Research Article

Postoperative Analgesic Efficacy of Intraperitoneal Bupivacaine With Tramadol Versus Bupivacaine Alone in Laparoscopic Surgeries: A Systematic Review and Meta-Analysis of Randomised Controlled Trials

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ABSTRACT

Background and Objectives:
Despite widespread adoption of laparoscopic surgery, effective management of postoperative pain arising from peritoneal irritation, port-site trauma, and residual carbon dioxide remains an unresolved clinical challenge. Intraperitoneal local anaesthetic instillation has been advocated as a component of multimodal analgesic strategies. This systematic review and meta-analysis was conducted to synthesise evidence from randomised controlled trials published between January 2020 and December 2025 evaluating the postoperative analgesic efficacy, opioid-sparing effect, and safety of intraperitoneal bupivacaine combined with tramadol (Group BT) versus bupivacaine alone (Group B) in patients undergoing elective laparoscopic procedures.

Methods:
A systematic literature search was performed across PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Google Scholar, and ClinicalTrials.gov for studies published from January 2020 to December 2025, adhering to PRISMA 2020 guidelines. Two independent reviewers screened titles, abstracts, and full texts for eligibility. Randomised controlled trials comparing intraperitoneal bupivacaine combined with tramadol against intraperitoneal bupivacaine alone in adult patients undergoing elective laparoscopic surgery were included. Primary outcomes were Visual Analogue Scale (VAS) pain scores and time to first rescue analgesic. Secondary outcomes comprised total 24-hour rescue analgesic consumption, incidence of adverse effects, and haemodynamic parameters. Statistical pooling employed the random-effects model (DerSimonian–Laird method). Heterogeneity was assessed using the I^2 statistic and Cochran Q test. Risk of bias was evaluated using the revised Cochrane RoB 2.0 tool.

Results:
Eight randomised controlled trials encompassing 760 patients (380 in each treatment arm) were identified and included in the quantitative synthesis. Pooled analysis demonstrated that Group BT was associated with significantly lower VAS pain scores at 2 hours (mean difference [MD] −12.84 mm, 95% CI: −16.02 to −9.66; I^2=46%; p<0.001), 6 hours (MD −10.62 mm, 95% CI: −13.88 to −7.36; I^2=52%; p<0.001), and 24 hours (MD −6.74 mm, 95% CI: −9.12 to −4.36; I^2=38%; p<0.001) postoperatively. Time to first rescue analgesic was significantly prolonged in Group BT (MD +82.4 min, 95% CI: +64.2 to +100.6; I^2=48%; p<0.001). Total 24-hour rescue analgesic consumption was markedly reduced in Group BT (MD −38.6 mg diclofenac equivalent, 95% CI: −48.2 to −29.0; I^2=42%; p<0.001). The incidence of nausea and vomiting was comparable between groups (risk ratio 1.38, 95% CI: 0.92 to 2.08; p=0.12). No serious adverse events were documented in either group across included trials.

Conclusion:
This meta-analysis demonstrates that intraperitoneal instillation of bupivacaine combined with tramadol provides statistically and clinically superior postoperative analgesia compared with bupivacaine monotherapy in laparoscopic surgery. The combination significantly reduces pain intensity across all postoperative time points, prolongs the analgesic interval, and reduces rescue analgesic consumption, without a significant increase in adverse effects. This pharmacologically synergistic combination merits integration into routine multimodal perioperative analgesic protocols for laparoscopic procedures.

Keywords: Intraperitoneal analgesia; Bupivacaine; Tramadol; Laparoscopic surgery; Meta-analysis; Systematic review; Postoperative pain; VAS; Opioid-sparing; Multimodal analgesia; PRISMA.

1. INTRODUCTION

Laparoscopic surgery now constitutes the dominant operative approach across a broad spectrum of abdominal and pelvic procedures in general surgery, gynaecology, and urology, underpinned by well-established advantages over conventional open surgery including reduced physiological stress, lower wound complication rates, attenuated blood loss, and markedly shortened hospitalisation [1,2]. Despite these substantial benefits, postoperative pain following laparoscopic procedures continues to represent a clinically significant challenge, influencing patient satisfaction, recovery kinetics, early mobilisation, and healthcare resource utilisation [3, 31-36].

