; additionally, inter-observer reliability could not be assessed because all measurements were obtained by a single operator. The absence of assured blinding represents a meaningful limitation: awareness of group allocation, even with a standardized scanning protocol, may have biased postoperative gastric measurements toward the expected direction (i.e., lower values in the packing group), potentially exaggerating the observed between-group differences in GCSA and gastric volume. This possibility should be considered when interpreting the magnitude of these findings.

Finally, because of the non-randomized design, the observed associations—particularly the high adjusted OR for early PONV—should be regarded as hypothesis-generating rather than as evidence of large causal effects. Prospective randomized multicenter trials are required to confirm these findings.

Conclusion

In this retrospective before-after cohort study, oropharyngeal packing was associated with lower rates of early postoperative sore throat, lower incidence of early PONV, and lower postoperative gastric volume among patients who underwent nasal surgery. These observations suggest that drinking-water-moistened oropharyngeal packing may serve as a simple, low-cost, non-pharmacological adjunct in this setting. However, given the non-randomized, before-after design and the potential for residual confounding, the present findings should be regarded as associative and hypothesis-generating; causality cannot be established within the current study design. Prospective, randomized, multicenter trials are required to confirm these findings and to determine the optimal packing technique and its role in perioperative management.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Kütahya University of Health Sciences Non-Interventional Clinical Research Ethics Committee (approval no.: 2025/08-50, date: 19.06.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions: Surgical and Medical Practices - S.C., M.Y.; Concept - S.T., S.C.; Design - S.T, S.C.; Data Collection and/or/Processing - S.T., S.C., M.Y.; Analysis and/or/Interpretation - S.T, S.C.; Literature Review - S.T.; Writing - S.T., S.C., M.Y.

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Case Report
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Anaesthesia for Caesarean Section in a Parturient with Klippel-Feil Syndrome: A Case Report

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Abstract

Klippel-Feil syndrome (KFS) is a rare congenital condition defined by the fusion of one or more cervical vertebrae, often associated with a range of skeletal and extra-skeletal abnormalities. The presence of cervical vertebral fusion and spinal deformities can make both airway management and neuraxial anaesthesia technically challenging in this population. This report describes a primigravida with KFS who underwent an elective caesarean section under spinal anaesthesia. The preparation included consideration of a potentially difficult airway, even though general anaesthesia had not initially been planned. We reviewed relevant literature on anaesthetic management in similar cases. There is no consensus on the optimal anaesthetic technique for the management of parturients with KFS undergoing caesarean section. Each case should be evaluated individually. It is essential to prepare for potential conversion to general anaesthesia and always prioritize patient safety.

Keywords: Klippel-Feil syndrome, caesarean section, spinal anaesthesia, difficult airway, obstetric anaesthesia

Main Points

- Patients with Klippel-Feil syndrome (KFS) have a difficult airway and spinal anatomy, which make both airway management and neuraxial anaesthesia challenging.
- Spinal anaesthesia can be used successfully in these patients, but preparation for a possible conversion to general anaesthesia is essential.
- Individualized anaesthetic plans are required, as no single technique is recommended for all KFS patients.

Introduction

Klippel-Feil syndrome (KFS), first described in 1912, is a rare congenital disorder characterized by the fusion of one or more cervical vertebrae, often accompanied by skeletal and extra-skeletal anomalies.[1] While some cases follow autosomal dominant or recessive inheritance, most are sporadic. Feil originally classified KFS into three variants based on the extent of spinal fusion.[2] Frequently associated anomalies include scoliosis, renal abnormalities, Sprengel deformity, deafness, congenital heart disease, and synkinesis.[2-12] Patients with KFS may present for various surgical procedures, including caesarean section. Cervical spine fusion and restricted neck mobility increase the risk of a difficult airway. Airway management in pregnancy is particularly challenging, emphasizing the need for detailed assessment.[12-14] Neuraxial anaesthesia may also be difficult due to abnormal spinal anatomy, increasing the risk of a failed or unpredictable block.[15] We report the successful anaesthetic management of a primigravida with KFS undergoing an elective caesarean delivery.

Case Report

A 32-year-old primipara with KFS was admitted at 40 weeks' gestation for surveillance and preparation for an elective caesarean section. Preoperative evaluation included medical history review, airway assessment, and spine imaging. Her KFS features included cervical fusion from C3 to T1, kyphoscoliosis, bilateral Sprengel deformity, and right-sided deafness. Overall, these findings are consistent with type 1 according to Feil classification.[2] She also had polycystic ovary syndrome. Family history was unremarkable for

