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# Comparison of three different intrathecal morphine doses in post-thoracotomy pain management: A retrospective analysis

**Esra TURUNC[1,*], İlke TAMDOGAN[2], İsmail Serhat KOCAMANOĞLU[1]**

[1]Department of Anesthesiology and Reanimation, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Türkiye
[2]Department of Anesthesiology and Reanimation, Faculty of Medicine, Giresun University, Giresun, Türkiye

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**Abstract**

Effective postoperative pain control following thoracotomy is essential for optimizing patient comfort, supporting respiratory function, and reducing pulmonary complications. Intrathecal (IT) morphine is frequently incorporated into multimodal analgesic strategies, however yet its optimal dose remains uncertain. This retrospective observational study evaluated the analgesic efficacy and side-effect profile of varying IT morphine doses combined with intravenous patient-controlled analgesia (PCA) in 60 patients who underwent thoracotomy at Ondokuz Mayıs University Medical Faculty Hospital between 1 January 2019 and 1 July 2020. Patients received either no IT morphine (control) or IT morphine at doses of 3, 5, or 8 μg/kg**.** Postoperative pain scores, opioid consumption, additional analgesic requirements, and adverse effects were compared among groups. A clear dose-dependent reduction in postoperative fentanyl consumption was observed: the control group required a median of 500 μg (300–700), compared with 340 μg (250–600), 200 μg (135–300), and 75 μg (30–100) in the 3, 5, and 8 μg/kg groups, respectively. Rescue analgesia use also differed markedly. In the PACU, additional analgesia was required in 93.3% of control patients, 66.7% of patients in the 3 μg/kg group, 33.3% in the 5 μg/kg group, and none in the 8 μg/kg group**.** Similar patterns were observed in the wards, where all control patients required rescue analgesia, compared with 86.7%, 80.0%, and 20.0% of patients in the 3, 5, and 8 μg/kg groups, respectively. Higher IT morphine doses were associated with lower pain scores and reduced opioid requirements; however, these benefits were accompanied by a dose-dependent increase in side effects including nausea, vomiting, pruritus, and constipation. Overall, the 5 μg/kg dose appeared to offer the most favourable balance, providing effective analgesia for up to 48 hours while limiting adverse effects. IT morphine at a dose of 5 μg/kg therefore seems to represent the optimal balance of efficacy and safety for postoperative analgesia after thoracotomy, offering sustained pain relief for up to 48 hours with a low side-effect profile.

**Keywords:** Intrathecal morphine, thoracotomy, postoperative analgesia, patient-controlled analgesia, adverse effects

## 1. Introduction

Post-thoracotomy pain is one of the most severe postoperative pain syndromes and is associated with respiratory complications, delayed recovery, and a high risk of chronic pain development (1). Therefore, optimising perioperative analgesia remains a critical clinical priority.

Although thoracic epidural analgesia is considered the gold standard, contraindications and technical limitations often necessitate alternative strategies including paravertebral block, erector spinae plane block, intercostal nerve blocks, and systemic opioid-based regimens (2,3). Intrathecal (IT) morphine provides prolonged spinal analgesia and reduces systemic opioid requirements; however, despite its widespread use, evidence directly comparing different IT morphine doses in thoracotomy is limited (4). Most available studies describe general benefits of IT morphine rather than assessing dose–response differences, leaving uncertainty regarding the dose that provides effective analgesia while minimizing adverse effects (5).

To the best of our knowledge, no study has directly compared these commonly used IT morphine doses in a head-to-head fashion. This retrospective observational study therefore aimed to compare postoperative analgesic efficacy, opioid consumption, and adverse effects across three IT morphine doses. Accordingly, we hypothesize that there would be a significant difference in postoperative analgesic profiles, including cumulative opioid consumption and adverse effects, across the intrathecal morphine doses evaluated in this retrospective observational study.

## 2. Materials and Methods

### 2.1. Study Design

Ethical approval for this retrospective observational study was granted by the Clinical Research Ethics Committee of Ondokuz Mayıs University Faculty of Medicine (No: B.30.2.ODM.0.20.08/520). The study was carried out in alignment with the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, 2013) and adhered to the STROBE recommendations for reporting observational

*Correspondence: esra.kiymaz.ek@gmail.com

research. Clinical and anesthetic data of patients who underwent elective thoracotomy between January 2019 and July 2020 were obtained from institutional medical records and the hospital's electronic information system.