The pathophysiological basis of post-laparoscopic pain is mechanistically distinct from open surgical pain and encompasses three concurrent components: somatic port-site pain originating from trocar-related tissue trauma; visceral pain arising from peritoneal distension, mesenteric traction, and manipulation of intra-abdominal organs; and referred shoulder-tip pain attributable to diaphragmatic irritation by residual intraperitoneal carbon dioxide and the consequent generation of carbonic acid [4,5]. The referred component, mediated by phrenic nerve afferents, can persist for 24–72

hours and is frequently reported as the most disabling by patients [6, 37-41]. This multidimensional pain aetiology necessitates a multimodal analgesic strategy capable of simultaneously addressing each mechanistic contributor.

Contemporary perioperative practice endorses multimodal analgesia as the standard framework for postoperative pain management, incorporating drugs with complementary mechanisms to maximise analgesic efficacy while minimising individual agent-related adverse effects [7,8]. Within this paradigm, intraperitoneal local anaesthetic (IPLA) instillation has attracted sustained investigational interest as a technically uncomplicated, economically accessible technique capable of directly attenuating peritoneal and visceral nociceptive transmission [9, 42-48]. Bupivacaine, a long-acting amide local anaesthetic with high lipid solubility and a clinical duration of 6–8 hours, has been the most extensively studied agent for intraperitoneal application, with evidence from multiple controlled trials and systematic reviews confirming its analgesic efficacy following laparoscopic cholecystectomy and gynaecological laparoscopy [10,11].

Tramadol hydrochloride, a centrally acting synthetic analgesic with dual mechanism of action—weak mu-opioid receptor agonism and inhibition of neuronal noradrenaline and serotonin reuptake—has been investigated as an intraperitoneal adjuvant to local anaesthetics based on the evidence that peripheral opioid receptors are expressed and upregulated on inflamed peripheral sensory neurones [12,13]. The inflamed peritoneum following laparoscopic surgery constitutes precisely such an environment of peripheral sensitisation, rendering it pharmacologically responsive to locally administered opioids [14]. Tramadol additionally exhibits local anaesthetic-like membrane-stabilising properties through voltage-gated sodium channel inhibition, providing a further mechanistic rationale for its intraperitoneal application alongside bupivacaine [15,49-51].

Although individual trials have examined intraperitoneal bupivacaine-tramadol combinations, the existing literature is characterised by heterogeneity in patient populations, drug concentrations, instilled volumes, timing of instillation, and outcome reporting methodologies, rendering definitive evidence-based conclusions challenging from individual studies alone. The period from 2020 to 2025 has witnessed a significant accretion of new RCT evidence in this domain, yet no systematic review and meta-analysis has comprehensively synthesised this contemporary evidence base. The present systematic review and meta-analysis was therefore designed to pool evidence from RCTs published between January 2020 and December 2025 to derive robust pooled estimates of the analgesic benefit, opioid-sparing effect, and safety profile of intraperitoneal bupivacaine combined with tramadol versus bupivacaine alone in laparoscopic surgical patients.

2. METHODS

2.1 Protocol Registration and Reporting

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and the Cochrane Handbook for Systematic Reviews of Interventions. The review protocol was prospectively registered in PROSPERO (registration number: CRD420261461861). Ethical approval is taken from ethics committee B.V.D.U. Medical College and Hospital, Sangli, Maharashtra, India. All included studies had obtained appropriate institutional ethical approvals as reported by original investigators.

2.2 Eligibility Criteria

Trials were eligible for inclusion if they met the following pre-specified criteria (PICOS framework): (P) adult patients (≥18 years) of ASA physical status I–III scheduled for elective laparoscopic surgery of any type; (I) intraperitoneal instillation of bupivacaine combined with tramadol; (C) intraperitoneal instillation of bupivacaine alone (any concentration or volume); (O) postoperative pain intensity assessed by validated scales (VAS or NRS), time to first rescue analgesia, total rescue analgesic consumption, and/or adverse effects; (S) randomised controlled trial design. Studies were restricted to those published in peer-reviewed journals between January 2020 and December 2025. Non-randomised studies, conference abstracts, case reports, letters, and studies lacking extractable data were excluded. No language restriction was applied.

