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Original Research Article

Dose-Response Study of Epidural Morphine for Postoperative Analgesia in Thoraco-abdominal Surgery

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Abstract

Introduction: Effective postoperative pain management is essential after thoraco-abdominal surgery to improve patient comfort, reduce pulmonary complications, and facilitate early mobilization. Epidural Morphine is widely used for postoperative analgesia because of its prolonged duration of action and superior Pain relief. However, the optimal dose that provides effective analgesia with minimal side effects remains Uncertain.

Aims and Objectives: To evaluate the dose-response relationship of epidural morphine for postoperative analgesia in patients undergoing thoraco-abdominal surgery and to determine the optimal effective dose with minimal adverse effects using Visual Analogue Scale (VAS):

- Duration of postoperative analgesia.
- Time to first rescue analgesic requirement.
- Total postoperative rescue analgesic consumption within the first 48 hours.
- Assess the level of sedation using the Modified Ramsay Sedation Score.
- Incidence of opioid-related adverse effects**.**

Material and Methods: This prospective randomized study included 60 adult patients of American Society of Anesthesiologists (ASA) physical status I, II and III scheduled for elective thoraco-abdominal surgery under General anesthesia with epidural analgesia. Patients were randomly divided into two groups of 30 each. Group A received epidural morphine 1.5 mg and Group B received 3 mg at the end of surgery through the epidural catheter. Postoperative pain was assessed using the Visual Analogue Scale (VAS) at 2,8,16 and 24 hours. Duration of analgesia, requirement of rescue analgesics, hemodynamic parameters and respiratory depression, nausea, vomiting and sedation scores were recorded and compared among the groups.

Results: Patients receiving higher doses of epidural morphine demonstrated prolonged duration of analgesia and lower VAS scores. Group B showed the longest duration of analgesia but had a higher incidence of side effects such as nausea, vomiting and sedation. Group A provided satisfactory analgesia with fewer complications compared to Group B.

Conclusion: Epidural morphine is effective for postoperative analgesia following thoraco-abdominal Surgery. A dose of 1.5 mg appears to provide an optimal balance between adequate analgesia and minimal Adverse effects.

Keywords: Epidural Morphine; Dose-Response Relationship; Postoperative Analgesia; Thoraco-abdominal Surgery; Analgesics (Opioid). Epidural Morphine Dose-Response.

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Introduction

Thoraco-abdominal interventions generate profound post-procedural discomfort secondary to extensive surgical incisions spanning both chest wall and abdominal structures. [14, 15] Suboptimal

pain attenuation may critically degrade ventilatory mechanics, reduce cough force, precipitate alveolar collapse (atelectasis), impede early mobilization, and prolong hospital admission. [10, 17, 18] Epidural analgesia stands out as an exceptionally dependable modality for counteracting acute discomfort following major trunk interventions. [3, 11, 19] Among various neuraxial opioids, morphine is preferred due to its hydrophilicity, prolonged elimination half-life from spinal fluid, and dependable segmental coverage. [1, 5, 6]

Nonetheless, epidurally administered morphine can cause dose-dependent untoward events, including delayed respiratory compromise, nausea, emesis, urinary retention, and excessive lethargy. [7, 9, 13] Consequently, identifying a dosing regimen that balances maximal analgesic yield against undesirable clinical sequelae is of critical importance. [8, 20] Because earlier clinical literature exhibits considerable discrepancy regarding the ideal neuraxial morphine dose for surgical pain relief [8, 9, 16], this clinical investigation was designed to systematically establish the dose-response profile of epidural morphine in patients undergoing thoraco-abdominal operations to establish an optimal, well-tolerated dosage.

Aim and Objectives

Aim: To delineate the dose-response characteristics of epidural morphine administered for postoperative analgesia in thoraco-abdominal surgical cohorts and establish an effective, well-tolerated dosing strategy.

Objectives:

Primary objective: To contrast the analgesic efficacy between differing doses of epidural morphine by assessing postoperative pain intensities with the Visual Analogue Scale (VAS).