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genetic or anaesthetic complications. During childhood, she underwent surgical correction of both scapulae. More recent procedures included a tonsillectomy and a right mastoidectomy, which were performed under general anaesthesia with videolaryngoscopy and a reinforced 6.0 endotracheal tube. Although intubation was not documented as difficult, bag-mask ventilation was difficult during one induction. She took no chronic medications, reported no allergies, and remained physically active prior to pregnancy. Her pregnancy was uneventful, except for mild exertional dyspnea and a newly observed left-sided cervical fat nodule. On examination, her height and weight were 154 cm and 81 kg, respectively (body mass index 34.2 kg m^{2-1}). She had a short neck with limited range of motion. Airway assessment revealed a Mallampati II classification and an adequate mouth opening. Palpation of the lumbar spine was unremarkable despite thoracic kyphoscoliosis. Postoperative scarring was present at the level of the thoracic spine. Laboratory studies demonstrated mild anemia (hemoglobin 102 g L^{-1}) and normal coagulation. Pre-pregnancy magnetic resonance imaging showed platybasia, basilar invagination, and significant cervical deformity (Figure 1), with a normal spinal canal width below the craniocervical junction. A neurosurgical review supported the feasibility of neuraxial anaesthesia.

The risks and benefits of regional anaesthesia were discussed, and informed consent was obtained. In the operating theatre, standard monitoring was applied, and a difficult airway cart containing equipment for emergency ventilation and intubation, including supraglottic devices, a videolaryngoscope, and a flexible bronchoscope, as well as a surgical cricothyrotomy kit, was prepared. After placement of intravenous access, aspiration prophylaxis with metoclopramide 10 mg was administered. The patient was positioned in a sitting position. Following two unsuccessful attempts, the subarachnoid space was accessed at L3-L4 using a 27-gauge Whitacre needle. Spinal anaesthesia was achieved with 10 mg of 0.5% hyperbaric bupivacaine and 20 µg of fentanyl. After block placement, she was positioned supine with left uterine displacement. High-flow nasal oxygenation (HFNO) was provided to optimize oxygen reserve in case conversion to general anaesthesia became necessary.

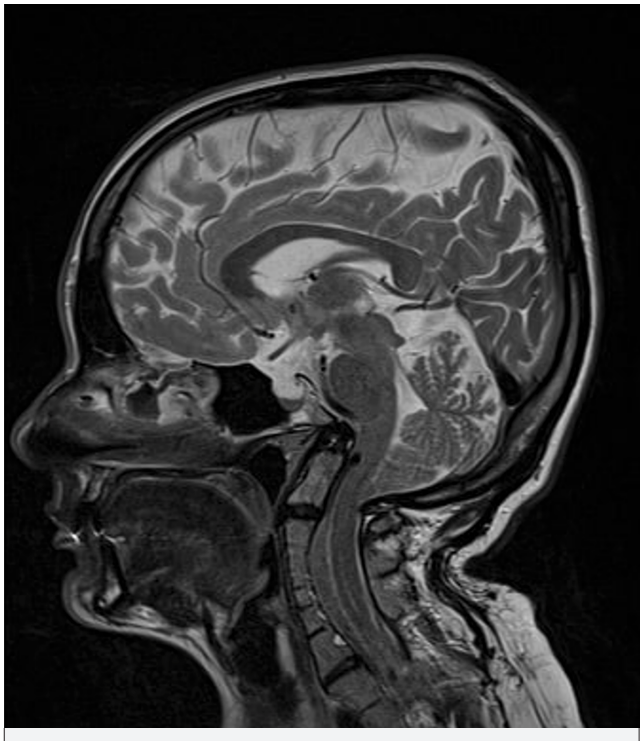

Figure 1. Pre-pregnancy magnetic resonance imaging showing fusion of vertebrae C3 to Th1.

A sensory level to pinprick at T6 was confirmed before incision. Since the patient tolerated the supine position and maintained adequate respiratory function, the high-flow nasal cannula was later removed. Caesarean delivery proceeded uneventfully, resulting in a healthy male infant weighing 3500 g, with Apgar scores of 9 and 10 at 1 and 5 minutes, respectively. Antibiotic prophylaxis (cefazolin, 2 g) and oxytocin infusion (20 IU over four hours) were administered. Hemodynamics remained stable throughout the procedure. The patient was transferred to the post-anaesthesia care unit for continued monitoring and analgesia for 24 hours. Overall, the postoperative course was uneventful. Visual analogue pain scale was monitored for every 2 hours and analgesia was titrated to keep visual analogue pain scale in the mild range (≤3-4). Over the first 12 postoperative hours, our patient received intravenous tramadol by continuous infusion (300 mg in total), and intravenous paracetamol (1 gram) combined with ibuprofen (300 mg) every six hours. After the patient resumed normal fluid intake and was able to sit in bed approximately 12 hours after caesarean, analgesia was converted from parenteral to peroral.