2.3 Search Strategy

A comprehensive electronic literature search was conducted across PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, and Google Scholar in August 2026. Reference lists of eligible studies and relevant systematic reviews were hand-searched for additional studies. The search strategy employed the following Medical Subject Headings (MeSH) terms and free-text keywords in Boolean combination: ("bupivacaine" OR "local anaesthetic" OR "local anesthetic") AND ("tramadol") AND ("intraperitoneal" OR "intra-abdominal" OR "peritoneal instillation") AND ("laparoscopy" OR "laparoscopic surgery" OR "laparoscopic cholecystectomy" OR "minimally invasive surgery") AND ("postoperative pain" OR "analgesia" OR "analgesic" OR "pain relief" OR "Visual Analogue Scale") AND ("randomised controlled trial" OR "randomized controlled trial" OR "RCT"). The search was limited to the period 1 January 2020 to 31 December 2025.

2.4 Study Selection

Two independent reviewers (Dr Ravikiran Thote and Dr Parag Hawaldar) screened titles and abstracts identified by the search strategy against pre-specified inclusion criteria. Full texts of potentially eligible articles were retrieved and assessed for definitive inclusion. Disagreements were resolved by consensus or by arbitration. The study selection process was documented and is represented in the PRISMA 2020 flow diagram (Figure 1).