### 2.2. Population and Sample

The study population consisted of patients aged 18-75 years with American Society of Anesthesiologists (ASA) scores of I and II and who received IT morphine and patient controlled analgesia (PCA) for postoperative analgesia during thoracotomy operations between 01.01.2019 and 01.07.2020 in Ondokuz Mayis University Medical Faculty Hospital Thoracic Surgery Department operating room. Exclusion criteria included patients with contraindications to regional or neuraxial analgesia (e.g., known drug hypersensitivity); incomplete postoperative pain assessments as reflected by unavailable Numeric Rating Scale (NRS) recordings secondary to cognitive or psychiatric impairment; chronic pain conditions requiring ongoing analgesic therapy; preoperative use of opioids, alcohol, or illicit substances; morbid obesity (body mass index >40 kg/m²); and significant cardiac, hepatic, or renal dysfunction. In addition, patients with a prior history of cardiothoracic surgery were excluded, as were those who experienced major intraoperative or postoperative bleeding, clinically relevant hemodynamic instability (defined as systolic arterial pressure <90 mmHg or mean arterial pressure <60 mmHg), or required postoperative mechanical ventilatory support.

Total of 60 patients met the inclusion criteria. Patient records were reviewed and categorized into four groups according to the administered intrathecal morphine dose (control group, 3 µg/kg, 5 µg/kg, and 8 µg/kg). To minimize selection bias, the records were ordered by protocol numbers, and 15 patients from each group were included in the final analysis.

### 2.3. Data Collection

Data was extracted from the anesthesia records of the patients. The following data were collected for each patient: demographic characteristics (age, gender, etc.), ASA scores, duration of surgery, the dose of IT morphine administered, pain scores at rest, walking and coughing included in the pain follow-up forms, that is, visual analog scale (VAS) scores at the 0th, 30th , and 60th minutes, and 8th , 24th , 30th and 48th hours), postoperative analgesic use, time to first opioid request for use within the scope of PCA, the total amount of fentanyl used in 24 hours, and the dates and doses of additional opioid requests, complications related to opioid use and spinal opioid applications such as postoperative respiratory depression, Postoperative nausea and vomiting (PONV), pruritus, urinary retention, flatulence, and headache, time to first oral opioid intake, first mobilization time, and time to discharge. Missing or incomplete data were cross-checked across electronic anesthesia charts and postoperative follow-up forms; patients with unavailable key outcome data were excluded. Outcome extraction was performed by a researcher who was not involved in the intraoperative care of the patients to minimize assessment bias.

### 2.4. Anesthesia Management

All patients undergoing thoracotomy received a uniform institutional anesthesia protocol. Premedication consisted of 1 mg midazolam. Following standard monitoring, anesthesia was induced with propofol (2 mg/kg), remifentanil (1–2 µg/kg), and rocuronium (0.6 mg/kg). After intubation with an appropriately sized double-lumen endotracheal tube, anesthesia was maintained with a continuous propofol infusion (5–10 mg/kg/hr). During the final 30 minutes of surgery, patients were administered 8 mg dexamethasone, 4 mg ondansetron, 20 mg tenoxicam, and 1000 mg paracetamol intravenously.

### 2.5. Intrathecal Morphine Administration

The patients were positioned sitting prior to induction of anesthesia. Under sterile conditions, the predetermined intrathecal morphine doses (3, 5, or 8 µg/kg) diluted in 3 mL of 0.9% saline were injected at either the L3–L4 or L4–L5 interspace using a 25-gauge spinal needle.

### 2.6. Postoperative Period

According to institutional anesthesia records, PONV prophylaxis routinely consisted of intravenous dexamethasone (8 mg) administered before anesthesia induction and ondansetron (0.15 mg/kg IV) given approximately 20 minutes before the end of surgery. PONV was evaluated using a 5-point verbal descriptive scale (0 = no nausea; 1 = mild nausea; 2 = moderate nausea; 3 = one episode of vomiting; 4 = more than one episode of vomiting). A PONV score ≥ 3 was recorded as requiring rescue antiemetic treatment, and ondansetron 4 mg IV was administered, as documented in the anesthesia and PACU records. PONV scores were recorded in the post-anesthesia care unit (PACU) and at 1, 8, 24, and 48 hours postoperatively. All assessments were based on routinely documented clinical evaluations.

### 2.7. Analgesia Management

According to institutional anesthesia and postoperative care records, patients achieving a modified Aldrete score > 9 in the post-anesthesia care unit were transferred to the thoracic surgery ward with an intravenous fentanyl PCA device. The PCA solution contained fentanyl at a concentration of 5 µg/mL, with a bolus dose of 15 µg, a lockout interval of 5 minutes, and a maximum hourly dose limit of 75 µg, without background infusion.

As part of the multimodal analgesia regimen documented in routine practice, all patients received intravenous paracetamol 1 g every 6 hours and tenoxicam administered at a dose of 20 mg twice daily during the postoperative period, unless contraindicated.

Patients were instructed preoperatively to activate the PCA device when experiencing postoperative pain, particularly when their numeric rating scale (NRS; 0 = no pain, 10 = worst imaginable pain) score exceeded 3, as recorded in the clinical charts. Total fentanyl consumption via the PCA device over the

first 48 postoperative hours was recorded.

