Volume 4, No. 11 November 2026, pp. 1795-1807
e-ISSN 3031-5786
DOI: https://doi.org/ 10.46799/adv.v4i11.722

ADVANCES IN SOCIAL HUMANITIES RESEARCH

Combined Spinal–General Anaesthesia with Low-Dose Intrathecal Morphine and Atropine for Abdominal Laparoscopy: A Randomised Controlled Trial of Postoperative Nausea, Vomiting and Pain

Weirna Winantiningtyas, Muhammad Sukri Dinihar, Raden Besthadi Sukmono, Pryambodho*
Universitas Indonesia, Indonesia
Email : pry@cbn.net.id*, ww.supriyanto@gmail.com

Keywords:
Atropine; Intrathecal; Laparoscopy; Morphine; Postoperative Nausea and Vomiting; Spinal Anesthesia; Combined anesthesia.

This is an open access article under the CC BY-SA license.

Copyright © 2026 by Author. Published by Publikasiku Publisher

Abstract

Postoperative nausea and vomiting (PONV) and pain remain significant concerns following abdominal laparoscopic surgery. This study compared combined spinal–general anesthesia (CSGA) incorporating low-dose intrathecal morphine and atropine with general anesthesia (GA) alone. A single-center, open-label, randomized controlled trial was conducted in Jakarta, Indonesia, from February to March 2026. Adults undergoing elective abdominal laparoscopic surgery received either CSGA with intrathecal bupivacaine (10 mg), morphine (100 µg), and atropine (100 µg) or GA alone. Both groups received prophylactic ondansetron and multimodal analgesia. Sixty patients were included in the per-protocol analysis, comprising 33 in the CSGA group and 27 in the GA group. The primary outcome was the incidence of PONV within 24 hours postoperatively, while secondary outcomes included pain scores, rescue medication requirements, fentanyl consumption, and hemodynamic parameters. PONV occurred in 6.1% of CSGA patients compared with 74.1% of GA patients ($P < 0.001$), corresponding to an absolute risk reduction of 68.0 percentage points. The CSGA group demonstrated lower pain scores at 6–24 hours, reduced postinduction fentanyl consumption, and decreased requirements for rescue ondansetron. No patients in the CSGA group required rescue morphine, compared with 59.3% in the GA group. Three CSGA patients required vasopressor support. These benefits may have been partially associated with reduced opioid exposure, although a mediating effect was not established. CSGA was associated with improved postoperative symptom control under the study conditions; however, the independent contribution of intrathecal atropine remains uncertain. Larger, blinded, multicenter randomized controlled trials are warranted to confirm efficacy and evaluate safety, particularly potential neurological complications associated with intrathecal atropine administration.

INTRODUCTION

Abdominal laparoscopic surgery involves several well-established risk factors for postoperative nausea and vomiting (PONV), including female sex, volatile anesthetic exposure, pneumoperitoneum, and postoperative opioid administration. Among high-risk patients without adequate prophylaxis, the incidence of PONV may reach 60–75% (Apfel et al., 2012; Gan et al., 2020), while intraoperative and postoperative opioid consumption,

neostigmine administration, and surgical duration have been identified as important independent predictors in gynecologic laparoscopy (Luo et al., 2024). Consensus guidelines recommend multimodal antiemetic prophylaxis tailored to individual risk, commonly assessed using the Apfel score. However, a single dose of a 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonist administered near the end of anesthesia may not provide sufficient protection throughout the postoperative period. Consequently, patients may remain vulnerable to nausea and vomiting during subsequent recovery, particularly between 6 and 12 hours postoperatively, when pain and opioid requirements may increase. The administration of systemic opioids for postoperative analgesia may further contribute to emetic symptoms, creating challenges for effective symptom management.

Neuraxial anesthetic techniques may help address these challenges by reducing the need for intraoperative and early postoperative systemic opioids. Intrathecal morphine provides prolonged postoperative analgesia, potentially lasting 18–24 hours, and its administration before induction of general anesthesia has been associated with reduced perioperative opioid requirements in abdominal laparoscopic surgery (Kumar et al., 2024; Meylan et al., 2009; Zheng et al., 2026). Nevertheless, intrathecal morphine is associated with dose-dependent adverse effects, including nausea, vomiting, and pruritus (Meylan et al., 2009; Renard et al., 2024). Strategies to mitigate these effects include administering lower doses, typically within the 100–150 μg range, as incorporated into selected enhanced recovery protocols (Russo et al., 2026), and investigating adjunctive agents with potential antiemetic properties. Atropine, a tertiary amine and muscarinic acetylcholine receptor antagonist, may influence central cholinergic pathways involved in emetic regulation, including those associated with the area postrema and nucleus tractus solitarius (Pedigo Jr. & Brizzee, 1985). Intrathecal atropine at a dose of 100 μg has been investigated in five randomized controlled trials, including three involving cesarean delivery, one involving perineal surgery, and one involving lower abdominal surgery, all performed under spinal anesthesia alone (Abdalla et al., 2019; Baciarello et al., 2011; Farahat & Abdelhafez, 2019; Soliman et al., 2023; Turai & Rachana, 2019). In a trial incorporating an intravenous comparator, intrathecal atropine was associated with a lower incidence of PONV (15%), whereas intravenous administration did not demonstrate a comparable reduction (37% versus 49% in the placebo group), suggesting a possible route-dependent effect. A 2025 systematic review of these trials reported reductions in PONV without significant differences in postoperative pain, spinal block onset, or hemodynamic parameters, and no serious adverse events were reported (Pramadika et al., 2025). However, these findings do not establish the neurological safety of intrathecal atropine across broader patient populations.