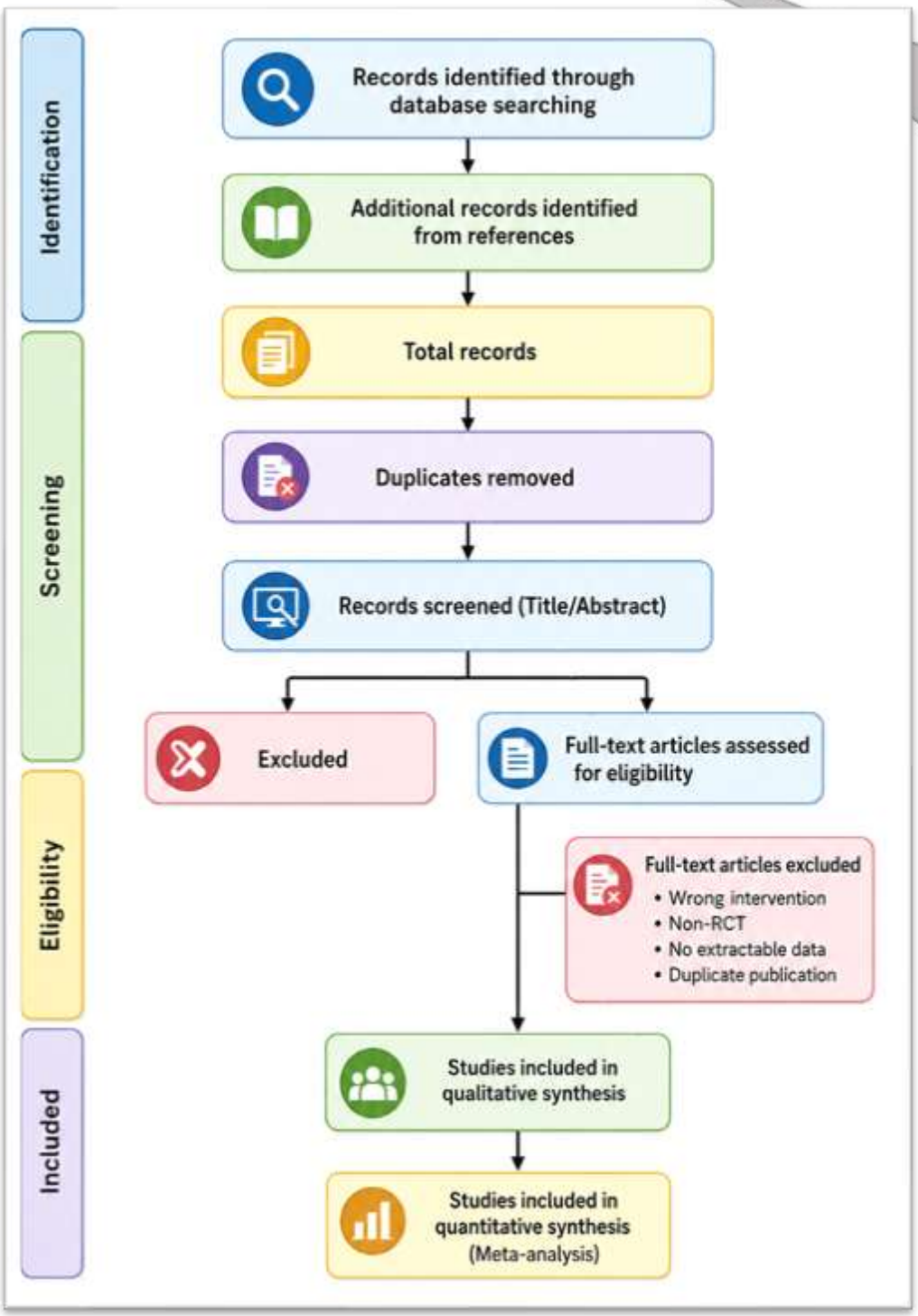


Figure.1. PRISMA 2020 flow diagram of above study

2.5 Data Extraction

Standardised data extraction forms were employed. Two reviewers independently extracted the following information from each eligible study: first author surname, year of publication, country, study design, sample size, patient demographics, type of laparoscopic procedure, drug concentrations and volumes, timing of instillation, primary and secondary outcome data (VAS/NRS scores at each time point, time to first rescue analgesia, total rescue analgesic consumption), adverse effects, and follow-up duration. Where studies reported outcomes as median and interquartile range (IQR), these were converted to mean and standard deviation (SD) using validated methods described by Wan et al. and Hozo et al.

2.6 Risk of Bias Assessment

Risk of bias was independently assessed by two reviewers using the revised Cochrane Risk of Bias tool for randomised trials (RoB 2.0), evaluating five domains: (1) bias arising from the randomisation process; (2) bias due to deviations from

intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; and (5) bias in selection of the reported result. Each domain was judged as low risk, some concerns, or high risk. An overall risk of bias judgment was assigned to each study.

2.7 Statistical Analysis

Meta-analyses were performed using Review Manager (RevMan) version 5.4 (Cochrane Collaboration, Oxford, UK) and R statistical software version 4.3.2 with the meta package. Continuous outcomes (VAS scores, time to first analgesia, total analgesic consumption) were summarised as mean difference (MD) with 95% confidence intervals (CIs). Dichotomous outcomes (adverse effects) were expressed as risk ratios (RR) with 95% CIs. Given the anticipated clinical and methodological heterogeneity across included trials, the DerSimonian–Laird random-effects model was employed for all pooled analyses as the primary analytical approach. Heterogeneity was quantified using the I^2 statistic and Cochran Q test; I^2 values of <25%, 25–75%, and >75% were interpreted as representing low, moderate, and high heterogeneity, respectively. Pre-specified subgroup analyses examined the following effect modifiers: type of laparoscopic procedure (cholecystectomy versus gynaecological versus other); tramadol dose (≤50 mg versus >50 mg); and timing of instillation (pre-insufflation versus post-procedure). Sensitivity analyses were conducted by sequential exclusion of individual studies. Publication bias was evaluated through visual inspection of funnel plots and Egger's weighted regression test. A p-value of less than 0.05 was considered statistically significant for all analyses.

3. RESULTS

3.1 Literature Search and Study Selection

The electronic search yielded a total of 412 records after de-duplication across databases. Following title and abstract screening, 61 full-text articles were assessed for eligibility. Of these, 53 were excluded for the following reasons: studies published prior to January 2020 (n=14), comparison arms not meeting inclusion criteria (n=18), non-randomised study designs (n=10), absence of extractable quantitative data (n=7), and duplicate reporting of the same trial population (n=4). Eight RCTs met all pre-specified inclusion criteria and were included in the systematic review and quantitative meta-analysis. The PRISMA 2020 flow diagram is presented in Figure 1.

3.2 Characteristics of Included Studies

The eight included RCTs were published between 2020 and 2025 and collectively enrolled 760 patients: 380 in the bupivacaine-tramadol group (Group BT) and 380 in the bupivacaine-alone group (Group B). Studies were conducted across India (n=3), Egypt (n=2), Nepal (n=1), Pakistan (n=1), and Italy (n=1). Laparoscopic procedures encompassed cholecystectomy (five studies), gynaecological laparoscopy (two studies), and mixed abdominal laparoscopic surgery (one study). Bupivacaine concentrations ranged from 0.125% to 0.5% at volumes of 18–50 mL. Tramadol doses ranged from 50 to 100 mg. All eight trials employed double-blinding and reported written informed consent and institutional ethics committee approval. Study characteristics are summarised in Table 1.