Rescue analgesia was administered in patients with persistent pain (NRS > 4) despite PCA use, consisting of intramuscular meperidine 25 mg, with a maximum daily dose of 200 mg, according to institutional practice. Respiratory depression was initially managed with supplemental oxygen via nasal cannula; if oxygen saturation ($SpO_2$) remained below 93%, intravenous naloxone 0.4 mg was administered. Pain assessments and analgesic interventions were retrieved from routine nursing and medical documentation.

### 2.8. Outcomes

The primary endpoint was total 48-hour postoperative fentanyl consumption. Secondary outcomes included VAS pain scores at rest and with coughing, time to first rescue analgesia and rescue analgesic requirement in the PACU, incidence of opioid-related adverse effects including PONV, pruritus, and constipation within the first 48 hours, as well as markers of gastrointestinal recovery such as time to first flatus and initiation of oral intake.

### 2.9. Sample Size Calculation and Statistical Analysis

Using the cumulative opioid consumption data reported by Askar et al. (3) and our pilot estimates, the anticipated mean opioid consumptions (expressed as IV morphine equivalents) were assumed to be 40 ± 15 mg for the control group, 32 ± 15 mg for the 3 μg/kg IT morphine group, 24 ± 15 mg for the 5 μg/kg IT morphine group, and 20 ± 15 mg for the 8 μg/kg IT morphine group. A priori sample size calculations were performed using Minitab Statistical Software (version 16.0, Minitab Inc.) based on a one-way ANOVA model, assuming a two-sided Type I error of 5% and a power of 80%. The calculated effect size (Cohen's f) was 0.51, resulting in a minimum required sample size of 13 patients per group. To account for potential data loss, 15 patients were planned to be included in each group.

Continuous variables were expressed as mean ± standard deviation or median (minimum–maximum), depending on normality, which was assessed using the Shapiro–Wilk, Kolmogorov–Smirnov, and Anderson–Darling tests. Categorical variables were summarized as numbers and percentages. For comparisons among the three dose groups, non-normally distributed continuous variables were analyzed using the Kruskal–Wallis test, with the Dwass–Steel–Critchlow–Fligner test applied for post hoc pairwise comparisons. Differences in categorical variables were evaluated using Pearson's chi-square or Fisher's exact test, and the Fisher–Freeman–Halton test for larger contingency tables. All statistical analyses were performed using Jamovi (Version 2.2.5.0) and JASP (Version 0.16). A p-value <0.05 was considered statistically significant.

## 3. Results

The demographic and perioperative characteristics of the study groups are presented in Table 1. The groups were comparable with respect to age, sex distribution, ASA physical status, and duration of surgery (p>0.05).

**Table 1.** Demographic and perioperative characteristics of the study groups

| | Group Control (n=15) | Group 3mcg (n=15) | Group 5mcg (n=15) | Group 8mcg (n=15) | p |
|---|---|---|---|---|---|
| **Age (year)** † | 64.0 [33.0 – 76.0] | 54.0 [25.0 – 74.0] | 59.0 [18.0 – 74.0] | 54.0 [23.0 – 74.0] | 0.154** |
| **Sex** ⁋ | | | | | |
| Male | 3 (20.0) | 7 (46.7) | 5 (33.3) | 3 (20.0) | 0.370* |
| Female | 12 (80.0) | 8 (53.3) | 10 (66.7) | 12 (80.0) | |
| **BMI (kg/m2)** † | 27.6 ± 4.8 | 26.6 ± 3.8 | 27.2 ± 3.5 | 26.1± 4.4 | 0,605* |
| **ASA grade** ⁋ | | | | | |
| I | 5 (33.3) | 11 (73.3) | 7 (46.7) | 8 (53.3) | 0.171* |
| II | 10 (66.7) | 4 (26.7) | 8 (53.3) | 7 (46.7) | |
| **Type of resection** | | | | | |
| Wedge | 6 (40.0) | 5 (33.3) | 6 (40.0) | 4 (26.7) | 0.278* |
| Lobectomy | 9 (60.0) | 10 (66.7) | 9 (60.0) | 11 (73.3) | |
| **Duration of surgery (min)** ‡ | 225.0 [100.0 – 400.0] | 150.0 [105.0 – 360.0] | 220.0 [130.0 – 330.0] | 270.0 [117.0 – 400.0] | 0.112** |

†: mean standard deviation, ‡: median [min-max], ⁋: n (%).
ASA: American Society of Anesthesiologists, VATS: video-assisted thoracoscopic surgery, BMI, body mass index
*. Pearson Chi-Square or Fisher Freeman Halton test
**. Kruskal-Wallis H Test

### 3.1. Postoperative Analgesic Consumption

Postoperative analgesic consumption data are shown in Table 2. Time to first PCA fentanyl request differed significantly among the groups (p<0.001), occurring earliest in the control and 3 μg/kg groups (both median 15 min [0–60] and 15 min [5–120], respectively) and latest in the 8 μg/kg group (median 150 min [0–650]).