Despite these findings, the potential benefits of intrathecal atropine when spinal anesthesia is combined with general anesthesia (GA) for abdominal laparoscopic procedures remain insufficiently investigated. In this setting, exposure to volatile anesthetics, systemic opioids, and pneumoperitoneum may increase the risk of PONV, while additional perioperative medications may influence postoperative symptoms. The present study therefore compared combined spinal–general anesthesia (CSGA), incorporating intrathecal bupivacaine, morphine (100 μg), and atropine (100 μg), with GA alone in adults undergoing abdominal laparoscopic surgery. The primary outcome was the incidence of PONV within 24 hours postoperatively,

while secondary outcomes included postoperative pain intensity, rescue antiemetic and opioid requirements, intraoperative fentanyl consumption, and perioperative hemodynamic parameters. Particular attention was given to the temporal distribution of postoperative symptoms and serial heart rate measurements to explore potential systemic anticholinergic effects associated with the intrathecal regimen.

Collectively, previous studies have identified an important evidence gap between the established use of neuraxial analgesia in abdominal laparoscopic surgery and investigations of intrathecal atropine as a potential antiemetic adjunct. Luo et al. (2024) examined predictors of PONV without evaluating the combined anesthetic intervention, whereas previous studies of intrathecal morphine in laparoscopic procedures primarily assessed analgesic regimens without atropine. Conversely, Baciarello et al. (2011) investigated intrathecal atropine in cesarean delivery without the additional anesthetic and physiological exposures associated with general anesthesia and abdominal laparoscopy. Consequently, the effectiveness of combining low-dose intrathecal morphine, atropine, and bupivacaine with general anesthesia remains uncertain. Importantly, evaluating this combination against GA alone permits assessment of the overall anesthetic regimen but does not establish the independent contribution of intrathecal atropine or distinguish its effects from those of the other neuraxial medications.

Addressing this research gap is clinically important because effective perioperative anesthetic management requires balancing sustained postoperative analgesia, prevention of PONV, and minimization of treatment-related complications. Although reducing systemic opioid exposure may improve postoperative recovery, the potential risks associated with neuraxial anesthesia, including hypotension and other neurological or hemodynamic complications, must also be considered. Furthermore, evaluating cumulative PONV incidence over 24 hours may overlook clinically relevant differences between immediate postoperative recovery and subsequent ward-based recovery. Repeated assessments of nausea, vomiting, pain intensity, and rescue medication requirements may therefore provide a more comprehensive understanding of postoperative symptom patterns. Conducted at Dr. Cipto Mangunkusumo National General Hospital in Jakarta, Indonesia, this investigation examined these outcomes among adults undergoing elective digestive, gynecologic, and urologic laparoscopic procedures, thereby contributing clinical evidence from a tertiary-care setting.

The novelty of this study lies in evaluating a specific low-dose intrathecal drug combination administered as part of CSGA across multiple categories of abdominal laparoscopic surgery. The intervention incorporated intrathecal bupivacaine (10 mg), morphine (100 μg), and atropine (100 μg) before the induction of general anesthesia, with postoperative outcomes assessed over 24 hours. Beyond comparing the cumulative incidence of PONV, the study examined postoperative pain trajectories, rescue antiemetic and opioid requirements, intraoperative fentanyl consumption, and perioperative hemodynamic responses. These complementary measures were intended to determine whether improvements in postoperative symptom control were accompanied by reduced systemic opioid exposure or clinically relevant circulatory changes. Accordingly, the investigation extended the clinical context of previous research while recognizing that the effects of individual intrathecal agents could not be independently determined from the study design.

Accordingly, this randomized controlled trial aimed to compare CSGA incorporating low-dose intrathecal morphine and atropine with GA alone in adults undergoing elective abdominal laparoscopic surgery. The primary objective was to determine whether the combined anesthetic regimen reduced the incidence of PONV within 24 hours postoperatively. Secondary objectives included evaluating postoperative pain intensity, rescue antiemetic and opioid requirements, intraoperative fentanyl consumption, and perioperative hemodynamic outcomes. The study sought to provide context-specific evidence regarding the balance between postoperative symptom control and the physiological consequences of incorporating neuraxial anesthesia into general anesthetic management. Its findings were intended to inform the design of future comparative trials, contribute to the refinement of multimodal perioperative management strategies, and support clinical decision-making regarding approaches aimed at improving postoperative patient comfort while minimizing systemic opioid requirements.

METHOD

Design and ethics

This single-center, open-label, parallel-group randomized controlled trial was conducted at the integrated surgical unit of Dr. Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia, from February to March 2026. Ethical approval was obtained from the Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia/Dr. Cipto Mangunkusumo National General Hospital (No. KET-1754/UN2.F1/ETIK/PPM.00.02/2025), and written informed consent was obtained from all participants. The trial was retrospectively registered at ClinicalTrials.gov (NCT07851870) and reported in accordance with the CONSORT 2010 guidelines (Schulz et al., 2010).