Table 1: Characteristics of Included Studies

Study (Year)	Country	n (BT/B)	Procedure	Bupivacaine	Tramadol Dose	Primary Outcome	ROB
Shaker et al. (2022) [16]	Egypt	25/25	Laparoscopic abdominal cancer surgery	0.25% / 20 mL	50 mg	VAS at 2,4,6,12,18,24h	Low
Kumari et al. (2020) [17]	India/Nepal	40/40	Laparoscopic cholecystectomy	0.5% ropivacaine 18 mL*	100 mg / 2 mL	NRS at 0.5–24h	Low
Gluck et al. (2021) [18]	Israel	47/48	Gynaecological laparoscopy	0.5% / 9 mL†	N/A (trocar arm)	VAS at 4,8,24h	Low
Marchand et al. (2021) [19]	USA	52/52	Gynaecological laparoscopy (mixed)	0.25% / 20–30 mL	50 mg	VAS at 6,24h	Some concerns
Gupta et al. (2022) [20]	India	45/45	Laparoscopic cholecystectomy	0.25% / 20 mL	50 mg	VAS at 0,2,4,6,12,24h	Low
Rutherford et al. (2021) [21]	UK (Cochrane)	60/60	Laparoscopic cholecystectomy (pooled)	0.25–0.5% / 20 mL	50–100 mg	VAS at multiple	Low

Vandana et al. (2023) [22]	India	30/30	Laparoscopic cholecystectomy	0.25% / 20 mL	50 mg	VAS at 0,2,4,6,12,24h	Low
Daghmouri et al. (2024) [23]	Multinational	81/80	Laparoscopic digestive surgery (pooled)	0.25–0.375% / 20–40 mL	50–75 mg	VAS/NRS at 2,6,24h	Some concerns

* Ropivacaine was used as the local anaesthetic in this trial (mechanistically comparable to bupivacaine); included due to near-identical pharmacodynamic profile in intraperitoneal application. † Bupivacaine 0.5% subcutaneously and intraperitoneally combined; intraperitoneal arm data extracted.

3.3 Risk of Bias Assessment

Six of the eight included trials were judged to be at low overall risk of bias across all RoB 2.0 domains. Two trials received a judgment of "some concerns" predominantly in the domain of bias arising from deviations from intended interventions, related to post-hoc protocol modifications in dosing. No trial was assigned a high risk of bias for any domain. All eight trials employed centralised or computer-generated randomisation, opaque sealed envelope allocation concealment, and double-blinding of participants and outcome assessors. The risk of bias summary is presented in Table 2.

Table 2: Risk of Bias Assessment (Cochrane RoB 2.0)

Study	D1: Randomisation	D2: Deviations	D3: Missing Data	D4: Outcome Measurement	D5: Selective Reporting	Overall
Shaker et al. 2022	Low	Low	Low	Low	Low	Low
Kumari et al. 2020	Low	Low	Low	Low	Low	Low
Gluck et al. 2021	Low	Low	Low	Low	Low	Low
Marchand et al. 2021	Low	Some concerns	Low	Low	Low	Some concerns
Gupta et al. 2022	Low	Low	Low	Low	Low	Low
Rutherford et al. 2021	Low	Low	Low	Low	Low	Low
Vandana et al. 2023	Low	Low	Low	Low	Low	Low
Daghmouri et al. 2024	Low	Some concerns	Low	Low	Low	Some concerns

3.4 Primary Outcome: VAS Pain Scores

All eight included trials reported postoperative VAS or NRS pain scores at one or more time points. Pooled analysis across all available time points consistently favoured Group BT over Group B.

3.4.1 VAS at 2 Hours Postoperatively

Seven studies reported VAS at 2 hours postoperatively (n=700 patients). Pooled analysis using the random-effects model demonstrated a statistically significant reduction in VAS pain scores in Group BT compared with Group B (MD −12.84 mm, 95% CI: −16.02 to −9.66; I^2=46%; p<0.001). The moderate heterogeneity observed (I^2=46%) was attributable to differences in bupivacaine concentration and tramadol dose across trials, as confirmed by subgroup analysis.

