Original Article

Comparison of two different intrathecal morphine doses for postoperative analgesia after video-assisted thoracoscopic surgery

Volkan Okbaz, Mediha Turktan, Ersel Gulec, Zehra Hatıpoglu, Cansu Bahcecı[1], Ismail C. Karacaoglu[2]

Departments of Anesthesiology and Reanimation and [2]Thoracic Surgery, Cukurova University Faculty of Medicine, Adana, [1]Department of Econometrics and Statistics, Adnan Menderes University Faculty of Economics, Aydın, Turkey

Abstract

Background and Aims: Postoperative pain is one of the most common problems after thoracic surgery. In this study, we aimed to investigate the analgesic effects of two different doses of intrathecal morphine (ITM) based on ideal body weight in patients who underwent video-assisted thoracoscopic surgery (VATS).

Material and Methods: Forty-six patients scheduled for elective lung resection were included in this study. Patients were allocated to receive 10 μg/kg (Group I) and 7 μg/kg (Group II) ITM according to the ideal body weight for postoperative analgesia. Intraoperative and postoperative hemodynamic variables, postoperative morphine consumption, pain scores (at rest and effort), side effects, and additional analgesic requirements were recorded.

Results: Postoperative pain scores did not differ in the first 12 h between the groups, but were significantly lower in Group I compared with Group II at 18 and 24 hours ($P = 0.024$ and $P = 0.017$ at rest, and $P = 0.025$ and $P = 0.002$ at effort, respectively). Postoperative morphine consumption was statistically significantly lower in Group I at all time periods ($P < 0.05$). The incidence of side effects was similar for both groups ($P > 0.05$).

Conclusions: The use of 10 μg/kg ITM according to the ideal body weight provides more effective analgesia without increasing the side effects compared to 7 μg/kg ITM after VATS.

Keywords: Intrathecal morphine, postoperative analgesia, side effect, thoracic surgery

Key Message: 1. The optimal dose of ITM to improve the analgesic effect for VATS is unclear. 2. According to the ideal body weight, 10 μg/kg ITM provides more effective analgesia without increasing side effects compared to 7 μg/kg.

Introduction

Video-assisted thoracoscopic surgery (VATS) has many advantages such as less postoperative pain, fewer complications, reduced cost, shortened hospital stay, and a cosmetically smaller incision compared to thoracotomy.[1] However, postoperative pain is still considered a major problem.

Although thoracic epidural analgesia has been accepted as the gold standard, nowadays, ultrasonography (USG)-guided thoracic plane and wall blocks have gained popularity. However, these techniques may not provide ease of application at all times and under all conditions due to the skill and experience required for the use of USG and possible complications. Intrathecal morphine (ITM), called "the forgotten child" by Cohen 10 years ago, could be an alternative technique for

Address for correspondence: Dr. Mediha Turktan, Department of Anesthesiology and Reanimation, Cukurova University Faculty of Medicine, Adana, Turkey.
E-mail: mediturktan@gmail.com

Access this article online

Quick Response Code:

Website: https://journals.lww.com/joacp

DOI: 10.4103/joacp.joacp_258_23

How to cite this article: Okbaz V, Turktan M, Gulec E, Hatıpoglu Z, Bahcecı C, Karacaoglu IC. Comparison of two different intrathecal morphine doses for postoperative analgesia after video-assisted thoracoscopic surgery. J Anaesthesiol Clin Pharmacol 2025;41:219-25.

Submitted: 12-Jun-2023
Accepted: 20-Oct-2023 **Published:** 22-Mar-2025

postoperative pain management.[2] This technique can be used for multimodal analgesia, either as a single-dose injection or with other analgesic techniques.[3,4]

However, the optimal dose of ITM to improve the analgesic effect and reduce complications is unclear.[5] In previous studies, ITM was administered either based on patients' actual body weight or at a fixed dose. In our study, we investigated the analgesic effects of two different ITM doses administered according to ideal body weight in patients who underwent VATS. The primary outcome measures were postoperative pain score and morphine consumption, the secondary outcome measures were hemodynamic variables and side effects.