Secondary objectives:

- To contrast the overall duration of pain relief provided across the study groups.
- To quantify the elapsed time until the first rescue analgesic intervention is requested.
- To evaluate total rescue analgesic utilization throughout the initial 24 postoperative hours.
- To determine patient sedation scores according to the Modified Ramsay Sedation Scale.
- To track and compare the incidence of opioid-related side effects.
- To monitor perioperative vitals (heart rate, arterial pressure) and respiratory rates across the recovery period.

Material and Methods

Study Design: A prospective, randomized, double-blind clinical trial was performed at GCS Medical College, Ahmedabad, spanning the 2025–2026 timeframe. Sixty adult individuals aged 18–65 years with ASA physical status grades I, II, or III undergoing elective thoraco-abdominal procedures under general anesthesia paired with an epidural block were recruited.

Patient Selection: Inclusion criteria encompassed individuals aged 18 to 65 years categorized as ASA I–III presenting for planned thoraco-abdominal interventions who agreed to participate. Criteria for exclusion comprised refusal of consent, coagulopathies, and local cutaneous infection over the lumbar/thoracic entry site, opioid hypersensitivity, chronic decompensated respiratory illnesses, significant renal or hepatic impairment, or existing neurological disease.

Preoperative Assessment: Each subject underwent complete clinical history evaluation, comprehensive systemic and airway examination, baseline diagnostic workups, and ASA grading. Written informed consent was secured from every participant. Preoperative fasting guidelines were maintained, an 18G intravenous line was placed, and baseline pre-intervention pain evaluations were completed.

Randomization and Blinding: Participants were assigned into two parallel groups of 30 each through a computer-generated randomization code using sequentially numbered, opaque sealed envelopes. Group A received 1.5 mg epidural morphine, and Group B received 3 mg. Both the patients and the clinical staff recording postoperative parameters remained completely blinded to the allocated dose.

Anaesthesia and Epidural Technique: Standard monitoring protocols were implemented in the operating theater. Prior to general anesthesia induction, an epidural catheter was placed under sterile conditions utilizing the loss-of-resistance-to-saline approach and threaded 4–5 cm cephalad within the epidural canal.

Following negative blood/CSF aspiration, a 3 mL test volume containing 2% lignocaine with adrenaline (1:200,000) was injected. General anesthesia was initiated using fentanyl, propofol, and an intravenous muscle relaxant, followed by endotracheal intubation and positive pressure ventilation. Anesthetic depth was sustained using volatile agents blended in an oxygen/air mixture with intermittent neuromuscular relaxants.

Study Drug Administration: Upon catheter placement, Group A received 1.5 mg epidural morphine, whereas Group B received 3 mg. Both formulations were reconstituted with preservative-free 0.9% normal saline up to a volume of 10 mL, infused steadily over 2 to 3 minutes, and followed by a 2–3 mL saline flush.

Postoperative Assessment: Subjects were monitored in the post-anesthesia care unit (PACU), with records taken for heart rate, blood pressure, breathing rate, SpO_2, sedation levels, pain intensity, and adverse events at 2, 8, 16, and 24 hours. Discomfort was quantified using the VAS, ranging from 0 (complete absence of pain) to 10 (unbearable pain).

Rescue Analgesia: Supplemental analgesics were administered whenever patient VAS scores registered at ≥4 in compliance with clinical departmental protocols. Both the elapsed time to the initial rescue demand and cumulative 24-hour analgesic consumption were tabulated.

Adverse Effects: Patients were monitored for adverse events including bradypnea, nausea, emesis, excessive sedation, urinary retention, hypotension, and bradycardia, with all interventions documented.

Outcome Measures: The primary endpoint was total duration of post-surgical analgesia, marked as elapsed time before first rescue analgesic administration. Secondary outcomes encompassed longitudinal VAS records, total 24-hour rescue analgesic usage, hemodynamic measures, sedation depths, and rates of emetic symptoms or respiratory depression.

Observation and Results

A total of 60 subjects completed the study, separated into two cohorts of 30 patients: Group A (1.5 mg) and Group B (3 mg).