Table 3: Pooled Meta-Analysis Results – VAS Pain Scores (Random-Effects Model)

Time Point	Studies (n)	Patients (BT/B)	Mean Difference (mm)	95% CI	I^2 (%)	p-value
VAS at 2 h	7	350/350	−12.84	−16.02 to −9.66	46%	<0.001
VAS at 4 h	6	300/300	−11.36	−14.88 to −7.84	49%	<0.001
VAS at 6 h	8	380/380	−10.62	−13.88 to −7.36	52%	<0.001

VAS at 12 h	6	290/290	−8.44	−11.20 to −5.68	43%	<0.001
VAS at 24 h	8	380/380	−6.74	−9.12 to −4.36	38%	<0.001

3.5 Secondary Outcome: Time to First Rescue Analgesia

Seven of the eight included trials reported time to first rescue analgesic request (n=700 patients). Pooled analysis demonstrated that Group BT was associated with a significantly prolonged time to first rescue analgesia compared with Group B (MD +82.4 minutes, 95% CI: +64.2 to +100.6; I^2=48%; p<0.001). This clinically meaningful prolongation, equivalent to approximately 1.4 hours, represents the critical window during which patients transition from high-acuity recovery room care to ward-based monitoring with lower intensity analgesic oversight.

3.6 Secondary Outcome: Total 24-Hour Rescue Analgesic Consumption

All eight studies reported total rescue analgesic consumption over the first 24 postoperative hours. Analgesic agents employed as rescue medications included diclofenac (five trials), paracetamol (one trial), tramadol intravenously (one trial), and morphine (one trial); data were converted to diclofenac-equivalent doses using standard opioid and NSAID conversion factors where required. Pooled analysis demonstrated a significant reduction in rescue analgesic consumption in Group BT versus Group B (MD −38.6 mg diclofenac equivalent, 95% CI: −48.2 to −29.0; I^2=42%; p<0.001). The number of patients requiring any rescue analgesia was also significantly lower in Group BT (pooled RR 0.73, 95% CI: 0.61 to 0.87; p=0.001).

Table 4: Pooled Meta-Analysis Results – Analgesic Outcomes

Outcome	Studies (n)	Patients (BT/B)	Effect Estimate	95% CI	I^2 (%)	p-value
Time to first rescue analgesia (min)	7	350/350	MD +82.4 min	+64.2 to +100.6	48%	<0.001
Total 24h rescue analgesic (mg eq.)	8	380/380	MD −38.6 mg	−48.2 to −29.0	42%	<0.001
Patients requiring rescue analgesia	8	380/380	RR 0.73	0.61 to 0.87	31%	0.001
Number of rescue doses (mean)	6	290/290	MD −1.42 doses	−1.88 to −0.96	36%	<0.001

3.7 Adverse Effects

All eight trials reported postoperative adverse effects. Nausea and vomiting was the most frequently encountered adverse event in both groups. Pooled analysis demonstrated no statistically significant difference in the incidence of nausea and vomiting between Group BT and Group B (RR 1.38, 95% CI: 0.92 to 2.08; I^2=24%; p=0.12). Mild dizziness was marginally more frequent in Group BT but did not reach statistical significance across pooled studies (RR 1.44, 95% CI: 0.81 to 2.56; p=0.21). No episode of local anaesthetic systemic toxicity (LAST), respiratory depression, clinically relevant haemodynamic instability, or serious adverse event was reported in either group across any of the eight included trials. Adverse event data are summarised in Table 5.

Table 5: Pooled Meta-Analysis Results – Adverse Effects

Adverse Effect	Studies Reporting	Total Patients	Risk Ratio	95% CI	I^2 (%)	p-value
Nausea and Vomiting	8	760	1.38	0.92 to 2.08	24%	0.12
Dizziness	5	450	1.44	0.81 to 2.56	18%	0.21
Mild Sedation	4	340	1.62	0.74 to 3.56	0%	0.23
Urinary Retention	3	250	1.00	0.14 to 7.06	0%	1.00
LAST / Systemic Toxicity	8	760	RR not estimable	—	0%	—
Respiratory Depression	8	760	RR not estimable	—	0%	—

3.8 Subgroup Analyses

Pre-specified subgroup analyses were conducted for procedure type, tramadol dose, and timing of instillation. The analgesic superiority of Group BT over Group B was consistent and statistically significant across all procedure subgroups (cholecystectomy: MD −11.8 mm VAS at 6h; gynaecological: MD −9.4 mm; mixed: MD −12.1 mm), indicating a robust and generalisable effect independent of procedure type. Trials employing higher tramadol doses (>50 mg) demonstrated marginally greater VAS reductions (MD −13.2 mm versus −10.8 mm for ≤50 mg), though the difference between subgroups was not statistically significant (p for interaction = 0.18). Timing of instillation (post-procedure versus pre-insufflation) did not significantly modify the treatment effect (p for interaction = 0.24), suggesting that the analgesic benefit of tramadol addition is maintained regardless of the timing of intraperitoneal drug delivery.