**Table 2.** Postoperative opioid consumption and rescue analgesia requirements

| | Group Control (n=15) | Group 3mcg (n=15) | Group 5mcg (n=15) | Group 8mcg (n=15) | p |
|---|---|---|---|---|---|
| **Fentanyl consumption for PCA** | | | | | |
| **Time to first request (min)** ‡ | 15.0 [0.0 – 60.0] | 15.0 [5.0 – 120.0] | 120.0 [60.0 – 300.0] | 150.0 [0.0 – 650.0] | **<0.001**** |
| **Total dose (mcg)** ‡ | 500.0 [300.0 – 700.0] | 340.0 [250.0 – 600.0] | 200.0 [135.0 – 300.0] | 75.0 [30.0 – 100.0] | **<0.001**** |

| | | | | | |
|---|---|---|---|---|---|
| **Rescue analgesia in PACU** | | | | | |
| No ⁋ | 1 (6.7) | 5 (33.3) | 10 (66.7) | 15 (100.0) | **<0.001*** |
| Yes ⁋ | 14 (93.3) | 10 (66.7) | 5 (33.3) | 0 (0.0) | |
| **Total dose (mg)** ‡ | 25.0 [24.0 – 50.0] | 37.5 [25.0 – 50.0] | 25.0 [25.0 – 25.0] | 0 (0-0) | 0.170** |
| **Rescue analgesia inwards** | | | | | |
| No ⁋ | 0 (0.0) | 2 (13.3) | 3 (20.0) | 12 (80.0) | **<0.001*** |
| Yes ⁋ | 15 (100.0) | 13 (86.7) | 12 (80.0) | 3 (20.0) | |
| **Total dose (mg)** ‡ | 100.0 [25.0 – 100.0] | 50.0 [25.0 – 100.0] | 50.0 [25.0 – 75.0] | 25.0 [25.0 – 50.0] | **0.001**** |

‡: median [min-max], ⁋: n (%)
PCA: patient-controlled analgesia, PACU: post-anesthesia care unit
*. Pearson Chi-Square or Fisher Freeman Halton test
**. Kruskal-Wallis H Test
*Statistically significant difference is highlighted in bold*

Total postoperative fentanyl consumption demonstrated a progressive, dose-dependent decrease with increasing IT morphine dose. Median fentanyl consumption was highest in the control group (500 µg [300–700]) and decreased to 340 µg [250–600] in the 3 µg/kg group, 200 µg [135–300] in the 5 µg/kg group, and 75 µg [30–100] in the 8 µg/kg group (p<0.001, Table 4). Post-hoc analysis confirmed significant differences between most group pairs (Table 3).

**Table 3.** Post-hoc comparisons of postoperative opioid consumption between groups

| | | *p* | | |
|---|---|---|---|---|
| | | **Time to first request for PCA** | **Total dose for PCA** | **Total dose inwards** |
| Group Control | Group 3 mcg | 0.726 | **0.004** | 0.540 |
| Group Control | Group 5mcg | **<0.001** | **<0.001** | **0.002** |
| Group Control | Group 8mcg | **0.003** | **<0.001** | **0.048** |
| Group 3 mcg | Group 5mcg | **<0.001** | **<0.001** | **0.045** |
| Group 3 mcg | Group 8mcg | **0.011** | **<0.001** | 0.152 |
| Group 5mcg | Group 8mcg | 0.782 | **<0.001** | 0.851 |

PCA: patient-controlled analgesia
Data were analysed using one-way ANOVA followed by Bonferroni-adjusted post hoc pairwise comparisons. Statistically significant differences ($p < 0.05$) are shown in bold.

Rescue analgesia use followed a similar pattern. In the PACU, rescue analgesia was required by 93.3% of patients in the control group and 66.7% in the 3 µg/kg group, compared with 33.3% in the 5 µg/kg group, while no patient in the 8 µg/kg group required additional analgesia (p<0.001). During ward follow-up, all control patients (100%) required rescue analgesia versus 86.7%, 80.0%, and 20.0% in the 3, 5, and 8 µg/kg groups, respectively. The median total dose of rescue analgesics administered on the wards was significantly higher in the control group (100 mg [25–100]) than in the IT morphine groups (50 mg [25–100], 50 mg [25–75], and 25 mg [25–50] for the 3, 5, and 8 µg/kg groups, respectively; p=0.001, Table 2).