Discussion

Neuraxial anaesthesia is considered the gold standard for caesarean delivery, with use exceeding 80% in some countries.[16,17] For patients with known or suspected difficult airways, regional techniques are generally preferred, particularly during pregnancy. However, anatomical anomalies may complicate neuraxial block placement. Spinal anaesthesia, even when successful, does not eliminate the possibility of airway intervention, including emergent conversion to general anaesthesia.[18] Accordingly, guidelines emphasize preparation, equipment readiness, and team communication.[14] HFNO was used proactively to extend safe apnea time should intubation become necessary, although evidence on its use in the pregnant population remains limited.[19,20]

Previous reports of anaesthetic management in KFS parturients describe varied strategies depending on clinical features.[3-12] Kavanagh et al.[3] outlined the advantages and limitations of several approaches, each carrying distinct risks. Structural spinal pathology is relatively common in pregnancy and may challenge neuraxial administration due to difficulty identifying landmarks, altered ligamentous structures, and unpredictable drug spread.[15,21,22]

Our anaesthetic choice was influenced by concerns about potential cervical spine instability and abnormal atlanto-occipital anatomy, which may increase the risk of neurological injury during airway manipulation. Spinal anaesthesia allowed the patient to maintain control of her own neck positioning and to communicate discomfort. Other available techniques, such as epidural and combined spinal-epidural anaesthesia, were also considered as potential options in our patient. However, epidural catheter placement was deferred primarily because of concern that a large volume administered epidurally may increase intracranial pressure, which is particularly notable in patients with craniovertebral junction abnormalities. Furthermore, epidural catheter placement can be technically more demanding when anatomy is distorted and carries a higher risk of a failed block. Therefore, we decided to administer spinal anaesthesia, which has been shown to be a reasonable and straightforward choice because of its rapid onset, reliability, and ease of performance without significant technical challenges.[3-10] A mixture of hyperbaric bupivacaine and fentanyl was utilized, with the dose of bupivacaine adjusted to patient's height and weight, as this dosing approach has been shown to provide adequate anaesthesia for elective caesarean section and is associated with a lower incidence of maternal hypotension.[23]

Even though we had ultrasound available in the operating theatre as a backup method, its application was not necessary in our case due to adequate anatomical landmarks and successful identification of the subarachnoid space on the second attempt. However, it is to highlight the advantages of ultrasonography as a guidance tool in patients with challenging anatomy or obesity.[24]

Conclusion

No consensus exists regarding the optimal anaesthetic management for parturients with KFS undergoing caesarean delivery. Each case requires individualized planning based on anatomy, clinical expertise, and resource availability. Preparation for potential conversion to general anaesthesia remains essential, with patient safety prioritized.

Ethics

Informed Consent: Informed consent was obtained.

Footnotes

Authorship Contributions: Surgical and Medical Practices - I.B.V., K.R.; Concept - I.B.V., K.R.; Design - I.B.V., K.R.; Data Collection and/or/Processing - I.B.V., K.R.; Analysis or Interpretation - I.B.V., K.R.; Literature Search - I.B.V., K.R.; Writing - I.B.V., K.R.

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Case Report
Paediatric Anaesthesia

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Anaesthetic Management of Hermansky-Pudlak Syndrome with Major Hemorrhage: Based on a Case Report

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Abstract

Hermansky-Pudlak Syndrome (HPS) is a rare autosomal recessive disorder characterized by oculocutaneous albinism, platelet dysfunction, and bleeding diathesis. This case discusses the anaesthetic and hemostatic management of a paediatric patient with HPS undergoing scoliosis surgery, which has not been previously documented. A 15-year-old female patient with HPS presented with scoliosis requiring surgical correction. Key clinical findings included albinism, neutropenia, cardiovascular abnormalities, and prolonged platelet function test results. Preoperative assessments identified significant risks of bleeding and pulmonary complications, necessitating multidisciplinary planning. Intraoperative interventions included the administration of 1-desamino-8 D-arginine vasopressin, tranexamic acid, and blood product transfusions to manage intraoperative hemorrhage. Postoperatively, the patient required intensive care support and was discharged without further complications. This case emphasizes the importance of early diagnosis, preoperative optimization, and individualized anaesthetic and hemostatic management for patients with HPS undergoing major surgery. Multidisciplinary collaboration and vigilance are essential to mitigating bleeding risks and ensuring favorable outcomes in this high-risk population.

Keywords: Hermansky-Pudlak syndrome, hemodynamics, paediatric anaesthesia, blood coagulation disorder, orthopaedic anaesthesia

Main Points

- Hermansky-Pudlak Syndrome (HPS) presents significant perioperative challenges due to platelet dysfunction and bleeding diathesis, particularly in major surgeries such as scoliosis correction.
- Multidisciplinary preoperative planning, including specialists in hematology, pulmonology, and anaesthesiology, is critical for assessing bleeding risk and pulmonary complications in patients with HPS.
- Intraoperative administration of vasopressin, tranexamic acid, and targeted blood-product transfusions can effectively manage hemorrhagic complications in HPS.
- Early diagnosis, individualized anaesthetic strategies, and vigilant perioperative care are essential for successful surgical outcomes in paediatric patients with HPS.