Material and Methods

Following faculty ethics committee approval and written informed patient consent, 46 patients were included in this randomized, prospective, and double blind study [Figure 1]. The study protocol was registered at ClinicalTrials.gov (NCT05588336). Inclusion criteria were as follows: the American Society of Anesthesiologists (ASA) physical status 1–3, over 18 years, and scheduled for elective video-assisted thoracoscopic lung resection under general anesthesia. Exclusion criteria were lack of patient consent, ASA >3, under 18 years old, a history of serious cardiac, hepatorenal, metabolic, endocrine or psychological diseases, coagulopathy

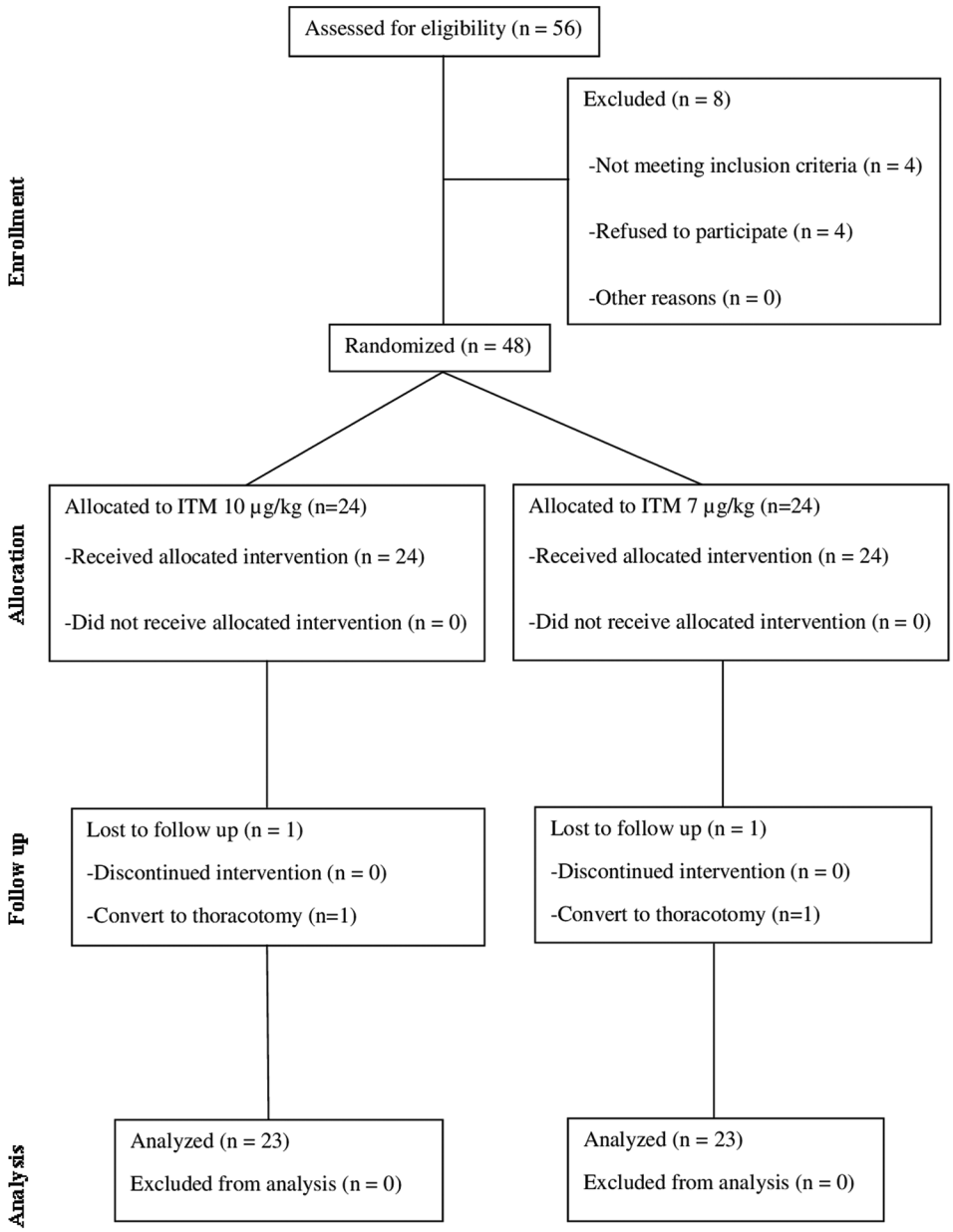

Figure 1: Consort flow diagram of study

or anticoagulant drug use, sensitivity or contraindication to study drugs, an infection at the site of injection, inability to comprehend pain scale and any contraindication to the use of patient-controlled analgesia (PCA) device.