Participants

Adults aged 18–64 years with ASA physical status I–II and body mass index (BMI) ≤ 30 kg/m² scheduled for elective digestive, gynaecological or urological laparoscopy were eligible. Exclusion criteria were uncontrolled stage 2 hypertension, heart failure or arrhythmia, valvular disease or atrioventricular block, cerebrovascular disease within 3 months, raised intracranial pressure, severe renal or hepatic disease, coagulopathy and infection at the puncture site. Participants were withdrawn for anaesthesia lasting longer than 6 h, conversion to laparotomy, intraoperative emergency, failed spinal after two attempts or a serious complication of spinal anaesthesia. Chronic opioid use was not an exclusion criterion; one patient receiving oral morphine for cancer pain was enrolled.

Randomisation

Patients were recruited consecutively and allocated 1:1 by a computer-generated random sequence (www.randomizer.org) prepared by the investigator. Allocation was revealed to the anaesthesia team on the day of surgery. Given the nature of the intervention, neither the anaesthesia team nor the outcome assessors were blinded.

Anaesthetic management

All patients received ranitidine 50 mg IV in the operating room and crystalloid 10 mL/kg before induction. In the CSGA group, spinal anaesthesia was performed in the sitting position at L4–5 with a 27-G Quincke needle (B. Braun), using 0.5% hyperbaric bupivacaine 10 mg (2 mL), preservative-free morphine 100 μg (0.1 mL of 1 mg/mL) and atropine sulphate

100 µg (0.4 mL of 0.25 mg/mL) made up to 4 mL with 0.9% saline, injected at 0.2 mL/s with the bevel cephalad. Patients were then positioned supine and the table adjusted to obtain a T6 sensory level to pinprick within 15 min. Systolic pressure < 90 mmHg was treated with crystalloid co-loading 15 mL/kg and phenylephrine 50–100 µg boluses (ephedrine 5 mg if phenylephrine was unavailable); heart rate < 50 beats/min was treated with atropine 0.5 mg IV.

Both groups then underwent GA induced with lidocaine 1.5 mg/kg, fentanyl 2 µg/kg, propofol 2 mg/kg and rocuronium 0.6 mg/kg, followed by tracheal intubation. Anaesthesia was maintained with sevoflurane 2 vol% (target MAC 0.8) in oxygen–air, with rocuronium 10 mg every 20 min. A rise in mean arterial pressure (MAP) or heart rate of more than 20% above baseline for longer than 1 min was managed first by increasing sevoflurane to 2–3 vol% and, if it persisted, by fentanyl 25–50 µg boluses; total post-induction fentanyl was recorded. Paracetamol 1 g and ketorolac 30 mg IV were given at skin closure and ondansetron 4 mg IV at the end of anaesthesia in both groups. Neuromuscular block was reversed with neostigmine 0.04 mg/kg and atropine 0.02 mg/kg, and patients were extubated awake. MAP and heart rate were recorded before induction, after the spinal (CSGA only), at insufflation, after insufflation, after desufflation and after extubation.

Outcomes

The primary outcome was the occurrence of PONV within 24 h, defined as a score ≥ 1 on a 5-point Analogue Visual Scale (0 = none; 1 = nausea < 10 min or one vomit, no treatment; 2 = nausea > 10 min or two vomits, no treatment; 3 = nausea > 10 min or > 2 vomits requiring treatment; 4 = refractory to treatment), assessed at 1 h in the recovery room and at 2, 6, 12 and 24 h on the ward. PONV was treated with ondansetron 4 mg IV. Secondary outcomes were pain on an 11-point Numeric Rating Scale (NRS) at 2, 6, 12 and 24 h; rescue morphine 2 mg IV for NRS > 6; rescue ondansetron; post-induction fentanyl; and haemodynamic variables. The Apfel score was recorded pre-operatively.

Sample size and statistics

Assuming PONV incidences of 75% with GA and 40% with CSGA ($\alpha = 0.05$, power 80%), 27 patients per group were required; 30 per group were recruited to allow for 10% attrition. A parallel calculation for a 1-point NRS difference (SD 1.15) required 22 per group. Analysis was per protocol. Continuous data are presented as mean ± SD or median [IQR] and compared by t-test or Mann–Whitney U test; categorical data were compared by chi-square or Fisher's exact test. The primary outcome is reported as a risk difference with 95% CI and number needed to treat (NNT). Logistic and linear regression were used to adjust the group effect for Apfel score, post-induction fentanyl and rescue morphine. Analyses were performed in SPSS (IBM, Armonk, NY) and Python 3.11; two-sided $P < 0.05$ was considered significant.

RESULTS AND DISCUSSION

Of 71 patients assessed, 63 were randomised (CSGA 33, GA 30). Three GA patients were withdrawn after conversion to laparotomy, leaving 60 for analysis (Figure 1). No spinal failed or needed repeating.