Introduction

Hermansky-Pudlak Syndrome (HPS) is a rare autosomal recessive disease with a prevalence of 1-9 per 1,000,000 individuals worldwide.[1] The disease's clinical manifestations primarily arise from defects in the formation and function of lysosome-related organelles, including melanosomes and platelet dense granules, due to a shared protein deficiency. It is characterized by oculocutaneous albinism; nystagmus; bleeding diathesis; platelet dysfunction; progressive pulmonary fibrosis; granulomatous colitis; immunodeficiency; and renal and cardiovascular pathologies.[2] Bleeding and respiratory problems constitute the main challenges in anaesthesia management.[3]

HPS often presents in childhood with symptoms such as easy bruising, nosebleeds, or prolonged bleeding after surgery. Despite having normal platelet counts, patients experience extended bleeding times.[2] Anaesthetic management and

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surgical procedures for patients with HPS require special considerations.[4] Preoperative optimization, including considerations for platelet transfusions or prophylactic administration of 1-desamino-8 D-arginine vasopressin (DDAVP), is recommended to enhance patient outcomes and mitigate potential perioperative complications.[5]

In this case, we aimed to present the anaesthetic management of bleeding in a paediatric patient with HPS who underwent scoliosis surgery in our institution in November 2023. Although some anaesthetic management strategies are specific to gynecological cases, to the best of our knowledge, this is the first reported case in the literature addressing the management of bleeding caused by a musculoskeletal disorder in a patient with HPS.[6-9]

Case Report

A 15-year-old girl diagnosed with a genetic defect in the *AP-3* gene of HPS type 2 (HPS-2), weighing 22.25 kg and measuring 134 cm in height, both below the second percentile, was scheduled for scoliosis surgery. The patient had a history of safe anaesthesia, including patent ductus arteriosus (PDA) ligation and aortic coarctation repair at 3.5 months of age, followed by residual PDA closure via transcatheter intervention at 2 years of age.

The patient did not have a prominent bleeding event in her medical history and was currently receiving filgrastim 300 µg three times a week. The preoperative complete blood count revealed neutropenia, while coagulation parameters were within the normal range (neutrophil: 0.5 K mcL^{-1}, hemoglobin: 14 g dL^{-1}, platelet: 182 K mcL^{-1}). The chest X-ray revealed advanced scoliosis (Figure 1). Paediatric pulmonology and hematology consultations were conducted preoperatively. Thrombocyte function tests (platelet function analyzer-200) revealed prolonged bleeding times for collagen/epinephrine (>300 seconds; normal: 85-157 seconds) and collagen/adenosine diphosphate (ADP) (253 seconds; normal: 65-125 seconds). Hematology advised that reserved platelet concentrates be prepared due to the risk of prolonged bleeding during and after surgery, even in the absence of dental, gingival, or mucosal bleeding. The pulmonology service recommended pre- and postoperative blood gas monitoring for paediatric patients who are unable to perform pulmonary function tests; noninvasive ventilation if needed; and paediatric intensive care unit (PICU) respiratory support if required.

After obtaining the informed consent for publication from the patient's parents, the patient was transferred to the operating room. Premedication was administered as an intravenous (IV) dose of 1 mg of midazolam, followed by induction of anaesthesia with propofol (2 mg kg^{-1}), fentanyl (1 µg kg^{-1}), and rocuronium (0.5 mg kg^{-1}). Intubation was successfully performed with a 5.0 cuffed endotracheal tube without complications. A central jugular venous catheter and a right radial arterial catheter were inserted after induction. General anaesthesia was maintained with continuous IV infusion of propofol (0.03-0.06 mg kg^{-1} h^{-1}) and remifentanil (0.03-0.06 µg kg^{-1} h^{-1}). The patient was turned to the prone position (Figure 2). After the first incision at the T2-L3 level, a tendency to bleed was observed.

IV fluid replacement was initiated via the central venous line, and DDAVP 6 µg IV and tranexamic acid 20 mg kg^{-1} IV bolus were administered immediately. A tranexamic acid infusion at 10 mg h^{-1} IV was started. Due to low blood pressure, a noradrenaline IV infusion at a rate of 0.3 µg kg^{-1} h^{-1} was initiated. Three units of erythrocyte suspension, one unit of fresh frozen plasma, and one unit of pooled platelet concentrate were used throughout the procedure, with 2500 mL of IV crystalloid administered in total. The procedure lasted five hours, during which a total blood loss of 3000 mL was detected.