All patients were informed about the study, visual analog scale (VAS, 0: no pain, 10: worst pain), and PCA device during the pre-anesthesia examination. Patients were allocated randomly using a closed envelope technique into two groups: Group I (n = 23): 10 μg/kg ITM group or Group II (n = 23): 7 μg/kg ITM group, according to ideal body weight. The ideal body weight was calculated using the formulas 45.5 + 0.91× (height–152.4) in female patients and 50 + 0.91× (height–152.4) in male patients. The study drugs were prepared in normal saline and the total volume was 2 mL.

The patients were given no premedication. In the operating room, after routine monitoring (electrocardiography, pulse oximetry, heart rate, and non-invasive blood pressure), anesthesia induction was performed with intravenous (i.v.) 1.5 to 2 mg/kg propofol and 1 μg/kg fentanyl. The patients were intubated with a double-lumen endobronchial tube after adequate muscle relaxation was achieved with i.v. 0.6 mg/kg rocuronium bromide. The correct position of the double-lumen tube was confirmed with a fiberoptic bronchoscope after tracheal intubation and final surgical position. An artery catheter was inserted into the radial artery. Anesthesia was maintained with 1 to 2% sevoflurane in O_2–air mixture and i.v. 0.15 mg/kg rocuronium, if required. The patients were warmed with a forced air warmer. Postoperative nausea and vomiting prophylaxis was provided with 8 mg ondansetron intravenously.

In the lateral decubitus position, ITM was performed for postoperative analgesia at L3-4 or L4-5 intervertebral space through a midline approach using a 27 G pencil point spinal needle. After a free flow of clear cerebrospinal fluid (CSF) was confirmed, a "pre-prepared study drug" was injected. All ITM injections were performed by the same experienced anesthesiologist, who was blinded to the study groups.

Ibuprofen (400 mg, i.v.) was added to all patients as part of multimodal analgesia at the closure of the thorax. At the end of the surgery, all anesthetic agents were discontinued, patients were turned to the supine position, and neuromuscular blockade was reversed by i.v. neostigmine (0.05 mg/kg) and atropine (0.015 mg/kg). Following extubation, patients were transferred to the postanesthetic care unit (PACU) and after total recovery from anesthesia (stable hemodynamic and respiratory variables, fully awake, ability to obey verbal commands), the patients were allowed to use PCA (CADD Legacy PCA pump, Smiths Medical MD, Inc., St. Paul, MN). The PCA was prepared with 40 mg morphine HCl in 100 mL saline. The PCA bolus dose was 0.02 mg/kg morphine every 10 min without a background infusion.

Demographic data of patients, duration of anesthesia, duration of surgery, and duration of extubation were recorded. Intraoperative systolic, diastolic and mean arterial blood pressures (SBP, DBP, MAP), and heart rate (HR) were recorded at baseline, post-intubation 15, 30, 45, 60 min and then at 30-min intervals. Postoperative SBP, DBP, HR, inspired oxygen fraction (FiO_2), peripheral oxygen saturation (SpO_2), respiratory rate (RR), pain scores, sedation scores, additional analgesic requirement, nausea–vomiting scores, cumulative doses of morphine, and side effects also were recorded at 1, 6, 12, 18 and 24 h postoperatively. Postoperative pain scores at rest and effort (during motion or coughing) were evaluated using VAS. If the patients complained of pain (VAS > 4 at rest), meperidine (0.5 mg/kg, i.v.) was given as a rescue analgesic. Sedation was assessed by a 6-point Ramsay sedation scale (1: awake, anxious, 2: awake, cooperative, oriented, 3: sleepy, response to verbal stimulus, 4: sleepy, brisk response to glabellar tactile stimulus, 5: sleepy, sluggish response to glabellar tactile stimulus, 6: no response). The severity of nausea was evaluated using a 5-point scale (1: absent, 2: mild, 3: moderate, 4: severe, 5: worst nausea), and if the nausea score was > 3, i.v. 8 mg ondansetron was given, repeated as needed. Pruritis was treated with i.v. 10 mg of chlorpheniramine, repeated as needed.