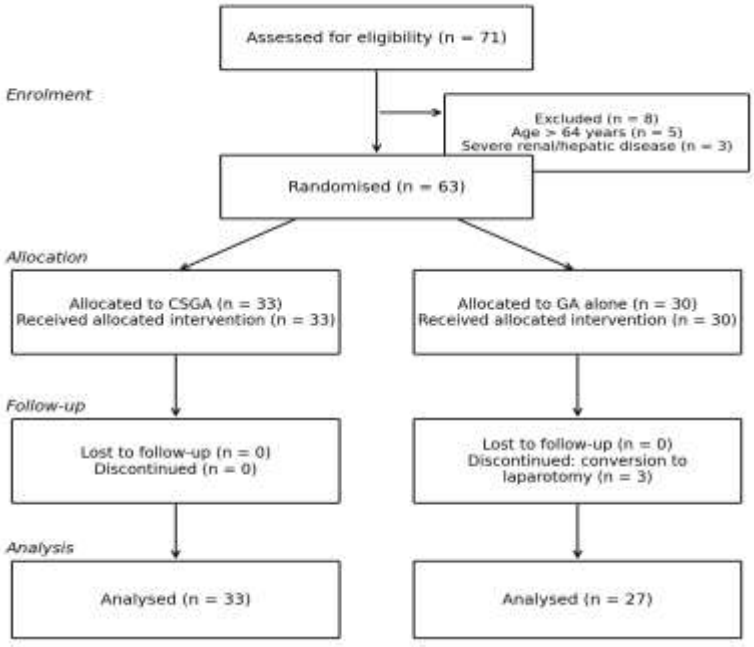


Figure 1. CONSORT flow diagram

Baseline and surgical characteristics were comparable (Table 1). Apfel scores ≥ 3 were more frequent in the CSGA group (5/33 vs 1/27). Post-induction fentanyl was lower with CSGA (median 0 [0–25] vs 75 [50–100] µg; P < 0.001); 20 of 33 CSGA patients received no fentanyl after induction, compared with 2 of 27 GA patients.

Table 1. Baseline and intraoperative characteristics

Characteristic	CSGA (n = 33)	GA (n = 27)	P
Age, years, mean ± SD	43.1 ± 12.2	41.3 ± 13.4	0.59
Female, n (%)	22 (66.7)	20 (74.1)	0.53
BMI, kg/m², mean ± SD	24.8 ± 5.5	26.2 ± 5.3	0.31
ASA I / II, n	2 / 31	1 / 26	1.00
Apfel score 0 / 1 / 2 / 3 / 4, n	4 / 7 / 17 / 4 / 1	6 / 1 / 19 / 1 / 0	0.21†
Surgery: digestive / gynaecological / urological, n	14 / 13 / 6	12 / 12 / 3	0.77
Duration of surgery, min, median	165	160	0.93
Duration of anaesthesia, min, median	255	220	0.53
Post-induction fentanyl, µg, median [IQR]	0 [0–25]	75 [50–100]	< 0.001
No post-induction fentanyl, n (%)	20 (60.6)	2 (7.4)	< 0.001

Postoperative nausea and vomiting

PONV within 24 h occurred in 2/33 (6.1%) CSGA and 20/27 (74.1%) GA patients (risk difference 68.0%, 95% CI 49.6–86.4; P < 0.001; NNT 1.5). The effect was time-dependent (Table 2). At 2 h PONV was infrequent in both groups (0 vs 4; P = 0.036). At 6 h the groups separated sharply (2/33 vs 19/27; P < 0.001), the difference persisted at 12 h (0 vs 9; P < 0.001), and by 24 h no patient in either group was symptomatic. Both CSGA events occurred at 6 h in women with an Apfel score of 3 undergoing gynaecological laparoscopy lasting ≥ 270 min, and both resolved with a single dose of ondansetron. Rescue ondansetron was required by 2/33 vs 17/27 patients (P < 0.001); 14 of the 17 GA doses were given at the 6-h assessment. In the

GA group, PONV occurred in 11/12 gynaecological, 6/12 digestive and 3/3 urological cases, and in all 8 patients whose surgery exceeded 4 h.

Table 2. PONV, rescue medication and pain by time point

	2 h	6 h	12 h	24 h	Cumulative 0–24 h
PONV, CSGA / GA, n (%)	0 (0) / 4 (14.8)	2 (6.1) / 19 (70.4)	0 (0) / 9 (33.3)	0 / 0	2 (6.1) / 20 (74.1)
P (Fisher)	0.036	< 0.001	< 0.001	–	< 0.001
Rescue ondansetron, CSGA / GA, n	0 / 4	2 / 14	0 / 1	0 / 0	2 / 17
NRS, median [IQR], CSGA	0 [0–1]	1 [0–2]	1 [0–1]	0 [0–0]	max 1 [1–2]
NRS, median [IQR], GA	0 [0–1]	6 [5–6.5]	3 [3–4]	2 [1–3]	max 6 [5–7]
P (Mann–Whitney)	0.48	< 0.001	< 0.001	< 0.001	< 0.001
Rescue morphine 2 mg, CSGA / GA, n	0 / 3	0 / 15	0 / 4	0 / 0	0 / 16

Pain and rescue analgesia

NRS did not differ at 2 h (median 0 [0–1] in both groups; P = 0.48) but was lower with CSGA at 6 h (1 [0–2] vs 6 [5–6.5]), 12 h (1 [0–1] vs 3 [3–4]) and 24 h (0 [0–0] vs 2 [1–3]) (all P < 0.001). Maximum 24-h NRS was 1 [1–2] vs 6 [5–7]. No CSGA patient reported NRS > 6 at any time and five reported NRS 0 throughout; 23/27 GA patients had NRS ≥ 4 at 6 h. Rescue morphine was given to 0/33 vs 16/27 (59.3%) patients (P < 0.001), with 15 of the 16 first doses given at 6 h. In the GA group, 16 of the 19 patients with PONV at 6 h had a concurrent NRS ≥ 5, and 12 of the 20 patients with PONV received rescue morphine within the same 24 h.