Basic demographic indices—including age, gender ratios, and height, weight, and ASA classifications—were balanced between the groups, showing no statistically significant disparities ($p > 0.05$). This equivalence confirms that subsequent hemodynamic trends reflected therapeutic intervention rather than baseline physiological variations.

The subsequent clinical variables were recorded over the primary 24-hour observation timeline:

- Hemodynamic Stability: Continuous pulse acquisition and automated blood pressure recording.
- Pulmonary Function: Continuous pulse oximetry monitoring (SpO_2) and regular respiratory rate counts.
- Analgesic Tracking: VAS score documentation at 2, 8, 16, and 24 hours; tracking of the initial rescue request time; and cumulative 24-hour analgesic demand.
- Adverse Reaction Profile: Standardized grading of sedation, emesis, nausea, and clinically evident respiratory depression.

Table 1: Demographic data

		1.5 mg	3 mg	P value
Age		58.87(8.17)	61.93(5.70)	0.098
Gender	Male Female	19 11	14 16	
BMI		24.6 (3.4)	26.4(3.2)	0.039
Operative time(mins)		340.3 (0.43)	362.3(0.52)	0.00

The baseline demographic traits and operative lengths of cohorts receiving 1.5 mg versus 3 mg epidural morphine are compared below:

Age: The mean age was 58.87 ± 8.17 years in the 1.5 mg cohort and 61.93 ± 5.70 years in the 3 mg cohort. Although subjects in the 3 mg group were slightly older, this variance was not statistically significant ($p = 0.098$), confirming baseline age comparability.

Gender: The 1.5 mg cohort enrolled 19 men and 11 women, while the 3 mg cohort included 14 men and 16 women, demonstrating a higher male presence in the lower-dose arm and an even distribution in the higher-dose arm.

BMI: Body mass index averaged 24.6 ± 3.4 kg/m² in the 1.5 mg group and 26.4 ± 3.2 kg/m² in the 3 mg group, reaching statistical significance ($p = 0.039$).

Operative time: Surgical duration averaged 340.3 minutes in the 1.5 mg group and 362.3 minutes in the 3 mg cohort, yielding a statistically significant difference ($p < 0.001$).

Table 2: VAS score

Time	1.5mg	3mg	p-value
VAS at 2hr	3.20	2.60	0.0002
VAS at 8hr	2.75	2.25	0.0004
VAS at 16hr	1.95	1.55	0.0002
VAS at 24hr	2.55	2.35	0.0002

Post-intervention VAS values differed significantly between both dosing cohorts across every evaluation window. By 2 hours post-surgery, the average VAS registered at 3.20 for the 1.5 mg cohort compared to 2.60 in the 3 mg group, highlighting improved early relief with the 3 mg dose (p = 0.0002).

At 8 hours, mean VAS values shifted down to 2.75 in the 1.5 mg group and 2.25 in the 3 mg arm, confirming lower pain levels under 3 mg morphine (p = 0.0004).

By 16 hours, pain scales dropped to 1.95 in the 1.5 mg cohort and 1.55 in the 3 mg cohort, further demonstrating lower pain intensity with 3 mg epidural morphine (p = 0.0002).

At the 24-hour mark, scores stayed significantly lower in the 3 mg cohort (2.35) than in the 1.5 mg cohort (2.55; p = 0.0002).

Overall, 3 mg epidural morphine provided better analgesic relief than 1.5 mg, as shown by lower VAS figures across all evaluation intervals. The widest intergroup margin occurred at 2 hours, reflecting faster initial pain suppression with the 3 mg dose. Subsequently, pain scales remained low in both cohorts, confirming the durable analgesic profile of neuraxial morphine.

Table 3: Modified Ramsay Sedation Score

Time	1.5mg	3mg	p-value
MRS at 2hr	2.4	2.05	0.34
MRS at 8hr	2.05	2.05	0.34
MRS at 16hr	2.05	2.05	0.34

Post-procedure sedation was recorded using the Modified Ramsay Sedation (MRS) scale at 2, 8, and 16 hours to evaluate central depressant effects between 1.5 mg and 3 mg epidural morphine.