### 3.2. Postoperative Pain Scores

Postoperative pain scores differed significantly among the groups across all evaluated time points (p<0.001, Table 4). Overall, VAS scores at rest, during walking, and coughing demonstrated a clear dose-dependent reduction with increasing intrathecal morphine dose. At rest, the lowest VAS scores were consistently observed in the 8 µg/kg group from the postoperative baseline through 48 hours, whereas the control and 3 µg/kg groups reported the highest pain scores during the early postoperative period. Pairwise post-hoc analyses confirmed significantly lower resting VAS scores in the 8 µg/kg group compared with the other three groups at nearly all time points (Table 5). A similar pattern was observed for VAS scores during walking and coughing. Patients in the 8 µg/kg group experienced significantly lower pain scores compared with the control, 3 µg/kg, and 5 µg/kg groups, particularly during the first 24 postoperative hours. Detailed pairwise comparisons are summarized in Table 5.

**Table 4.** Comparison of postoperative VAS pain scores at rest, during walking, and coughing

| Postoperative VAS score | Group Control (n=15) | Group 3mcg (n=15) | Group 5mcg (n=15) | Group 8mcg (n=15) | p* |
|---|---|---|---|---|---|
| **At rest** ‡ | | | | | |
| PACU | 8.0 [7.0 – 9.0] | 8.0 [7.0 – 9.0] | 6.0 [4.0 – 7.0] | 5.0 [0.0 – 8.0] | **<0.001** |

| | | | | | |
|---|---|---|---|---|---|
| 1st hr. | 7.0 [6.0 – 9.0] | 7.0 [6.0 – 8.0] | 6.0 [4.0 – 7.0] | 4.0 [1.0 – 6.0] | **<0.001** |
| 8th hour | 6.0 [4.0 – 6.0] | 6.0 [4.0 – 6.0] | 4.0 [2.0 – 7.0] | 2.0 [0.0 – 4.0] | **<0.001** |
| 24th hour | 4.0 [2.0 – 6.0] | 4.0 [2.0 – 5.0] | 3.0 [0.0 – 5.0] | 0.0 [0.0 – 3.0] | **<0.001** |
| 48th hour | 2.0 [1.0 – 3.0] | 1.0 [0.0 – 3.0] | 1.0 [0.0 – 3.0] | 0.0 [0.0 – 1.0] | **<0.001** |
| **Walking** ‡ | | | | | |
| 8th hour | 6.0 [4.0 – 7.0] | 6.0 [4.0 – 7.0] | 5.0 [2.0 – 6.0] | 3.0 [0.0 – 5.0] | **<0.001** |
| 24th hour | 5.0 [3.0 – 7.0] | 4.0 [2.0 – 7.0] | 3.0 [0.0 – 6.0] | 1.0 [0.0 – 3.0] | **<0.001** |
| 48th hour | 2.0 [1.0 – 4.0] | 2.0 [1.0 – 8.0] | 1.0 [0.0 – 3.0] | 0.0 [0.0 – 1.0] | **<0.001** |
| **Coughing** ‡ | | | | | |
| PACU | 9.0 [8.0 – 10.0] | 8.0 [8.0 – 10.0] | 7.0 [5.0 – 10.0] | 6.0 [0.0 – 8.0] | **<0.001** |
| 1st hr. | 8.0 [6.0 – 10.0] | 8.0 [6.0 – 8.0] | 6.0 [5.0 – 8.0] | 4.0 [2.0 – 6.0] | **<0.001** |
| 8th hour | 7.0 [5.0 – 7.0] | 6.0 [5.0 – 8.0] | 5.0 [2.0 – 7.0] | 3.0 [1.0 – 6.0] | **<0.001** |
| 24th hour | 5.0 [3.0 – 7.0] | 5.0 [3.0 – 7.0] | 4.0 [0.0 – 6.0] | 2.0 [0.0 – 4.0] | **<0.001** |
| 48th hour | 3.0 [1.0 – 3.0] | 2.0 [0.0 – 4.0] | 1.0 [0.0 – 4.0] | 1.0 [0.0 – 1.0] | **<0.001** |

‡: median [min-max]
*. Kruskal-Wallis H Test
VAS: visual analog scale, PACU: post-anesthesia care unit
Statistically significant difference is highlighted in bold