The patient was transferred to the PICU postoperatively, where she was intubated and sedated for three days. Her hemodynamics remained stable, and the noradrenaline infusion was discontinued on postoperative day two. The patient was successfully discharged from the PICU to the surgical ward without further complications. No bleeding issues were recorded during her stay in the hospital ward. Postoperative transfusions included three units of erythrocyte suspension, three units of fresh frozen plasma, and two units

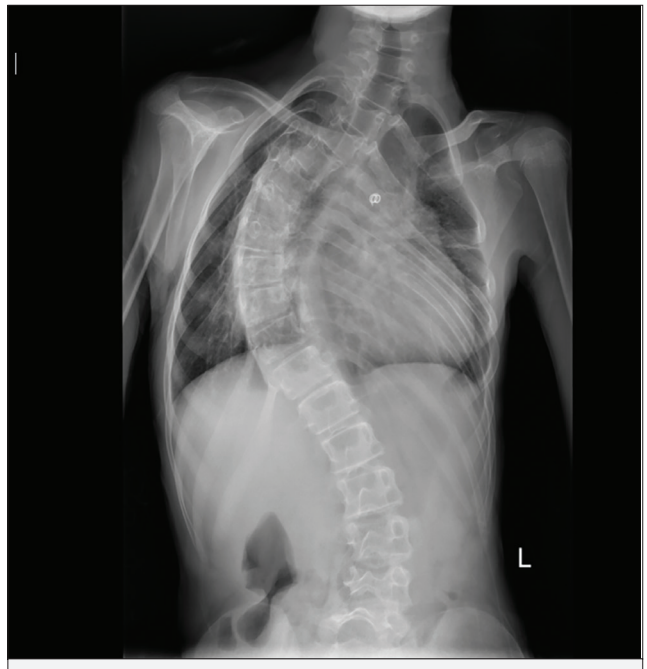

Figure 1. Chest X-ray revealing advanced scoliosis of the patient.

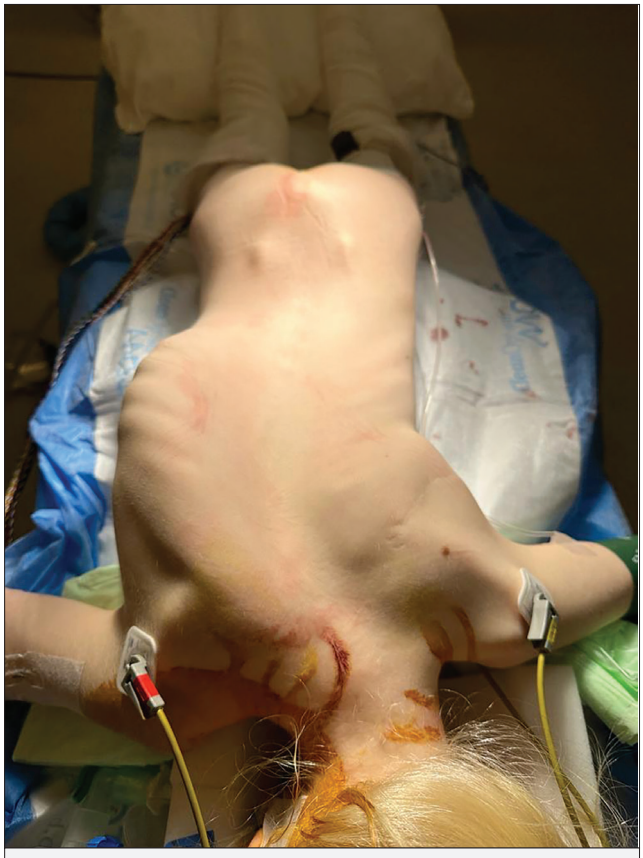

Figure 2. The position of the patient during surgery.

of platelet concentrate. Additional replacements included cryoprecipitate and vitamin K. No further episodes of thrombocytopenia were observed.

Discussion

HPS, particularly the AP-3 (HPS2) subtype (AP3B1), is associated with cellular abnormalities, including defects in melanosomes, dense granules, and Weibel-Palade bodies, leading to manifestations such as pulmonary fibrosis, oculocutaneous albinism, bleeding diathesis, and immunodeficiency. Additional complications include interstitial lung disease, periodontitis, and increased susceptibility to infections.[10] Platelet dense granules contain serotonin, ADP, and calcium, and their deficiency results in prolonged bleeding times and abnormal platelet aggregation tests. Electron microscopy is particularly useful in diagnosing dense granule deficiencies.[2]

Mucocutaneous bleeding is common in HPS, and DDAVP shortens bleeding time by increasing plasma levels of Factor VIII and von Willebrand factor. Antifibrinolytics, such as tranexamic acid, are also beneficial. Preoperative assessment and perioperative platelet transfusion are critical to mitigating bleeding risk. Despite variable efficacy, DDAVP and platelet transfusions are often effective in surgical contexts.[2]

The anaesthetic management of HPS requires special considerations, as bleeding times may be prolonged even with normal platelet counts. Preoperative hematology consultation is essential for optimizing outcomes.[7] Prophylactic DDAVP and platelet transfusion significantly reduce perioperative blood loss, although responses to DDAVP vary.[4,5] Recombinant factor VIIa may be an option for patients who are unresponsive to DDAVP.[5]

Studies show that platelet transfusions effectively limit blood loss, whereas outcomes with DDAVP are less consistent.[6,11] Vigilant perioperative planning is crucial, as untreated bleeding can lead to severe complications.[12] This case underscores the importance of early diagnosis, individualized hemostatic management, and multidisciplinary collaboration. Pre-procedural pulmonary assessments also help address ventilation challenges and ensure stable postoperative outcomes.