Respiratory depression was defined as SpO_2 < 90 in room air, respiratory rate < 10 breaths/min, or Ramsay sedation scale > 3. Over-sedation was defined as a sedation scale > 3 combined with respiratory depression, and if observed, treatment with i.v. naloxone was planned. Hypotension was considered a decrease in MAP by 20% of the baseline value or MAP < 60 mmHg or SBP < 90 mmHg for more than 3 min, and was treated by i.v. bolus dose of norepinephrine 10 μg. Bradycardia was defined as HR < 50 beats/min, and if observed, it was treated by i.v. atropine 0.5 mg.

All postoperative data were recorded by a separate anesthesiologist in the postoperative pain team of our department who was blinded to the study.

Statistical analysis

All analyses were performed using the IBM SPSS Statistics Version 25.0 statistical software package (IBM Corp. Released 2011, IBM SPSS Statistics for Windows, Version 25.0 Armonk, NY: IBM Corp). Categorical variables are expressed as numbers and percentages and continuous variables as mean

and standard deviation (if necessary, median and minimum–maximum) were evaluated. The Chi-square test, Fisher's exact test, or Yates' Chi-square test, whichever was appropriate, was used to compare the categorical measurements. Whether the data were normally distributed or not was examined by the Shapiro–Wilk test. The independent samples *t*-test was used for normally distributed data and the Mann–Whitney *U* test was used if variables had an abnormal distribution. The Friedman test was used to compare within-group series for non-normally distributed. The statistical level of significance for all tests was considered to be 0.05.

Power analysis was performed using the G*Power software version 3.1.9.4 program to determine the sample size. Based upon previous study data of Askar *et al.*,[6] the sample size was determined as at least 23 patients per group, with a two-sided design at a significance level of 5%, an effect size of 85%, and a power of 80% (with using the postoperative pain scores variable with a mean difference of 1.7 and standard deviation of 2).

Results

Forty-six patients completed the study for final analysis [Figure 1]. There was no statistical difference between the two groups in terms of demographic data and surgical characteristics ($P > 0.05$) [Table 1].

Intraoperative and postoperative hemodynamic variables were similar between the two groups ($P > 0.05$). Postoperative respiratory depression was not observed in any of the patients for both groups.

Postoperative pain scores at rest and effort during the first 12 h were generally lower in Group I than in Group II, but this difference was not statistically significant ($P > 0.05$). However, both pain scores (at rest and effort) were significantly lower in Group I at other assessment time points compared with Group II [Figure 2].

In both groups, approximately half of the patients ($n = 12$ in Group I, $n = 13$ in Group II) needed rescue analgesics in the first postoperative hour. The dose of meperidine was similar (21.7 ± 26.4 mg for Group I, 27.2 ± 27.1 mg for Group II) ($P > 0.05$). No rescue analgesia was required in either group at other assessment time points. The total amount of PCA morphine consumed by 24 h was significantly lower in Group I (11.4 ± 6.0 mg) compared with Group II (19.7 ± 11.3 mg) ($P = 0.004$) [Table 2].

There was no statistically significant difference between the groups in terms of the frequency of side effects ($P > 0.05$) [Table 3]. There was no statistically significant difference between the groups in terms of the postoperative sedation scores ($P > 0.05$) and there was no case of over-sedation. None of the patients had a nausea score above 3.

Table 1: Demographic data and surgical characteristics

	Group I (*n*=23)	Group II (*n*=23)	*P*
Gender (female/male)	9/14	8/15	1.000
Age	52.7±15.7 59 (18-83)	57±15.91 60 (18-76)	0.239
Actual body weight (kg)	71.9±14.0 70 (51-100)	73.5±12.9 75 (50-92)	0.687
Ideal body weight (kg)	61.3±9.5 63 (44-77)	61.3±10.3 66 (43-75)	0.775
Height (cm)	166.5±9.2 169 (150-183)	166.6±9.4 170 (150-180)	0.817
Surgery type			
Wedge resection	14	18	0.405
Lobectomy	8	4	
Bulla resection	1	1	
Duration of surgery (min)	115.4±40.1 105 (55-180)	103.5±34.4 110 (30-180)	0.284
Duration of anesthesia (min)	125.2±39.7 115 (65-188)	120.6±37.0 120 (60-195)	0.691
Extubation time (min)	5.1±1.3 5 (3-8)	6.1±3.2 5 (3-15)	0.654