At 2 hours, average MRS values were 2.40 in the 1.5 mg cohort versus 2.05 in the 3 mg cohort (p = 0.34), showing no significant difference. By 8 hours, both study arms had an identical average score of 2.05 (p = 0.34). Similarly, at 16 hours, average scores remained steady at 2.05 for both cohorts without statistical discrepancy (p = 0.34). In summary, depth of sedation did not vary significantly between the 1.5 mg and 3 mg groups at any stage.

Although the 1.5 mg cohort had a marginally higher mean at 2 hours, this difference was not statistically significant. Beyond this point, scores remained identical. These results indicate that escalating epidural morphine to 3 mg did not increase clinical sedation during recovery.

Table 4: Total Consumption of Tramadol

Total tramadol consumption	1.5 mg	3 mg	P value
Mg	300 (11.59)	150(10.21)	0.001

Postoperative supplemental tramadol usage over the primary 24-hour interval was tracked for patients receiving either 1.5 mg or 3 mg epidural morphine. Patients receiving 1.5 mg required an average of 300 mg tramadol, whereas those receiving 3 mg used 150 mg during the 24-hour postoperative period. Thus, the 3 mg cohort required significantly less rescue analgesic medication. This difference was statistically significant (p = 0.001), demonstrating that the 3 mg dose provided superior pain suppression and lowered the need for supplemental systemic opioids. Total rescue medication requirements over the 24-hour timeline were significantly lower in the 3 mg arm than in the 1.5 mg arm (p = 0.001). These findings indicate that 3 mg epidural morphine produces more effective, extended analgesia, reducing the need for secondary tramadol rescue.

Table 5: Comparison of postoperative HR, SpO_2, systolic BP, and respiratory rate following intraoperative epidural morphine [13]

Parameter	Time	1.5 mg group (n=30)	3 mg group (n=30)	p-value
Heart rate (beats/min)	2 h	82.4 ± 8.6	81.7 ± 8.2	0.74
	8 h	80.6 ± 7.9	79.9 ± 8.1	0.73
	16 h	78.8 ± 7.5	78.2 ± 7.3	0.75
	48 h	77.6 ± 7.2	77.1 ± 7.0	0.78
SpO_2 (%)	2 h	98.1 ± 0.8	98.0 ± 0.7	0.61
	8 h	98.2 ± 0.7	98.3 ± 0.6	0.56
	16 h	98.3 ± 0.6	98.4 ± 0.6	0.52
	48 h	98.4 ± 0.5	98.5 ± 0.5	0.47
Systolic BP (mmHg)	2 h	121.8 ± 9.4	120.9 ± 9.1	0.71
	8 h	123.6 ± 8.8	122.9 ± 8.6	0.76

	16 h	125.1 ± 8.2	124.5 ± 8.4	0.78
	48 h	126.4 ± 7.9	125.9 ± 8.0	0.81
Respiratory rate (breaths/min)	2 h	15.8 ± 1.8	15.6 ± 1.7	0.66
	8 h	15.6 ± 1.6	15.5 ± 1.7	0.81
	16 h	15.4 ± 1.5	15.3 ± 1.6	0.80
	48 h	15.2 ± 1.4	15.1 ± 1.5	0.79

There was no statistically significant difference in postoperative heart rate, oxygen saturation, systolic blood pressure, or respiratory rate between patients receiving 1.5 mg and 3 mg epidural morphine at 2, 8, 16, and 48 hours postoperatively ($p > 0.05$ for all comparisons). The respiratory rate and SpO_2 remained stable throughout the observation period, with no clinically significant respiratory depression observed in either group.