Managing HPS during surgery demands meticulous planning and tailored therapeutic strategies. While platelet transfusions are the cornerstone of hemostatic management, variability in DDAVP efficacy highlights the need for individualized care.

Ethics

Informed Consent: Informed consent for publication was obtained from the patient's parents.

Footnotes

Authorship Contributions: Surgical and Medical Practices - A.A., D.Y., Y.S., Y.G.; Concept - A.A., D.Y., Y.S., Y.G.; Design - A.A., D.Y., Y.S., Y.G.; Data Collection and/or/Processing - A.A., D.Y., Y.S., Y.G.; Analysis or Interpretation - A.A., D.Y., Y.S., Y.G.; Literature Search - A.A., D.Y., Y.S., Y.G.; Writing - A.A., D.Y., Y.S., Y.G.

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Letter to the Editor

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Postherpetic Neuralgia Mimicking Lumbar Radiculopathy in the Same Dermatome: A Diagnostic Challenge

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Keywords

Dorsal root ganglion, pain, postherpetic neuralgia, pulsed radiofrequency

Dear Editor,

Postherpetic neuralgia (PHN) is a well-recognized and often debilitating complication of herpes zoster, characterized by persistent neuropathic pain after resolution of cutaneous lesions.[1,2] Although thoracic dermatomes are most commonly involved, lumbosacral herpes zoster is relatively rare and may easily be misinterpreted as lumbar radiculopathy, particularly during the prodromal phase when neuropathic pain precedes the appearance of skin lesions.[3,4]

The coexistence of herpes zoster-related dorsal root ganglion (DRG) irritation and structural nerve root compression within the same dermatome creates a unique diagnostic dilemma. Previous reports have described patients in whom herpes zoster–related sciatic pain closely mimicked lumbar disc herniation or spinal canal stenosis, resulting in misdiagnosis and delayed targeted treatment.[5,6]

The patient presented with persistent low back pain and left gluteal pain radiating along the L5 dermatome. Two weeks before presenting to our clinic, vesicular lesions developed in the same dermatome, and he was diagnosed with herpes zoster. Lumbar magnetic resonance imaging demonstrated a concomitant L5-S1 disc herniation compressing the left L5 nerve root. Prominent neuropathic pain features, including a burning quality and allodynia, suggested viral involvement, whereas imaging findings supported a concomitant mechanical component, resulting in diagnostic uncertainty.

We therefore applied a combined interventional approach, consisting of pulsed radiofrequency (PRF) to the L5 DRG, followed by a transforaminal epidural steroid injection, to address both virus-induced neuronal hyperexcitability and inflammatory radicular compression (Figure 1). DRG-targeted interventions play a central role in PHN due to the involvement of sensory neurons in the initiation and maintenance of neuropathic pain.[7] In addition, systematic reviews indicate that early nerve block and PRF applications may reduce the incidence and severity of PHN in patients with acute herpes zoster.[8]

Following the combined intervention, the patient's numeric rating scale score decreased from 7 to 1 and the leeds assessment of neuropathic symptoms and signs score from 15 to 0 within the first hour, with sustained analgesic benefit at the three-week follow-up.

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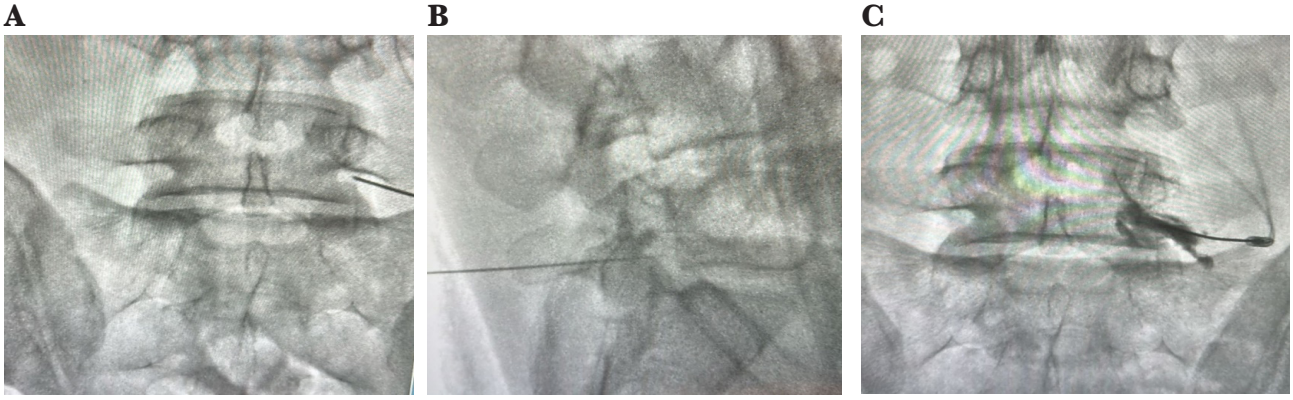

Figure 1. Left L5 transforaminal epidural steroid injection: A, AP view; B, Lateral view; C, AP view with contrast distribution. AP, anteroposterior.