Haemodynamics

After the intrathecal injection, MAP fell by 15.0 ± 10.5 mmHg (range −36 to +7); 10/33 patients had a decrease of more than 20% and two had MAP < 65 mmHg. Heart rate fell by 8.8 ± 12.5 beats/min (range −41 to +19); two patients had a rate below 60 and none below 50 beats/min. Three CSGA patients required a vasopressor (phenylephrine n = 2; norepinephrine infusion n = 1) versus none with GA. The heart-rate change at insufflation relative to pre-induction was the same in both groups (−7.7 ± 15.9 vs −6.1 ± 10.7 beats/min; P = 0.85), and no patient in either group reached a rate below 50 beats/min at any measurement. After extubation, heart rate remained lower with CSGA (81.8 ± 10.0 vs 88.8 ± 12.4 beats/min; P = 0.019), with a similar trend in MAP (85.2 ± 11.7 vs 90.4 ± 9.2 mmHg; P = 0.060) (Table 3).

Table 3. Haemodynamic variables (mean ± SD)

Time point	MAP, CSGA	MAP, GA	HR, CSGA	HR, GA
Pre-induction	98.8 ± 13.5	95.1 ± 16.1	87.2 ± 12.9	86.3 ± 14.3
After spinal (CSGA only)	83.8 ± 12.0 (Δ −15.0 ± 10.5)	–	78.4 ± 12.9 (Δ −8.8 ± 12.5)	–
At insufflation	84.5 ± 12.7	90.2 ± 14.2	79.5 ± 14.2	80.2 ± 16.6
After insufflation	87.1 ± 14.1	93.6 ± 12.0	77.4 ± 11.8	81.6 ± 13.6
After desufflation	83.0 ± 10.5	85.6 ± 10.3	76.9 ± 11.9	81.2 ± 12.6
After extubation	85.2 ± 11.7	90.4 ± 9.2	81.8 ± 10.0*	88.8 ± 12.4
MAP < 65 mmHg at any time, n	2	0		
HR < 50 beats/min at any time, n	0	0		
Vasopressor required, n	3	0		

*P < 0.05 vs GA (t-test). MAP in mmHg; HR in beats/min.

Adjusted analyses

The odds of PONV with GA relative to CSGA rose after adjustment for Apfel score (OR 133.6, 95% CI 15.0–1191) and fell after post-induction fentanyl (OR 61.0, 6.0–622.5) and rescue morphine (OR 56.3, 4.5–706.6) were added. For maximum NRS, the group coefficient fell from 4.25 (95% CI 3.39–5.12) to 3.27 (2.20–4.35) after adjustment for fentanyl and to 1.70 (0.70–2.71) after rescue morphine was added (Table 4). Both patterns are consistent with partial mediation through opioid exposure.

Table 4. Regression models for the effect of GA (reference: CSGA)

Model	PONV, OR (95% CI)	Maximum NRS, β (95% CI)
Unadjusted	44.3 (8.3–235)	4.25 (3.39–5.12)
+ Apfel score	133.6 (15.0–1191)	–
+ Post-induction fentanyl	61.0 (6.0–622.5)	3.27 (2.20–4.35)
+ Rescue morphine	56.3 (4.5–706.6)	1.70 (0.70–2.71)

Covariates were added sequentially. The NRS models were adjusted for fentanyl and rescue morphine without Apfel score.

The opioid-tolerant patient

The single patient with an Apfel score of 4, a woman receiving oral morphine for cancer pain who underwent laparoscopic nephrectomy in the CSGA group, had no PONV and required no rescue analgesia, although her NRS trajectory (1, 5, 4, 2) was the highest in her group. She was haemodynamically stable throughout.

Adding a low-dose spinal with morphine 100 μg and atropine 100 μg before GA for abdominal laparoscopy reduced 24-h PONV from 74% to 6%, abolished the need for rescue morphine and allowed most patients to go through surgery without any fentanyl after induction. Three features of these data deserve attention beyond the headline effect.

The first is that the benefit is a 6–12 h phenomenon. At 2 h both groups were almost symptom-free and pain scores were identical; the entire separation in PONV and pain emerged at 6 h and had resolved by 24 h. Two hours after extubation, every patient was still within the effective window of end-of-case ondansetron, the intravenous atropine given with neostigmine, residual fentanyl and the closure-time paracetamol–ketorolac. Six hours later those single systemic doses had dissipated and the GA group showed a synchronous peak in pain (23/27 with NRS ≥ 4), rescue morphine (15 first doses) and PONV (19/27), with 16 of the 19 nauseated patients in NRS ≥ 5 pain at the same assessment. The adjusted models confirm what this pattern suggests: a substantial part of the group effect on PONV ran through opioid exposure. Emesis in the GA arm was to a large degree rescue-opioid emesis, and the CSGA regimen prevented it chiefly by making the opioid unnecessary. Guidelines rightly recommend layering prophylaxis by risk,2 but our data argue that in laparoscopy the more decisive intervention is to close the analgesic gap that generates the opioid requirement in the first place. Meta-analyses of opioid-free anaesthesia point the same way: removing the intraoperative opioid lowers the odds of PONV by about three-quarters in gynaecological laparoscopy17 and reduces early pain and analgesic consumption across laparoscopic procedures.18 An NNT of 1.5 for PONV is far

beyond what any antiemetic achieves; it is the effect of removing the emetogen (Alcalay et al., 1992; Ali-Melkkilä et al., 1991; Ho et al., 2005).