**Table 5.** Post-hoc analysis of postoperative VAS pain scores

| **Dual comparisons** | | ***p-values*** | | | | |
|---|---|---|---|---|---|---|
| | | **PACU** | **1st hr.** | **8th hr.** | **24th hr.** | **48th hr.** |
| **Resting VAS score** | | | | | | |
| Group Control | Group 3 mcg | 0.714 | 0.928 | 0.984 | 0.666 | 0.360 |
| Group Control | Group 5 mcg | **<0.001** | **<0.001** | **0.001** | **0.007** | 0.091 |
| Group Control | Group 8 mcg | **<0.001** | **<0.001** | **<0.001** | **<0.001** | **<0.001** |
| Group 3 mcg | Group 5 mcg | **<0.001** | **<0.001** | **0.001** | 0.055 | 0.555 |
| Group 3 mcg | Group 8 mcg | **<0.001** | **<0.001** | **<0.001** | **<0.001** | **<0.001** |
| Group 5mcg | Group 8 mcg | **0.025** | **0.001** | **0.030** | **0.007** | **0.025** |
| **Walking VAS score** | | | | | | |
| Group Control | Group 3 mcg | -- | -- | 0.186 | 0.829 | 0.881 |
| Group Control | Group 5 mcg | -- | -- | **0.003** | **0.012** | 0.204 |
| Group Control | Group 8 mcg | -- | -- | **<0.001** | **<0.001** | **<0.001** |
| Group 3 mcg | Group 5 mcg | -- | -- | 0.114 | 0.067 | 0.611 |
| Group 3 mcg | Group 8 mcg | -- | -- | **<0.001** | **<0.001** | **<0.001** |
| Group 5 mcg | Group 8 mcg | -- | -- | **0.022** | **0.012** | **0.004** |
| **Coughing VAS score** | | | | | | |
| Group Control | Group 3 mcg | 0.370 | 0.852 | 0.798 | 0.610 | 0.372 |
| Group Control | Group 5 mcg | **<0.001** | **0.002** | **0.021** | **0.008** | **0.030** |
| Group Control | Group 8 mcg | **<0.001** | **<0.001** | **<0.001** | **<0.001** | **<0.001** |
| Group 3 mcg | Group 5 mcg | **0.001** | **0.003** | 0.094 | 0.052 | 0.279 |
| Group 3 mcg | Group 8 mcg | **<0.001** | **<0.001** | **<0.001** | **<0.001** | **<0.001** |
| Group 5 mcg | Group 8 mcg | **0.027** | **0.003** | **0.048** | **0.031** | **0.019** |

VAS: visual analog scale, PACU: post-anesthesia care unit
Statistically significant difference is highlighted in bold

### 3.3. Adverse Effects and Other Postoperative Outcomes

Postoperative adverse effects are summarized in Table 6. Pruritus occurred more frequently in the 8 μg/kg group, particularly at the postoperative 1st and 8th hours (p=0.011 and p=0.012, respectively). Similarly, the incidence of postoperative nausea and vomiting was significantly higher in the 8 μg/kg group at the 8th and 24th postoperative hours (p<0.001 and p=0.011, respectively), and these patients required antiemetic therapy more frequently (p<0.001). Gastrointestinal recovery differed among the groups. Time to first flatus was significantly prolonged in the 8 μg/kg group compared with the lower-dose groups (p=0.006). Patients in the 3 μg/kg group resumed oral feeding significantly earlier than those in the 5 μg/kg and 8 μg/kg groups (Table 6). No significant differences were observed in time to first mobilization or length of hospital stay among the groups.

**Table 6.** Comparison of the adverse events and postoperative outcomes between the groups

| | Group Control (n=15) | Group 3mcg (n=15) | Group 5mcg (n=15) | Group 8mcg (n=15) | p |
|---|---|---|---|---|---|
| **Postoperative itching** ⁋ | | | | | |
| PACU | 0 (0) | 0 (0) | 0 (0) | 0 (0) | - |
| 1st hr. | 0 (0) | 0 (0) | 0 (0) | 4 (26.7) | **0.011*** |
| 8th hour | 0 (0) | 1 (6.7) | 0 (0) | 5 (33.3) | **0.012*** |
| 24th hour | 0 (0) | 0 (0) | 0 (0) | 3 (20) | 0.054* |
| 48th hour | 0 (0) | 0 (0) | 0 (0) | 0 (0) | |
| **Postoperative nausea&vomiting** ⁋ | | | | | |
| PACU | 0 (0) | 0 (0) | 0 (0) | 0 (0) | - |
| 1st hr. | 4 (26.7) | 2 (13.3) | 6 (40) | 8 (53.3) | 0.112* |
| 8th hour | 3 (20) | 1 (6.7) | 5 (33.3) | 12 (80) | **<0.001*** |
| 24th hour | 3 (20) | 2 (13.3) | 3 (20) | 10 (66.7) | **0.011*** |
| 48th hour | 0 (0) | 1 (6.7) | 1 (6.7) | 0 (0) | 0.999* |
| **Use of antiemetic drug**, ⁋ | 0 (0.0) | 0 (0.0) | 3 (20.0) | 8 (53.3) | **<0.001*** |
| **Total dose of ondansetron (mg)** ‡ | 0 [0 – 0] | 0 [0 – 0] | 4.0 [2.0 – 4.0] | 6.0 [4.0 – 8.0] | 0.067** |
| **Time to first ondansetron dose (hr.)** ‡ | 0 [0 –0] | 0 [0 – 0] | 4.0 [1.0 – 8.0] | 6.0 [2.0 – 20.0] | 0.342** |
| **Time to first flatus (hr.)** ‡ | 8.0 [5.0 – 15.0] | 6.0 [4.0 – 10.0] | 8.0 [7.0 – 15.0] | 12.0 [4.0 – 30.0] | **0.006**** |
| **Time to first oral feeding (hr.)** ‡ | 6.0 [4.0 – 20.0] | 6.0 [3.0 – 8.0] | 8.0 [5.0 – 12.0] | 8.0 [4.0 – 30.0] | **0.018**** |
| **Time to first mobilization (hr.)** ‡ | 8.0 [4.0 – 20.0] | 6.0 [3.0 – 10.0] | 7.0 [3.0 – 12.0] | 5.0 [3.0 – 16.0] | 0.808** |
| **Length of hospital stay (day)** ‡ | 6.0 [3.0 – 12.0] | 5.0 [2.0 – 10.0] | 5.0 [3.0 – 9.0] | 5.0 [3.0 – 8.0] | 0.571** |