This experience underscores the importance of recognizing overlapping viral and mechanical pain mechanisms in patients presenting with atypical lumbosacral radicular pain. Early consideration of combined DRG-targeted interventions may not only provide rapid diagnostic clarification, but may also play a critical role in preventing progression to chronic PHN in complex clinical scenarios. In patients with prominent neuropathic pain features (e.g., burning pain and allodynia), herpes zoster should be considered even in the absence of rash (zoster sine herpete). In such cases, diagnostic tests (VZV DNA detection and VZV-specific IgM and IgG antibodies) may support the differential diagnosis.

Footnotes

Authorship Contributions: Surgical and Medical Practices - O.B., S.T., R.R.; Concept - O.B., S.T.; Design - S.T.; Data Collection or Processing - O.B., S.T.; Literature Review - O.B., S.T., R.R.; Writing - O.B., S.T.

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Letter to the Editor

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When Distance Matters: The Quadro-iliac Plane Block in Complex Multilevel Posterior Spinal Fusion Surgery

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Dear Editor,

Complex multilevel spinal surgeries are associated with severe postoperative pain due to extensive paraspinal muscle dissection, prolonged operative time, and multilevel instrumentation. Consistent with our prior institutional experience and the literature, patients undergoing multilevel spinal fusion without regional analgesia demonstrate an increased need for rescue opioid analgesia.[1] Although several regional techniques have been proposed, effective options that do not interfere with the surgical field remain limited. Thoracolumbar interfascial plane and erector spinae plane (ESP) blocks are commonly used; however, their efficacy may be compromised in multilevel procedures where surgical trauma, edema, and instrumentation disrupt local anatomy and impair local anaesthetic spread.[1]

In this context, the quadro-iliac plane (QIP) block may overcome some of these limitations.[2-4] It targets the posterior aspect of the quadratus lumborum muscle at its iliac crest attachment, enabling, with a single injection, the spread of local anaesthetic into the interfascial planes between the erector spinae and quadratus lumborum and between the quadratus lumborum and psoas muscles, thereby providing a plausible basis for lumbosacral paraspinal analgesia. While QIP block has shown efficacy in single-level lumbar discectomy and may be non-inferior to ESP block,[5] evidence in multilevel spinal stabilization remains limited to a few small case series involving patients undergoing three-level spinal instrumentation.[3,6]

Based on this rationale, QIP block was applied in four consecutive patients undergoing multilevel posterior spinal fusion and decompression via laminectomy at a single institution as part of routine clinical practice, as previously described (Figure 1).[2] Following informed consent, a bilateral ultrasound-guided QIP block was performed postoperatively using 20 mL of 0.25% bupivacaine per side. Patients were monitored in the recovery unit for approximately four hours. Postoperative analgesia was standardized as an alternating regimen of dexketoprofen and paracetamol every 12 hours; rescue opioids were administered if pain scores exceeded 3.

The cohort included three female patients and one male patient (aged 61-73 years), all undergoing four-level stabilization (T11-L2, L1-L4, and two at L2-L5). All patients received scheduled non-opioid analgesics, and none required rescue opioids. Pain scores remained low at rest [numeric rating scale (NRS) 1-2] and did not exceed NRS 3 with movement. One patient with T11-L2 instrumentation reported mild pain at the cranial extent of the incision during the first postoperative hour, suggesting limited cranial coverage; however, the discomfort remained tolerable. All patients were able to reposition comfortably, showed no motor blockade, and were mobilized on the first postoperative day.

In practice, a QIP block applied at a site distant from the operative area was readily accepted by the surgical team and addressed concerns regarding blocks performed near fresh posterior incisions. Moreover, observations from our four cases suggest a potential opioid-sparing effect in this surgical population, and this effect was well received by both the surgical and anaesthesiology teams and by the patients.

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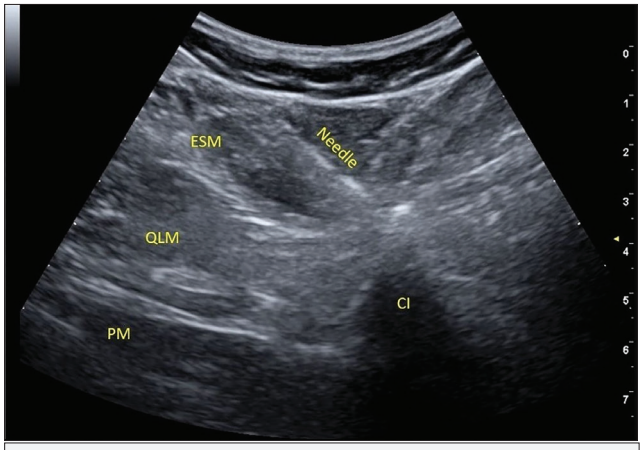

Figure 1. Quadro-iliac plane block-ultrasound view.