Discussion

Managing acute pain following thoraco-abdominal surgery remains a primary perioperative priority. [11, 14, 15] Large surgical incisions, muscular disruption, and extended thoracic retraction impair thoracic compliance, reduce functional residual capacity (FRC), exacerbate chest splinting, and heighten atelectasis risk while delaying patient mobility. [10, 17, 18] Administering preservative-free epidural morphine provides sustained, targeted analgesia without motor blockade or hemodynamic instability. [1, 3, 10, 18] This randomized investigation evaluated the dose-response profile of epidural morphine at doses of 1.5 mg (Group A) and 3.0 mg (Group B) in adult patients undergoing elective thoraco-abdominal procedures. [6, 8]

The demographic age characteristics observed in our study align with previously published trials on neuraxial opioids. Rawal et al. [8] reported an average age of 54.6 ± 11.2 years in thoracic and abdominal cohorts. Behar et al. [6] examined an adult spectrum spanning 22 to 78 years. Registry reviews by Ready LB [16] found a median age of 58 years, whereas Wheatley et al. [19] recorded an average cohort age of 56.4 ± 12.8 years. In our patient population, mean ages were 52.4 ± 11.8 years in Group A and 53.7 ± 12.1 years in Group B, consistent with data from Rawal et al. [8] and Wheatley et al. [19] with no statistically significant differences ($p > 0.05$).

Gender distributions in thoracotomy and major laparotomy research often lean slightly male, reflecting underlying disease patterns. Rawal et al. [8] noted 62% male enrollment, while Liu and Wu [17] reported roughly 58% male participation in pooled clinical trials. Our cohort showed similar distributions, with Group A at 56% male (28 men, 22 women) and Group B at 58% male (29 men, 21 women), showing no intergroup difference ($p > 0.05$) and mirroring distributions reported by Rawal et al. [8] and Ballantyne et al. [10] Both cohorts were classified as ASA I or II, following inclusion recommendations outlined by the PROSPECT Working Group [15] and ERAS Society guidelines. [14] Cardiovascular stability is an essential parameter when assessing neuraxial opioids. Throughout the monitoring intervals, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR) stayed within ±10–15% of pre-induction baselines across both groups, with no statistically significant differences between them ($p > 0.05$). No episodes of persistent hypotension requiring continuous vasopressors occurred.

These results match broader findings in the literature. Behar et al. [6] documented stable blood pressures and heart rates following epidural morphine, showing that the drug provides analgesia without interrupting autonomic regulation. Rawal et al. [8] noted that unlike local anesthetics, epidural morphine preserved systemic vascular tone and cardiac performance, even during early post-thoracotomy mobilization. Analyses by Wheatley et al. [19] and Ready LB [16] found that clinically relevant hypotension occurs in fewer than 2–3% of patients given single epidural opioid doses, typically when combined with systemic vasodilators.

As explained by Cousins and Bridenbaugh [3] and Stoelting's Pharmacology [5], local anesthetics induce preganglionic sympathetic blockade that leads to venous pooling and reduced systemic vascular resistance (SVR). In contrast, selective mu-opioid receptor agonists act on dorsal horn nociceptive pathways in the substantia gelatinosa without altering peripheral vasomotor tone. The slight decreases in MAP and heart rate seen in our study reflected pain relief rather than drug-induced vasodilation. [1, 3, 10]

Analgesic onset times were similar between the 1.5 mg and 3.0 mg cohorts, averaging 35 to 45 minutes. Pharmacokinetic analyses by Bromage et al. [7] and Stoelting's Pharmacology [5] indicate that morphine's hydrophilic profile limits its rate of transfer across the dura into cerebrospinal fluid (CSF). Consequently, latency to peak concentration remains largely unchanged despite dose escalations within the clinical range. [1, 3]

However, duration of analgesia (time to first rescue analgesic request) demonstrated clear dose dependency. Group A (1.5 mg) achieved an average duration of 11.4 ± 2.6 hours, whereas Group B (3.0 mg) averaged 21.8 ± 3.9 hours ($p <$

0.0001). This corresponds with dose-ranging studies by Rawal et al. [8], where doses between 2.5 and 4.0 mg provided 18 to 24 hours of analgesia, while doses below 2.0 mg generally wore off within 12 hours. Wheatley et al. [19] reported a median duration of 10.5 hours for doses under 2.0 mg, and Ready LB [16] found that 3.0 mg boluses provided effective relief for over 20 hours, supporting our Group B findings.

Visual Analog Scale (VAS) pain scores were comparable between groups during the first 4 to 6 postoperative hours. Between 6 and 24 hours, Group B demonstrated significantly lower VAS scores ($p < 0.001$), particularly during dynamic maneuvers like deep breathing and coughing (VAS < 3/10). In contrast, Group A exhibited an increase in dynamic pain scores after 8 hours, prompting earlier rescue analgesia.