All values are presented as number of patients (n) or mean±SD and median (min-max)

Table 2: Postoperative PCA morphine consumption (mg)

Time periods	Group I (*n*=23)	Group II (*n*=23)	*P*
1 h	3.0±1.6 3 (0-5.9)	4.3±2.5 4.2 (0-9.2)	0.041*
6 h	5.5±4.2 4.68 (0-16.5)	10.51±7.75 9.36 (0.7-30)	0.023*
12 h	7.1±4.5 5.4 (1.4-18.3)	13.0±9.1 11 (0.7-30)	0.041*
18 h	9.0±4.8 8.01 (2.8-21.6)	15.7±10.2 16 (0.7-34)	0.032*
24 h	11.4±6.0 10.8 (2.8-25)	19.7±11.3 19.3 (0.7-40)	0.004*

*All values are presented as mean±SD and median (min-max). PCA; patient controlled analgesia. *P<0.05, compared with Group II*

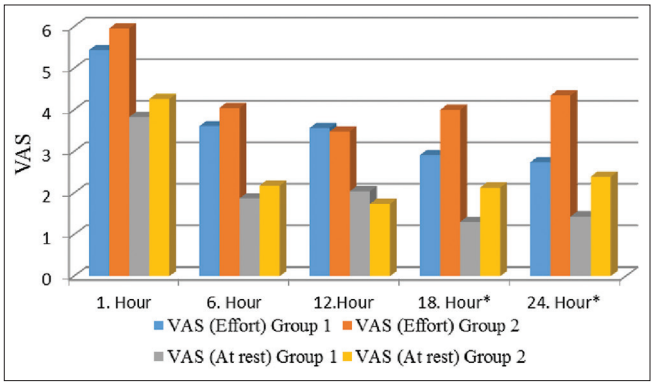

Figure 2: Postoperative pain scores at rest and effort

Table 3: The frequency of postoperative side effects

Time periods	Side effects	Group I (*n*=23)	Group II (*n*=23)	*P*
1 h	None	21 (91.3)	18 (78.3)	0.414
	Nausea	2 (8.7)	4 (17.4)	
	Dizziness	0 (0)	1 (4.3)	
6 h	None	17 (73.9)	16 (69.6)	0.750
	Pruritus	3 (13.1)	1 (4.3)	
	Nausea	2 (8.7)	4 (17.4)	
	Pruritus + nausea	1 (4.3)	1 (4.3)	
	Hypotension + nausea	0	1 (4.3)	
12 h	None	14 (60.9)	17 (74)	0.385
	Pruritus	4 (17.4)	1 (4.3)	
	Nausea	5 (21.7)	4 (17.4)	
	Pruritus+nausea	0	1 (4.3)	
18 h	None	18 (78.3)	18 (78.3)	1.000
	Pruritus	3 (13)	2 (8.7)	
	Nausea	2 (8.7)	3 (13)	
24 h	None	20 (87)	20 (87.0)	0.353
	Pruritus	3 (13)	1 (4.3)	
	Nausea	0	2 (8.7)	

All values are presented as the number of patients (n) and percent (%)

Discussion

The results of this study suggest that according to the ideal body weight, 10 μg/kg ITM significantly reduced postoperative morphine consumption and provided more effective analgesia, without increasing the incidence of side effects, compared to 7 μg/kg ITM in patients who underwent VATS.

Unlike other short-acting opioids (alfentanil, fentanyl, and sufentanil), the hydrophilic property of morphine prevents rapid distribution to other tissues.[7,8] This situation explains the slow onset and long duration of action of morphine, and its long half-life compared to others. Intrathecally administered morphine loses its effect through redistribution; firstly, it redistributes from the CSF (cerebro spinal fluid) to the brain, and then leaves the central nervous system and redistributes to lean body tissues.[7-9] The side effects of ITM are thought to be mainly due to redistribution in the brain and body. Due to the lipophilic nature of morphine, dose calculation based on ideal body weight instead of actual body weight will minimize the risk of side effects, especially in overweight patients. Therefore, in our study, we thought that it would be more appropriate to calculate the ITM dose according to the ideal body weight for an individual effective and sufficient dose. This is the most important difference of our study from the others in the literature.