CI, crista iliaca; ESM, erector spinae muscle; PM, psoas muscle; QLM, quadratus lumborum muscle.

In the cadaveric study by Tulgar et al.,[2] injection of 40 mL of dye per side demonstrated spread extending from the iliac crest to the 12th rib, involving the transversalis fascia, adjacent retroperitoneal fat, and mid-level lumbar plexus structures.[2] This distribution may explain the limited cranial coverage observed in the T11-L2 case. Furthermore, despite the use of a lower volume of local anaesthetic, effective analgesic coverage from L1 to L5 was achieved in our cases. Although cadaveric findings suggest a theoretical risk of motor blockade due to lumbar plexus involvement, no motor blockade was observed in our patients, possibly because of the lower volume and concentration used. However, this risk should be considered when reliable postoperative neurological assessment is required.

Finally, patients undergoing multilevel spinal fusion often have chronic back pain, which may alter thoracolumbar fascia micro- and macro-structure and function, thereby influence the spread, diffusion, and absorption of local anaesthetics and lead to variability in block efficacy;[7] thus, beyond cadaveric findings these factors should be taken into account in clinical practice.

Evidence for QIP block in multilevel spinal stabilization remains limited to a few case reports, including our four cases. Thus, these findings should be considered hypothesis-generating rather than generalizable, and further prospective studies are needed to clarify its role.

Footnotes

Authorship Contributions: Surgical and Medical Practices - H.G., P.N.Ş.; Concept - H.G., P.N.Ş., Ç.B.; Design - H.G., P.N.Ş., Ç.B.; Data Collection and/or Processing - H.G., P.N.Ş.; Analysis or Interpretation: H.G., Ç.B.; Literature Search - H.G.; Writing - H.G., Ç.B.

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Letter to the Editor

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Quality of Recovery (QoR)-15 Scale: From Statistical Significance to Clinical Relevance and Beyond

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Keywords

Analgesia, epidural morphine, perioperative care, recovery scale, regional anaesthesia

Dear Editor,

We read with great interest the article titled "Continuous Low-dose Epidural Morphine and Ketamine Analgesia Improves Quality of Recovery (Qor) after Major Lumbar Spine Surgery: A Randomised Controlled Trial" by Karri et al.[1] We appreciate that the authors compared the effects of continuous epidural opioid (morphine) plus ketamine (Group A) and opioid plus ketamine administered via intravenous (IV) patient-controlled analgesia (Group B) on QoR-15 following major spine surgery in 40 American Society of Anesthesiologists I or II patients scheduled for transforaminal thoracolumbar/lumbar spine instrumentation under general anaesthesia in their randomized clinical trial. Total QoR-15 scores in Group A were found to be significantly better than that of Group B at 24 hours (134.8±6.65 and 128.9±6.12, respectively P=0.006) and at 48 hours (136.7±6.02 vs. 132.10±6.8, P=0.029) with significantly lower pain scores in group A at rest and during movement. All other secondary outcomes were comparable between the groups. There might be few limitations of of this QoR 15 scale of well proven validity in assessing all dimensions of postoperative recovery[2] which could affect the interpretation of the results of Karri et al.[1]

First, the authors concluded that Group A was statistically superior to Group B; the difference in QoR-15 scores was four points at the 48th hour. This can be considered clinically negligible, as a minimal clinically important difference of 6 is needed on the QoR-15 scale to show a meaningful effect of any perioperative intervention.[3] Due to the nature of the interventions for lumbar laminectomies, significant pain and functional disability are anticipated, with a greater likelihood of changes in QoR scores.[4] Therefore, measuring preoperative QoR-15 scores could help to determine the clinical significance of postoperative scores.

Second, physical independence is a subdomain of QoR-15 which assesses the ability to do daily activities and work independently. This difference in Karri et al.'s[1] study is 1.5 points with statistical significance which is clinically meaningless not only by numbers but also taking into account that IV analgesia group received mean morphine dose of 18.25±11.36 mg at the rate of 0.09 mg kg^{-1} hr^{-1} (5.76 mg kg^{-1} hr^{-1} for mean weight of 64 kg with same dose of ketamine in 24 hours), which could potentially affect cognitive and motor functions.[5]

Third, emotional support is another subdomain of QoR 15, which measures feelings of general well-being, comfort, and anxiety or depression. The difference in QoR -15 score of this subdomain in Karri et al.[1] study was 12 points at 24 hours and one point at 48 hours. At both time points, this difference was statistically significant with the same P value of 0.027 (Table 3 of Karri et al.[1]). This identical P value in the same sample size could indicate a typographical error or a statistical flaw. Similarly, emotional support scores were low in group B, which received continuous infusion of ketamine and morphine in a 1:1 ratio. Ketamine can cause functional disorganization by its depressive effects on the thalamocortical system and its stimulatory effects on the limbic system. This may also affect the patient's emotional response and pain scores.[6] Lastly, one of the subdomains

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has to be mentioned as psychological support rather than physical support.[1,2]

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