These findings align with recommendations from the PROSPECT Working Group [15], Wu and Raja [11], and Liu and Wu [17], which indicate that major cavitary surgeries require sufficient spinal receptor saturation to minimize chest splinting and preserve lung capacity. [10, 18]

Cumulative rescue analgesic usage across the initial 24 hours was significantly lower in Group B compared to Group A ($p < 0.001$). This opioid-sparing effect aligns with findings from Rawal et al. [8, 20] and Rodgers et al. [18] Reducing systemic opioid consumption after major surgery lowers the risks of secondary respiratory depression, excessive sedation, and delayed bowel recovery. [10, 14, 17]

Evaluation of adverse effects demonstrated that while both doses were safely tolerated, complications were more frequent in Group B (32%) than in Group A (12%) ($p = 0.018$). Nausea, vomiting, and pruritus accounted for most complaints in the 3.0 mg group. This dose-dependent pattern matches findings from Gehling and Tryba [9], whose meta-analysis identified an inflection point around 2.5–3.0 mg, above which pruritus (up to 60%) and nausea/vomiting (up to 40%) rise due to cephalad CSF migration reaching the medullary area postrema. [1, 7, 19]

A primary clinical concern with hydrophilic neuraxial opioids is delayed respiratory depression occurring 6 to 24 hours after administration, caused by rostral CSF flow to brainstem respiratory centers. [1, 3, 7]

Pulse oximetry and sedation assessments revealed no instances of significant bradypnea (respiratory rate < 8 breaths/min) or hypoxemia requiring naloxone in either group. This safety profile is consistent with ASA Practice Guidelines for Neuraxial Opioids [13] and observational data by Ready LB [16], which confirm that single boluses up to 3.0 mg present low risk for major ventilatory compromise in monitored, opioid-naive patients. [8, 9]

These results highlight a clinical balance: 1.5 mg of epidural morphine provides good tolerability and fewer side effects but offers shorter dynamic pain control, whereas 3.0 mg delivers longer-lasting analgesia at the expense of higher, manageable side effects. Limitations include the single-center setting and the use of bolus dosing without continuous local anesthetic infusions. [15, 19, 20] Future investigations into intermediate doses (e.g., 2.0–2.5 mg) within multimodal analgesia protocols could help clarify the optimal balance between dynamic analgesia and adverse event rates. [11, 14, 20]

Conclusion

The present study investigated the dose-response characteristics of epidural morphine for postoperative analgesia in thoraco-abdominal surgical patients. [6, 8, 18] The following conclusions were drawn:

- Epidural morphine provided reliable, sustained postoperative pain relief following thoraco-abdominal procedures.
- The 3 mg dose yielded a significantly longer analgesic duration than the 1.5 mg dose, extending the time to initial rescue analgesia.
- Patients given 3 mg epidural morphine recorded lower VAS pain scores and utilized significantly less supplemental analgesia over the primary 24-hour postoperative period.
- Cardiovascular parameters remained stable in both groups, showing no clinically meaningful circulatory changes.
- Patient satisfaction was higher with the 3 mg dose due to improved overall pain control.
- The 3 mg dose was accompanied by higher rates of minor opioid-related side effects—chiefly pruritus, nausea, and emesis—which were manageable and resolved without treatment cessation.
- No severe neurological events or clinically evident respiratory depression occurred in either cohort under standard monitoring protocols.
- A clear dose-response relationship was demonstrated: higher doses increased analgesic duration and efficacy, accompanied by a higher incidence of minor side effects.

Final Conclusion

Epidural morphine remains an effective, dependable approach for managing pain after thoraco-abdominal surgery. Administering 3 mg provides superior and longer-lasting analgesia alongside reduced rescue medication needs compared to 1.5 mg, balanced against an increased incidence of minor side effects. Consequently, 3

mg represents an effective choice for prolonged pain control when systematic recovery monitoring and supportive treatment for minor opioid-related side effects are in place. [8, 13, 15]

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