To provide postoperative analgesia, ITM has been used in several types of surgery. Theoretically, ITM can be administered before or after general anesthesia, depending on the preference of the practitioner or the patient.[4,6,10] In these studies, ITM is more frequently applied after general anesthesia and we also preferred to apply ITM after general anesthesia in our study. However, there is no consensus on the optimal dosage of morphine. It was stated that as the dose of ITM increased, the duration of analgesia and the frequency of side effects also increased in cesarean section.[11] Murphy *et al.*[12] found that sufficient analgesia could not be achieved with 50 μg of ITM in patients undergoing hip arthroscopy. Rathmell *et al.*[13] showed that effective postoperative analgesia for hip arthroplasty was provided with ITM morphine (100–200 and 300 μg), and PCA morphine consumption was similar between the groups, but patient satisfaction scores were higher with 200 and 300 μg of ITM. However, they observed that 100 μg, 200 μg, or even 300 μg of ITM did not reduce postoperative morphine requirements after knee arthroplasty. This may be because knee arthroplasty is more painful and requires more analgesic agents than hip arthroplasty. Vijitpavan *et al.*[14] demonstrated that ITM (200 μg) reduced pain scores and opioid consumption compared to i.v. opioids after VATS, but this reduction was not satisfactory. Suksompong *et al.*[10] also found that postoperative opioid consumption was similar between 200 and 300 μg ITM groups after thoracotomy. However, the doses of ITM in these studies were quite low for thoracic surgery patients.

The main question here is: Does the optimal dose of ITM for adequate analgesia and minimal side effects depend on the type of surgery? In our opinion, one of the most important points in ITM administration is the use of the "adequate" dose for each patient and each type of surgery. For this reason, the optimal dose of ITM should be also adjusted for each type of surgery. Rathmell *et al.*[8] recommended ITM doses of < 100 μg after cesarean surgery, ≥500 μg after major surgery such as thoracotomy for pain control. Although VATS is a minimally invasive procedure, it does not eliminate the problem of postoperative pain. Some cases may complain of mild-to-moderate or even severe pain, which can interfere with a patient's ability to breathe and cough. Azizoğlu *et al.* used a standard dose of 0.6 mg of ITM alone and in addition to serratus anterior plane block for pain control after VATS.[4] They stated that the combination of serratus anterior plane block and 0.6 mg of ITM is a safe and effective analgesia technique for VATS. In our study, we used two different doses of ITM (10 μg/kg and 7 μg/kg) for pain relief after VATS. Although 10 μg is considered a high dose, the average ideal body weight of our patients is 61.3 ± 9.5 kg; therefore, the administered dose of ITM is close to this study. We found the pain scores (both at rest and effort) after postoperative 12 h and PCA morphine consumption at all time points were statistically significantly lower in the 10 μg/kg ITM group.

The major concern with dose escalation is an increase in the frequency and severity of adverse effects without an increase in

analgesic efficacy.[12,15] The most feared side effect is respiratory depression and it may occur as an undesirable consequence of the binding of morphine to mu receptors in the central nervous system. Because the intrathecal dose of morphine is lower than for parenteral use, the concentration at the mu receptors is also lower, and respiratory depression (if occurs) may be treated with small doses of naloxone without loss of analgesic effect.[2] Definitions of respiratory depression include low respiratory rate, high arterial $PaCO_2$, low SpO_2, high sedation scores, and/or need for naloxone treatment.[16] Hypercarbia may occur even in patients with a normal respiratory rate; therefore, sedation scores may be more sensitive than the peripheral oxygen saturation and end-tidal CO_2 values for detecting respiratory depression.[17] The risk of respiratory depression with ITM may occur even at doses as low as 200 or 300 μg, but the need for re-intubation has not been reported yet.[18,19]

It was noted that ITM (range 300 μg to 1.6 mg) had no clinically significant effect on extubation time after CABG (coronary artery bypass graft) surgery.[20,21] Aşkar *et al.*[6] demonstrated that 10 μg/kg ITM, and Liu *et al.* stated that 500 μg of ITM provides effective analgesia without respiratory depression in thoracic surgery patients.[22] In another study, the incidence of respiratory depression was similar to i.v. morphine and ITM, but lasted longer after ITM.[23] As seen, it is not clear at which dose of ITM can cause respiratory depression, and this effect appears to be dose-independent. In the present study, all patients were extubated in the operating room, and there was no significant difference in terms of extubation time between the two groups. In addition, all patients were closely followed up postoperatively with hemodynamic and respiratory monitoring and the Ramsay Sedation Scale. No patient suffered from over-sedation or respiratory depression and need for postoperative respiratory support.