The second is that intrathecal atropine at 100 µg left no haemodynamic footprint. Heart rate fell after the spinal by a mean of 9 beats/min, as expected from sympathetic blockade alone; the chronotropic response to pneumoperitoneum was identical in the two groups; and after extubation heart rate was lower, not higher, in the CSGA group, even after every patient had received a further 0.02 mg/kg intravenously at reversal. This is unsurprising on pharmacological grounds. Systemic atropine below 0.4 mg is vagomimetic rather than vagolytic, and tachycardia appears only from about 0.5 mg, so the heart-rate data confirm the absence of a clinically relevant systemic anticholinergic effect but cannot by themselves locate where the drug acted. The systematic review reached the same conclusion on safety, with no haemodynamic signal across 242 treated patients. The evidence for a route-specific central action comes instead from Baciarello et al., who found the same 100 µg effective intrathecally but not intravenously, and from the anatomy: the area postrema and nucleus tractus solitarius lie at the floor of the fourth ventricle, within reach of a drug carried rostrally in cerebrospinal fluid. The reverse experiment supports the same reading: intrathecal neostigmine, a cholinergic agonist, produces nausea with an odds ratio of 5 and bradycardia requiring atropine (Nelson et al., 2026; Pan et al., 1999), and in a multicentre analysis of gynaecological laparoscopy the use of neostigmine at reversal was an independent predictor of PONV. Our trial adds one observation the spinal-only trials could not make. Every patient in both arms received intravenous atropine at reversal, and it did not protect the GA arm. Protection was specific to the arm that received atropine, and morphine, intrathecally (Bianchi et al., 2026; Song et al., 2026).

The third is that the contribution of atropine cannot be isolated, and we do not claim it. Opioid sparing, dense neuraxial analgesia and a putative central anticholinergic action are confounded in this design, as they are in every published trial of the adjuvant; none has compared intrathecal morphine with and without atropine under otherwise identical conditions (Cheng et al., 2025; Xu et al., 2025). The animal literature adds a caution in the other direction: intrathecal atropine at microgram doses abolishes spinal cholinergic analgesia in rats, a theoretical reason to keep the human dose minimal and not to expect an analgesic benefit. None has been found. The definitive test is a three-arm trial of CSGA with intrathecal morphine alone versus morphine plus atropine versus GA alone, powered for the 6–12 h window.

Two further observations are hypothesis-generating. First, both CSGA failures were long (≥ 270 min) gynaecological procedures in Apfel-3 women, and in the GA arm every operation exceeding 4 h produced PONV. Duration of surgery appears to be the residual risk that a single-shot neuraxial technique does not cover, and a second prophylactic dose at 6 h might be considered for such cases. Second, the opioid-tolerant patient with cancer pain, a group usually excluded from PONV trials, obtained complete PONV protection but the least analgesia in the CSGA group, as would be expected from reduced sensitivity to 100 µg intrathecal morphine. Her Apfel point for "postoperative opioids" was in fact assigned for pre-existing opioid use, an ambiguity in the score worth noting.

The haemodynamic cost of the technique was modest but real: 10 of 33 patients had a fall in MAP of more than 20% after the spinal and three required a vasopressor, compared with

none under GA alone. Heart rate remained lower in the CSGA group through extubation, with a similar trend in blood pressure. In a population screened for cardiovascular disease this was managed without difficulty, but it is the price of the sympathectomy and should be weighed in frailer patients. Against it stands a profile that fits enhanced-recovery goals for laparoscopy:23 61% of CSGA patients received no opioid after induction, none received rescue morphine and five reported no pain at any assessment in 24 h.

Our findings are consistent with earlier comparisons of spinal anaesthesia added to general anaesthesia for laparoscopic surgery,24 and with the analgesic and adverse-effect profile of intrathecal morphine described in meta-analyses.4,7,25 They extend that literature in three ways. The adjuvant was applied within a combined technique rather than under spinal-only anaesthesia; the antiemetic effect persisted through 12 h despite volatile anaesthesia, pneumoperitoneum and systemic atropine in both arms; and the serial heart-rate data confirm that the dose carries no systemic chronotropic cost, even on top of intravenous atropine at reversal.

Limitations

The trial was open-label with unblinded outcome assessors, single-centre, and analysed per protocol after three post-randomisation withdrawals in the GA arm; a 1:1 sequence yielded unequal groups (33 vs 27). Registration was retrospective. The comparator received no neuraxial analgesia, so the pain result was expected; the informative comparator, intrathecal morphine without atropine, was not included. Rescue morphine was triggered at NRS > 6, a higher threshold than many protocols use, which may have understated opioid need in the GA arm. Sedation, dry mouth and pruritus, the side effects reported with intrathecal atropine elsewhere, were not systematically recorded. The 100 μg dose was inherited from prior trials without dose-finding. Intrathecal atropine is an off-label use for which formal neurotoxicity data do not exist; a preservative-free preparation was used and this should be a condition of any replication. Finally, the observation windows (2, 6, 12, 24 h) were too coarse to locate the onset of the 6-h separation precisely; a time-to-first-PONV design would do so.