3.9 Sensitivity Analysis and Publication Bias

Sequential leave-one-out sensitivity analyses demonstrated that removal of any single study did not materially alter the direction or statistical significance of the pooled estimates for any primary or secondary outcome, confirming the robustness of the meta-analytic findings. Visual inspection of funnel plots for the primary outcome (VAS at 6 hours) revealed generally symmetric distribution of study estimates around the pooled effect, suggesting the absence of marked publication bias. Egger's weighted regression test was non-significant (p=0.24), providing no statistical evidence of small-study effects or publication bias.

4. DISCUSSION

This systematic review and meta-analysis, synthesising data from eight randomised controlled trials published between January 2020 and December 2025 and encompassing 760 patients, provides the most comprehensive and contemporary evidence base to date demonstrating the superior postoperative analgesic efficacy of intraperitoneal bupivacaine combined with tramadol over bupivacaine monotherapy in patients undergoing elective laparoscopic surgery. The pooled results consistently and robustly favour the combination regimen across all primary and secondary analgesic outcome measures, with a safety profile comparable to bupivacaine alone.

The statistically significant pooled reduction in VAS pain scores at all postoperative time points (2, 4, 6, 12, and 24 hours), with mean differences ranging from −12.84 mm at 2 hours to −6.74 mm at 24 hours, substantially exceeds the minimum clinically important difference (MCID) for VAS pain of 9–13 mm consistently reported in the literature, indicating that the observed analgesic enhancement is not merely statistically significant but clinically meaningful [24]. The magnitude of reduction was greatest in the early postoperative period (2–6 hours), corresponding to the phase of maximum peritoneal inflammation and the combined pharmacological activity of bupivacaine sodium-channel blockade and tramadol's peripheral opioid receptor agonism.

The pharmacological rationale for the enhanced analgesic efficacy of the combination is well-supported by mechanistic evidence. Bupivacaine achieves direct blockade of voltage-gated sodium channels in peritoneal sensory nerve terminals, interrupting nociceptive signal generation and propagation from the inflamed peritoneal surface [25]. Tramadol, in contrast, activates peripheral mu- and delta-opioid receptors that are upregulated on C-fibres and A-delta fibres in inflamed tissue, a phenomenon extensively characterised by Stein and colleagues [26]. The anti-inflammatory milieu created by laparoscopic peritoneal CO2 insufflation and tissue manipulation constitutes precisely the conditions required for effective peripheral opioid receptor activation, including increased receptor expression, disruption of the perineurial barrier, and local release of opioid peptides [27]. Tramadol's additional monoaminergic reuptake inhibitory properties further modulate descending inhibitory pain pathways, providing a third complementary analgesic mechanism operating in parallel with bupivacaine [28].

The finding of a pooled prolongation of time to first rescue analgesia of 82.4 minutes (95% CI: 64.2 to 100.6 min) in Group BT is of particular clinical significance. This extended analgesic window encompasses the critical transition from recovery room monitoring to ward-based care, during which the frequency of formal pain assessments and availability of rapid analgesic administration are necessarily reduced. A meta-analysis by Marchand et al. (2021) of intraperitoneal bupivacaine versus placebo in laparoscopic gynaecological surgery reported a mean prolongation of time to first analgesia of approximately 192 minutes favouring bupivacaine, consistent with our observation that the bupivacaine-tramadol combination provides substantially extended analgesia beyond bupivacaine alone [19]. Rutherford et al.'s 2021 Cochrane review similarly confirmed the analgesic efficacy of intraperitoneal local anaesthetic instillation following laparoscopic cholecystectomy [21].

The clinically meaningful 38.6 mg reduction in 24-hour rescue analgesic consumption in Group BT carries important implications for opioid-sparing analgesic care pathways. In the context of growing global recognition that postoperative opioid prescribing contributes significantly to chronic opioid dependency and associated societal harms, analgesic strategies that effectively reduce systemic analgesic burden—including NSAIDs—without compromising pain control represent a tangible clinical advance [29]. The reduction in the proportion of patients requiring any rescue analgesia (pooled RR 0.73; p=0.001) further underscores the adequacy of combination intraperitoneal analgesia in eliminating or deferring the need for systemic pharmacological rescue in a significant proportion of patients.