Opioid-related pruritus is a dose-dependent side effect and the mechanism is still unclear.[19,24] Regardless of the route of administration, all opioids can cause nausea and vomiting, the mechanism is multifactorial, and the predominant cause is unknown.[25] Although ITM increases the frequency of emesis in a dose-related manner, this relationship is not clear in painful surgeries.[25] Rathmell *et al.*[13] reported an increased frequency of pruritus, nausea, and vomiting with ITM in hip surgery compared to the control group. Sultan *et al.*[11] also emphasized higher ITM doses are associated with increased maternal opioid-related nausea, vomiting, and pruritus in cesarean section. Gehling and Tryba[19] demonstrated that the patients who received ITM had a higher incidence of postoperative nausea, vomiting, and pruritus compared to the control group. However, the frequency of pruritus increased with the dose of ITM, but the complaints of nausea and vomiting did not. Murphy *et al.*[12] found that pruritus was observed significantly more frequently with 200 μg of ITM than with 50 and 100 μg in patients undergoing hip arthroscopy, but they could not find a relationship between other opioid-related side effects (nausea, vomiting, sedation, and respiratory depression) and morphine doses. Rebel *et al.*[26] stated that the most common ITM-related (maximum 1 mg) side effects were nausea, vomiting, and pruritus in radical prostatectomy patients, but respiratory depression, the most feared side effect, was almost never observed. In our study, pruritus was the most frequently observed side effect and it was more common in the 10 μg/kg ITM group than the 7 μg/kg ITM group, but that difference was not statistically significant. Conversely, nausea was observed more frequently with a 7 μg/kg dose of ITM compared to 10 μg/kg ITM. Our findings support that pruritus is opioid dose-related and nausea is a dose-independent side effect.

We accept that this study has certain limitations. First, because the main purpose of our study was to investigate the effect of ITM doses on postoperative analgesia and side effects in patients undergoing VATS, we did not assess intraoperative anesthetic agent consumption. Second, our study did not include a true control group because a dural puncture is an invasive procedure and this approach would be unethical. Third, urinary catheterization was removed after 24 h postoperatively, so we could not evaluate urinary retention as a side effect.

Conclusion

According to the ideal body weight, 10 μg/kg ITM provides more effective analgesia without significantly increasing the incidence of side effects compared to 7 μg/kg ITM in patients undergoing VATS. However, multicenter, prospective studies are needed to determine the ideal ITM dose in VATS.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Pu Q, Ma L, Mei J, Zhu Y, Che G, Lin Y, *et al*. Video-assisted thoracoscopic surgery versus posterolateral thoracotomy lobectomy: A more patient-friendly approach on postoperative pain, pulmonary function and shoulder function. Thorac Cancer 2013;4:84-9.
2. Cohen E. Intrathecal morphine: The forgotten child. J Cardiothorac Vasc Anesth 2013;27:413-6.
3. Bujedo BM. A clinical approach to neuraxial morphine for the treatment of postoperative pain. Pain Res Treat 2012;2012:612145. doi: 10.1155/2012/612145.