CONCLUSION

Combined spinal–general anesthesia incorporating intrathecal bupivacaine, low-dose morphine, and atropine was associated with a lower incidence of postoperative nausea and vomiting (PONV) and improved postoperative analgesia compared with general anesthesia alone in adults undergoing abdominal laparoscopic surgery. Within 24 hours, PONV occurred in 6.1% of patients receiving the combined regimen compared with 74.1% receiving general anesthesia alone, with the greatest difference observed between 6 and 12 hours postoperatively. The combined regimen was also associated with reduced postinduction fentanyl consumption, lower pain scores between 6 and 24 hours, and no requirement for rescue morphine in the analyzed patients. However, reductions in blood pressure following spinal anesthesia were observed, and three patients required vasopressor support. Although these findings suggest potential clinical benefits, the open-label design, small single-center sample, and per-protocol analysis limited the certainty and generalizability of the results. Furthermore, the independent contribution of intrathecal atropine could not be established from the study design.

Future research should prioritize prospectively registered, adequately powered, multicenter randomized controlled trials incorporating blinded outcome assessment and intention-to-treat analysis. A three-arm design comparing general anesthesia alone, combined spinal–general anesthesia with intrathecal morphine, and the same combined technique with additional intrathecal atropine could help distinguish the effects of neuraxial analgesia from the specific contribution of atropine. Standardized, risk-adjusted multimodal PONV prophylaxis and postoperative analgesic protocols should be applied across treatment groups. More frequent postoperative symptom assessments and accurate documentation of rescue medication administration could further clarify the temporal relationships among pain intensity, systemic opioid exposure, and PONV. Additional investigations should evaluate optimal dosing and systematically monitor respiratory depression, pruritus, sedation, urinary retention, anticholinergic adverse effects, and neurological complications, particularly given the off-label intrathecal administration of atropine and the limited evidence regarding its neurological safety.

FUNDING

This research was self-funded by the author, without any financial support, grants, or sponsorship from any other party.

CONFLICT OF INTEREST

None declared. No external funding was received; the study was supported by departmental resources.

AUTHOR CONTRIBUTION

WW: manuscript drafting, data re-analysis, interpretation, co-corresponding author. MSD: concept, protocol, data collection, statistical analysis, first draft of the thesis. RBS: supervision, protocol review, critical revision. P: supervision, study design, critical revision, corresponding author. All authors approved the final manuscript.

GENERATIVE ARTIFICIAL INTELLIGENCE USAGE STATEMENT

In preparing this manuscript, the author used Artificial Intelligence (AI) in a limited capacity, solely to check grammar and refine language use. AI was not involved in any way in data collection, substantive analysis, or the drawing of the study's conclusions.

REFERENCES

Abdalla, E., Kamel, E. Z., & Farrag, W. S. (2019). Intravenous dexamethasone combined with intrathecal atropine to prevent morphine-related nausea and vomiting after cesarean delivery: a randomized double-blinded study. *Egyptian Journal of Anaesthesia*, *35*(1), 65–70. https://doi.org/10.1080/11101849.2019.1636497

Alcalay, M., Izraeli, S., Wallach-Kapon, R., Tochner, Z., Benjamini, Y., & Akselrod, S. (1992). Paradoxical pharmacodynamic effect of atropine on parasympathetic control: a study by spectral analysis of heart rate fluctuations. *Clinical Pharmacology & Therapeutics*, *52*(5), 518–527. https://doi.org/10.1038/clpt.1992.180

Ali-Melkkilä, T., Kaila, T., Antila, K., Halkola, L., & Iisalo, E. (1991). Effects of glycopyrrolate and atropine on heart rate variability. *Acta Anaesthesiologica Scandinavica*, *35*(5), 436–441. https://doi.org/10.1111/j.1399-6576.1991.tb03324.x

Apfel, C. C., Heidrich, F. M., Jukar-Rao, S., Jalota, L., Hornuss, C., & Whelan, R. P. (2012).

Evidence-based analysis of risk factors for postoperative nausea and vomiting. *British Journal of Anaesthesia*, *109*(5), 742–753. https://doi.org/10.1093/bja/aes276

Baciarello, M., Cornini, A., Zasa, M., Pedrona, P., Scrofani, G., & Venuti, F. S. (2011). Intrathecal atropine to prevent postoperative nausea and vomiting after Cesarean section: a randomized, controlled trial. *Minerva Anestesiologica*, *77*(8), 781–788.

Bianchi, E., Seidl, A., Krombholz, E., Frey, M. C., Obrecht, I., & Hasler-Gehrer, S. (2026). Spinal anesthesia in laparoscopic colorectal surgery: analgesia and recovery outcomes, a cohort study and systematic review of randomized controlled studies. *Langenbeck's Archives of Surgery*. https://doi.org/10.1007/s00423-026-04152-w

Cheng, L., Liu, J., Qin, S., Geng, X., Jing, L., & Fang, S. (2025). Safety and effectiveness of multimodal opioid-free anaesthesia for pain and recovery after laparoscopic surgery: a systematic review and meta-analysis. *BMJ Open*, *15*(3), e085988. https://doi.org/10.1136/bmjopen-2024-085988

Farahat, T. E. M., & Abdelhafez, M. S. (2019). Intrathecal atropine versus intravenous metoclopramide for prevention of nausea and vomiting during cesarean section under spinal anesthesia. *Research and Opinion in Anesthesia and Intensive Care*, *6*(4), 393–398.