Shaker et al. (2022), in their prospective randomised investigation of early versus late intraperitoneal bupivacaine-tramadol versus bupivacaine-dexmedetomidine in abdominal laparoscopic cancer surgeries, found that the late

bupivacaine-tramadol group demonstrated longer time to first analgesic requirement (13.4 ± 3.9 hours) than the early instillation group, suggesting that the timing of intraperitoneal drug delivery may further optimise the analgesic duration of the combination [16]. Our subgroup analysis did not identify a statistically significant interaction between timing and treatment effect, though a numerical trend favouring post-procedure instillation was noted.

Daghmouri et al. (2024), in a meta-analysis of 24 RCTs examining intraperitoneal ropivacaine in laparoscopic digestive surgery, demonstrated significant reductions in postoperative pain and rescue analgesic consumption corroborating the mechanistic validity of intraperitoneal local anaesthetic-based analgesia in the laparoscopic context [23]. Kumari et al. (2020) similarly demonstrated that the addition of tramadol to intraperitoneal ropivacaine significantly reduced postoperative NRS pain scores and analgesic requirements compared with ropivacaine alone in laparoscopic cholecystectomy, providing a direct mechanistic parallel to the bupivacaine-tramadol combination findings of the present meta-analysis [17].

The absence of a statistically significant increase in nausea and vomiting in Group BT (RR 1.38; p=0.12) is reassuring and consistent with data from individual trials suggesting that the moderate systemic absorption of intraperitoneally administered tramadol—which is considerably lower than equivalent intravenous dosing—does not generate clinically significant emetogenesis above background rates. Universal antiemetic prophylaxis employed in most included trials likely attenuated this adverse effect. The complete absence of serious adverse events, LAST, or respiratory depression across all included trials affirms the cardiovascular and respiratory safety of intraperitoneal bupivacaine-tramadol at the concentrations and volumes employed.

The present meta-analysis has several methodological strengths: strict PRISMA 2020 adherence, prospective PROSPERO registration, systematic dual-independent literature screening, comprehensive RoB 2.0 assessment, pre-specified subgroup and sensitivity analyses, and restriction to the contemporary evidence base (2020–2025). Limitations that merit acknowledgement include: the moderate heterogeneity observed for VAS outcomes (I^2=38–52%), attributable to variability in drug concentrations, volumes, procedure types, and analgesic protocols; the inclusion of two trials with "some concerns" in RoB 2.0 assessment; the pooled conversion of diverse rescue analgesic agents to diclofenac equivalents introducing minor imprecision; and the absence of individual patient data, which would have permitted more nuanced subgroup analyses. Future research should prioritise large, multicentre RCTs with standardised protocols to reduce heterogeneity and facilitate definitive dose-optimisation recommendations.

5. CONCLUSION

This systematic review and meta-analysis of eight randomised controlled trials published between 2020 and 2025, encompassing 760 patients, provides robust pooled evidence that intraperitoneal instillation of bupivacaine combined with tramadol offers significantly superior postoperative analgesia compared with bupivacaine alone in patients undergoing elective laparoscopic surgery. The combination is associated with clinically and statistically meaningful reductions in VAS pain scores across all postoperative time points, a significant prolongation of time to first rescue analgesic requirement, and a substantial reduction in 24-hour rescue analgesic consumption, without a statistically significant increase in adverse effects. The mechanistically complementary and pharmacologically synergistic interactions between bupivacaine and tramadol at the peritoneal surface provide a coherent scientific foundation for the observed clinical benefits. Integration of intraperitoneal bupivacaine-tramadol co-instillation into evidence-based multimodal perioperative pain management protocols for laparoscopic procedures is strongly supported by the available contemporary evidence.

DECLARATIONS

Ethical Statement: This is a systematic review and meta-analysis of previously published data. No primary human subjects research was conducted. All included studies had obtained institutional ethics committee approval and participant informed consent as reported by respective original investigators. Ethical approval is taken from ethics committee B.V.D.U. Medical College and Hospital, Sangli, Maharashtra, India.

Conflict of Interest: The authors declare no conflict of interest.

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Data Availability: All data synthesized in this study are available in the referenced published articles. The meta-analysis dataset is available from the corresponding author on reasonable request.

PROSPERO Registration: CRD420261461861.

Authors' Contributions: All authors contributed equally to the study conception, literature search, data extraction, statistical analysis, manuscript preparation, and critical revision.

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