4. Azizoğlu M, Yapıcı D, Bayülgen A, Sagün A, Özdemir L, Rumeli Ş. The effect of ultrasound-guided serratus anterior plane block in addition to intrathecal morphine on early postoperative period after video-assisted thoracoscopic surgery. Turk Gogus Kalp Damar Cerrahisi Derg 2021;29:471-9.
5. Giovannelli M, Bedforth N, Aitkenhead A. Survey of intrathecal opioid usage in the UK. Eur J Anaesthesiol 2008;25:118-22.
6. Askar FZ, Kocabas S, Yucel S, Samancilar O, Cetin H, Uyar M. The efficacy of intrathecal morphine in post-thoracotomy pain management. J Int Med Res 2007;35:314-22.
7. De Gregori S, De Gregori M, Ranzani GN, Allegri M, Minella C, Regazzi M. Morphine metabolism, transport and brain disposition. Metab Brain Dis 2012;27:1-5. doi: 10.1007/s11011-011-9274-6.
8. Rathmell JP, Lair TR, Nauman B. The role of intrathecal drugs in the treatment of acute pain. Anesth Analg 2005;101:S30-43.
9. Ummenhofer WC, Arends RH, Shen DD, Bernards CM. Comparative spinal distribution and clearance kinetics of intrathecally administered morphine, fentanyl, alfentanil, and sufentanil. Anesthesiology 2000;92:739-53.
10. Suksompong S, Pongpayuha P, Lertpaitoonpan W, von Bormann B, Phanchaipetch T, Sanansilp V. Low-dose spinal morphine for post-thoracotomy pain: A prospective randomized study. J Cardiothorac Vasc Anesth 2013;27:417-22.
11. Sultan P, Halpern SH, Pushpanathan E, Patel S, Carvalho B. The effect of intrathecal morphine dose on outcomes after elective cesarean delivery: A meta-analysis. Anesth Analg 2016;123:154-64.
12. Murphy PM, Stack D, Kinirons B, Laffey JG. Optimizing the dose of intrathecal morphine in older patients undergoing hip arthroplasty. Anesth Analg 2003;97:1709-15.
13. Rathmell JP, Pino CA, Taylor R, Patrin T, Viani BA. Intrathecal morphine for postoperative analgesia: A randomized, controlled, dose-ranging study after hip and knee arthroplasty. Anesth Analg 2003;97:1452-7.
14. Vijitpavan A, Kittikunakorn N, Komonhirun R. Comparison between intrathecal morphine and intravenous patient control analgesia for pain control after video-assisted thoracoscopic surgery: A pilot randomized controlled study. PloS One 2022;17:e0266324. doi: 10.1371/journal.pone.0266324.
15. Fléron MH, Weiskopf RB, Bertrand M, Mouren S, Eyraud D, Godet G, *et al*. A comparison of intrathecal opioid and intravenous analgesia for the incidence of cardiovascular, respiratory, and renal complications after abdominal aortic surgery. Anesth Analg 2003;97:2-12.
16. Ko S, Goldstein DH, VanDenKerkhof EG. Definitions of "respiratory depression" with intrathecal morphine postoperative analgesia: A review of the literature. Can J Anaesth 2003;50:679-88.
17. Law CJ, Visser EJ. Unconsciousness and severe respiratory depression following intrathecal morphine analgesia for lumbar spinal surgery. Acute Pain 2007;9:163-7.
18. Meylan N, Elia N, Lysakowski C, Tramer MR. Benefit and risk of intrathecal morphine without local anaesthetic in patients undergoing major surgery: Meta-analysis of randomized trials. Br J Anaesth 2009;102:156-67.
19. Gehling M, Tryba M. Risks and side-effects of intrathecal morphine combined with spinal anaesthesia: A meta-analysis. Anaesthesia 2009;64:643-51.
20. Metz S, Schwann N, Hassanein W, Yuskevich B, Nixon T. Intrathecal morphine for off-pump coronary artery bypass grafting. J Cardiothorac Vasc Anesth 2004;18:451-3.
21. Alhashemi JA, Sharpe MD, Harris CL, Sherman V, Boyd D. Effect of subarachnoid morphine administration on extubation time after coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 2000;14:639-44.
22. Liu N, Kuhlman G, Dalibon N, Moutafis M, Levron JC, Fischler M. A randomized, double blinded comparison of intrathecal morphine, sufentanil and their combination versus IV morphine patient-controlled analgesia for postthoracotomy pain. Anesth Analg 2001;92:31-6.
23. Bailey PL, Lu JK, Pace NL, Orr JA, White JL, Hamber EA, *et al*. Effects of intrathecal morphine on the ventilatory response to hypoxia. N Engl J Med 2000;343:1228-34.
24. Szarvas S, Harmon D, Murphy D. Neuraxial opioid-induced pruritus: A review. J Clin Anesth 2003;15:234-9.
25. Borgeat A, Ekatodramis G, Schenker CA. Postoperative nausea and vomiting in regional anesthesia: A review. Anesthesiology 2003;98:530-47.
26. Rebel A, Sloan P, Andrykowski M. Postoperative analgesia after radical prostatectomy with high-dose intrathecal morphine and intravenous naloxone: A retrospective review. J Opioid Manag 2009;5:331-9.