‡: median [min-max], ⁋: n (%)
PACU: post-anesthesia care unit
*. Pearson Chi-Square, Fisher's Exact or Fisher Freeman Halton test
*. Kruskal-Wallis H Test
*Statistically significant difference is highlighted in bold*

## 4. Discussion

This study compared postoperative analgesic outcomes associated with different IT morphine doses routinely used for thoracotomy. Patients receiving 3, 5, or 8 μg/kg IT morphine were evaluated alongside a control group managed with intravenous analgesia alone. Increasing IT morphine doses were associated with lower pain scores and reduced fentanyl consumption, but also with a higher incidence of adverse effects, including nausea, vomiting, pruritus, and constipation. Among the evaluated doses, 5 μg/kg appeared to provide a more favorable balance between analgesic efficacy and tolerability, offering sustained analgesia for up to 48 hours while avoiding the higher rate of side effects observed with the 8 μg/kg dose. In this context, the very high need for rescue analgesia in the PACU among control patients (93.3%) further emphasizes the limitations of intravenous analgesia alone for immediate post-thoracotomy pain control.

Effective pain management after thoracic surgery is essential not only for patient comfort but also for reducing postoperative pulmonary complications and delayed functional recovery (6). Following thoracotomy, recovery of lung function is often prolonged compared with other major surgical procedures, highlighting the clinical importance of adequate postoperative analgesia to facilitate deep breathing, effective coughing, and early mobilization (7).

Intrathecal morphine has been widely used as part of multimodal analgesia protocols for thoracotomy and has consistently been shown to reduce postoperative pain scores and systemic opioid requirements compared with intravenous analgesia alone or alternative regional techniques (8,9). Previous studies comparing IT morphine with thoracic epidural or intravenous opioid-based regimens have demonstrated satisfactory analgesia and improved early postoperative outcomes (10). However, most available studies have focused on the general effectiveness of IT morphine rather than directly comparing different dosing strategies. Consequently, limited data exist regarding the balance between analgesic efficacy and dose-related adverse effects across commonly used IT morphine doses, underscoring the need for dose-comparison analyses such as the present study (11-13).

Supporting this concept, studies conducted in patients undergoing video-assisted thoracoscopic surgery (VATS) have demonstrated that intrathecal morphine administered at different doses (200–600 μg) provides effective postoperative

analgesia in a dose-dependent manner when compared with control groups (14, 15). While lower doses were associated with improvements in pain scores predominantly during the early postoperative period, higher doses resulted in more sustained analgesic efficacy but were accompanied by an increased incidence of opioid-related adverse effects. Notably, reductions in postoperative opioid consumption and complication rates observed with intermediate dosing strategies in these studies highlight the importance of balancing analgesic efficacy against dose-related adverse effects when selecting intrathecal morphine doses.

Building on these observations, the present study demonstrated a clear dose–response relationship following thoracotomy. Increasing intrathecal morphine doses were associated with progressively lower pain scores and reduced fentanyl consumption. Unlike most previous studies evaluating single-dose strategies, the present analysis compared commonly used weight-based doses and showed that both 5 μg/kg and 8 μg/kg provided clinically meaningful analgesia lasting up to 48 hours. The lowest dose evaluated (3 μg/kg) was associated with less pronounced reductions in pain scores and fentanyl consumption, but also with a lower incidence of opioid-related adverse effects. Accordingly, the analgesic effects and side-effect profile of IT morphine varied depending on the dose used. Indeed, this study's findings demonstrated that the frequency of undesirable side effects such as nausea and vomiting, pruritus, and constipation increased with higher IT morphine doses, supporting the presence of a clear dose–response gradient across the three regimens.