Gan, T. J., Belani, K. G., Bergese, S., Chung, F., Diemunsch, P., & Habib, A. S. (2020). Fourth consensus guidelines for the management of postoperative nausea and vomiting. *Anesthesia & Analgesia*, *131*(2), 411–448. https://doi.org/10.1213/ANE.0000000000004833

Ho, K. M., Ismail, H., Lee, K. C., & Branch, R. (2005). Use of intrathecal neostigmine as an adjunct to other spinal medications in perioperative and peripartum analgesia: a meta-analysis. *Anaesthesia and Intensive Care*, *33*(1), 41–53. https://doi.org/10.1177/0310057X0503300107

Kumar, L., Anantharaman, R., Thomas, D. E., Nair, A. S., Kartha, A. P., & Kumar, K. (2024). Evaluation of the analgesic efficacy of a low dose of intrathecal morphine in laparoscopic abdominal surgery: a randomised control trial. *Journal of Minimal Access Surgery*, *22*(3), 261–267. https://doi.org/10.4103/jmas.jmas_141_24

Luo, D., Huang, Z., Tang, S., Cheng, J., Deng, Y., & Zhang, X. (2024). Risk analysis of postoperative nausea and vomiting in patients after gynecologic laparoscopic surgery. *BMC Anesthesiology*, *24*(1), 345. https://doi.org/10.1186/s12871-024-02727-y

Meylan, N., Elia, N., Lysakowski, C., & Tramèr, M. R. (2009). Benefit and risk of intrathecal morphine without local anaesthetic in patients undergoing major surgery: meta-analysis of randomized trials. *British Journal of Anaesthesia*, *102*(2), 156–167. https://doi.org/10.1093/bja/aen368

Nelson, G., Altman, A. D., Metcalfe, A., Fotopoulou, C., Taylor, J., & Glaser, G. (2026). Enhanced recovery after surgery (ERAS) society guidelines for gynecologic oncology: 2026 update. *Gynecologic Oncology*, *210*, 153–173. https://doi.org/10.1016/j.ygyno.2026.05.022

Pan, H. L., Chen, S. R., & Eisenach, J. C. (1999). Intrathecal clonidine alleviates allodynia in neuropathic rats: interaction with spinal muscarinic and nicotinic receptors. *Anesthesiology*, *90*(2), 509–514. https://doi.org/10.1097/00000542-199902000-00027

Pedigo Jr., N. W., & Brizzee, K. R. (1985). Muscarinic cholinergic receptors in area postrema and brainstem areas regulating emesis. *Brain Research Bulletin*, *14*(2), 169–177. https://doi.org/10.1016/0361-9230(85)90076-0

Pramadika, T., Mochamat, Nurcahyo, W. I., Wicaksono, S. A., Saputra, T., & Manapa, C. H. (2025). Intrathecal atropine as an adjuvant in spinal anesthesia: a systematic review of efficacy and safety. *Anaesthesia, Pain & Intensive Care*, *29*(7), 796–807. https://doi.org/10.35975/apic.v29i7.2947

Renard, Y., El-Boghdadly, K., Rossel, J. B., Nguyen, A., Jaques, C., & Albrecht, E. (2024). Non-pulmonary complications of intrathecal morphine administration: a systematic review and meta-analysis with meta-regression. *British Journal of Anaesthesia*, *133*(4), 823–838. https://doi.org/10.1016/j.bja.2024.05.045

Russo, A., Perelli, F., Aceto, P., Arcieri, M., Bernardini, F., & Pregnolato, S. (2026). Intrathecal morphine dose optimization in robotic-assisted laparoscopic hysterectomy: a dual-center cohort study. *Journal of Robotic Surgery*, *20*(1). https://doi.org/10.1007/s11701-026-03445-y

Schulz, K. F., Altman, D. G., Moher, D., & Group, C. (2010). CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ*, *340*, c332. https://doi.org/10.1136/bmj.c332

Soliman, F. I., Mousa, E. A., Ahmed, S. M., & Hassan, A. H. (2023). Intrathecal atropine versus preoperative intravenous ondansetron for prevention of postoperative nausea and vomiting due to intrathecal morphine in perineal surgery. *Research and Opinion in Anesthesia and Intensive Care*, *10*(3). https://doi.org/10.4103/roaic.roaic_24_23

Song, M., Hu, H., Jiang, L., & Wei, J. (2026). Comparative efficacy of regional analgesic interventions in open versus laparoscopic hepatic surgery: a network meta-analysis. *Journal of Pain Research*, *19*, 577411. https://doi.org/10.2147/JPR.S577411

Turai, A., & Rachana, P. P. (2019). A clinical study to evaluate the effect of intrathecal atropine on postoperative nausea and vomiting in patients receiving intrathecal morphine and hyperbaric bupivacaine for spinal anaesthesia: prospective randomized trial. *Karnataka Anaesthesia Journal*, *17*(Suppl), 1–2.

Xu, P., Hu, Z., & Chen, J. (2025). The effect of opioid-free anaesthesia on pain and prognosis in gynaecological laparoscopic surgery: a systematic review and meta-analysis. *Journal of Obstetrics and Gynaecology*, *45*(1), 2583014. https://doi.org/10.1080/01443615.2025.2583014

Zheng, L., Lu, Y., Lu, X., You, L., Yu, C., & Lai, J. (2026). Intrathecal morphine for enhanced recovery after laparoscopic colorectal surgery: a randomized clinical trial. *JAMA Surgery*, *161*(2), 124–131. https://doi.org/10.1001/jamasurg.2025.5699