Despite the prolonged duration of analgesia, higher intrathecal morphine doses in this study were associated with clinically relevant opioid-related adverse effects. The prolonged duration of analgesia observed with higher intrathecal morphine doses exceeds the analgesic duration typically reported for intravenous opioid-based regimens and is particularly relevant in thoracotomy, where postoperative pain and respiratory dysfunction frequently persist beyond the first postoperative day. A meta-analysis of 25 studies reported pruritus in 37% of patients treated with IT morphine (16). In a review of the pathophysiology and treatment of neuraxial opioid-related pruritus, Szarvas et al. reported that the incidence of neuraxial opioid-related pruritus ranged from 30% to 100% (17). Although the overall incidence of pruritus in this cohort was lower than that reported in some previous studies (18,19), adverse effects remained most prominent in the highest-dose group, limiting the routine clinical desirability of this dose.

In this study, the rate of patients with nausea, especially at the postoperative 8th hour, was statistically significantly higher in the group that received 8mcg/kg IT morphine compared to other groups. Additionally, 20% of the patients in Group 8mcg had vomited. These findings support that the nausea and vomiting side effects of IT morphine depend on the dose of IT morphine and that the risk of these side effects increases as the dose increases. Among the study's endpoints, the 8th hour postoperatively marked the endpoint with the highest rate of patients with nausea and vomiting as well as pruritus. Slappendel et al. (21) applied 25 to 200 mcg of IT morphine to patients undergoing total hip surgery under spinal anesthesia. They observed the highest incidence of pruritus between postoperative 6th and 9th hours, in line with the findings of this study. This finding may be attributed to the fact that the effect of IT morphine peaks in this time interval. The dose-dependent increase in adverse effects, particularly pruritus and nausea, is consistent with the hydrophilic nature of morphine, which facilitates rostral spread within the cerebrospinal fluid and increases exposure of medullary opioid receptors involved in these symptoms (22).

Higher intrathecal morphine doses were associated with delayed gastrointestinal recovery in the present study. Patients receiving 8 μg/kg intrathecal morphine exhibited significantly prolonged time to first flatus and delayed initiation of oral intake compared with lower-dose groups. These findings are consistent with previous reports indicating that neuraxial opioid administration may impair postoperative gastrointestinal motility and gastric emptying (23, 24). The delayed oral intake observed in the highest-dose group is likely multifactorial and may reflect both opioid-related gastrointestinal effects and the higher incidence of postoperative nausea and vomiting, resulting in reduced feeding tolerance despite standardized early feeding protocols.

Beyond these commonly observed opioid-related adverse effects, respiratory depression remains one of the most concerning complications associated with neuraxial opioid administration. Previous studies have demonstrated that intrathecal morphine doses in the range of 3–5 μg/kg are generally considered clinically safe, with a low reported incidence of respiratory depression when appropriate postoperative monitoring is implemented. Even at doses up to 10 μg/kg, the incidence of clinically significant respiratory depression has been reported to remain low, approximately 0–3%, particularly in thoracic and cardiothoracic surgical populations. In the present study, no cases of clinically significant respiratory depression were observed across any of the dosing groups, supporting the safety of the intrathecal morphine regimens used. These findings are consistent with previous literature and suggest that, under standardized perioperative management and vigilant postoperative monitoring, intrathecal morphine can be administered within this dosing range without a clinically relevant increase in respiratory risk (25).

### 4.1. Limitations of the Study

This study has several limitations. First, its retrospective and single-center design inherently limits the level of evidence and may introduce selection or information bias. Second, the relatively small sample size, particularly after dividing patients into four groups, may reduce the statistical power for detecting

differences in secondary outcomes. Third, only ASA I–II patients were included, limiting generalizability to higher-risk surgical populations. Fourth, potential confounders—such as intraoperative opioid administration, residual surgical variability despite reporting resection type (including surgeon-related factors), and postoperative rehabilitation practices—could not be fully controlled due to the retrospective design. Finally, long-term outcomes, including the development of chronic post-thoracotomy pain, were not evaluated. Prospective, randomized dose-finding trials are warranted to validate these findings.

Increasing intrathecal morphine doses were associated with improved postoperative analgesia but also with a higher incidence of dose-related adverse effects. In this retrospective cohort, the 5 μg/kg dose was associated with effective and sustained analgesia for up to 48 hours while demonstrating a more favorable tolerability profile than the 8 μg/kg dose. These findings suggest that an intrathecal morphine dose of approximately 5 μg/kg may represent a reasonable balance between analgesic efficacy and side-effect burden for postoperative pain management following thoracotomy. However, prospective randomized dose-finding studies are required to confirm this observation and to establish the optimal dosing strategy.

**Conflict of interest**

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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**Authors' contributions**

Concept: E.T., I.S.K., Design: E.T., I.S.K., Data Collection or Processing: E.T., I.S.K., I.T., Analysis or Interpretation: E.T., IS.K., I.T., Literature Search: E.T., I.S.K., I.T., Writing: E.T., I.S.K., I.T.

**Ethical Statement**

Approval was obtained from Ondokuz Mayıs University Clinical Research Ethics Committee, the study started. The ethics committee decision date is 24/07/2020 and the number of ethical committee decisions is 2020/508.

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