Randomized Trial

High Dose Intrathecal Morphine for Major Abdominal Cancer Surgery: A Prospective Double-Blind, Dose-Finding Clinical Study

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Background: Despite 30 years of clinical research, we still do not know the optimal dose of intrathecal morphine (ITM) when used alone.

Objectives: A safety investigation and comparison of the analgesic efficacy of ITM 0.2 mg, 0.5 mg, and 1 mg in patients undergoing major abdominal cancer surgery.

Study Design: A randomized, double-blind trial.

Setting: Academic medical center.

Methods: Ninety patients were randomly assigned to receive morphine intrathecally either 0.2 mg (Group I, ITM 0.2 mg, n = 30), 0.5 mg (Group II, ITM 0.5 mg, n = 30), or 1 mg (Group III, ITM 1 mg, n = 30) dissolved in 5 mL physiological saline before general anesthesia. Assessment parameters included hemodynamics, respiratory rate, peripheral arterial oxygenation, sedation score, pain severity, time of first analgesic request, total analgesic consumption, and side effects in the first 72 hours.

Results: The mean time to first request for rescue analgesia was significantly prolonged in Group II (22.13 ± 5.21 hours, $P < 0.001$) and Group III (30.83 ± 4.89 h, $P < 0.001$), compared with Group I (0.50 ± 0.66 hours). The mean tramadol consumption dose was significantly reduced in Group II (383.33 ± 91.28 mg, $P < 0.001$) and Group III (300 ± 69.48 mg, $P < 0.001$) compared with Group I (770 ± 114.92 mg). Patients received 1 mg ITM showed lower VAS scores in the first 48 h postoperative ($P < 0.04$) compared with Group I and Group II. No significant differences were observed in the mean systolic and diastolic blood pressure values, respiratory rate, and peripheral arterial oxygen saturation between groups. Lower mean heart rate values were observed in Group III patients at 6 hours ($P < 0.01$) and 12 hours ($P < 0.03$) postoperative compared with Group I and Group II patients. Six patients (20%) in Group II and 8 (26.7%) in Group III exhibited pruritus compared with 2 patients (6.66%) in Group I ($P < 0.01$). No intergroup statistical differences were observed for other studied side effects.

Limitations: This study is limited by its small sample size.

Conclusion: One mg ITM provided superior analgesia for 48 hours postoperative compared with 0.2 mg and 0.5 mg ITM with a nonsignificant difference in the incidence of side effects. Further studies of larger sample size are recommended to confirm these findings.

Key words: Anesthesia, analgesia, abdominal cancer, opioids, intrathecal, morphine

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Surveys indicate that more than 80% of patients undergoing major abdominal surgery experience moderate to severe postoperative pain in spite of recent advances in pharmacology and sophisticated drug delivery systems (1). Inadequate postoperative pain relief can prolong recovery and length of hospitalization, increase health care costs, and reduce patient satisfaction.

Myelan et al (2), in their meta-analysis of randomized trials, concluded that intrathecal morphine injection (ITM), without local anesthetic, in patients undergoing major abdominal surgery under general anesthesia has provided adequate postoperative analgesia. Patients who received ITM needed less fentanyl equivalents introperatively and received considerably less IV morphine for rescue analgesia after operation (2). The single-shot spinal injection should be attractive because it is simple, reliable, lacks catheter insertion, and costs less than its epidural or peripheral nerve block counterparts (3). However, the dosing and efficacy of intrathecal opioids remain limited due to fear of respiratory depression.

In a meta-analysis of ITM, the seriousness of the induced respiratory depression was related to the dose of ITM (4). The incidence of late respiratory depression is reported to be 4% to 7% for patients receiving ITM (0.8 mg to 2 mg), compared with 0.25% to 0.4% for those receiving epidural morphine (2 mg to 4 mg) (5). Lower doses of ITM (0.3 mg to 0.4 mg) are linked to minimal risks of respiratory depression (4,6). However, there is evidence that respiratory depression may occur with doses as low as 0.2 mg to 0.3 mg of ITM (7).

Despite 30 years of clinical research, we still do not know the optimal dose of ITM when used alone. The optimal dose, the dose that has adequate analgesic efficacy without causing life-threatening respiratory depression, remains unknown, as does the method and adequate length of monitoring of respiratory depression.

The aim of the present study was to establish the safety profile and efficacy of 1 mg ITM compared with 0.2 mg and 0.5 mg ITM in patients undergoing major abdominal cancer surgery.

Methods

This study was approved by the local research ethics committee in the South Egypt Cancer Institute, Faculty of Medicine, Assiut University, Egypt. After obtaining an informed written consent, 90 ASA I – III cancer patients, aged 30 – 50 years and scheduled for major abdominal surgery (e.g. hemicolectomy or cystectomy), were included in the study. Excluded from the study were patients with a known allergy to the study drugs; significant cardiac, respiratory, renal, or hepatic disease; coagulation disorders; low back pain or other back problems; drug or alcohol abuse; BMI > 30 kg\m2, and psychiatric illnesses that would interfere with perception and assessment of pain.

Using an online research randomizer (www.randomizer.org), patients were randomly allocated into 3 groups of 30 patients each to receive either; 0.2 mg morphine (Group I ITM 0.2 mg), 0.5 mg morphine (Group II ITM 0.5 mg) or 1 mg morphine (Group III ITM 1 mg). The assigned drugs were dissolved in 5 mL physiological saline and administered intrathecal before induction of general anesthesia.

Preoperatively, patients were instructed in the Visual Analogue Pain scale (VAS) score ranging from 0 to10 (with 0 = no pain and 10 = the worst pain imaginable). Patients received 5 mg oral diazepam the night before surgery and the anesthetic technique was standardized in all groups.

Patients were placed in the sitting position and the low back area was cleaned with povidine-iodine and draped. After local anesthesia had been provided with 1.0 mL of 2% lidocaine, subarachnoid puncture was performed with a 25-gauge Whitacre spinal needle at the L3-4 interspace, and the assigned intrathecal treatment was administered. No local anesthetic was added to the intrathecal medication. The needle was then removed, patients were placed in the supine position, and general anesthesia was induced. Anesthesia was induced with fentanyl 1.5 – 2 µg/kg, propofol 2 – 3 mg/kg, and lidocaine 1.5 mg/kg. Endotracheal intubation was facilitated by cis-atracurium 0.15 mg/kg. Monitoring included electrocardiography, noninvasive blood pressure, SPO2%, temperature, and a Foley catheter was inserted for monitoring urine output and remained in situ for 24 hours. Anesthesia and muscle relaxation were maintained by isoflurane 1 – 1.5 MAC in 50% oxygen/air mixture and cis-atracurium 0.03 mg/kg bolus given every 30 minutes, respectively. At the conclusion of surgery, muscle relaxation was reversed by neostigmine 50 µg/kg and atropine 20 µg/kg. Patients were extubated and transferred to the surgical intensive care unit (SICU).

The SICU data included heart rate, noninvasive systolic and diastolic blood pressure, respiratory rate, and oxygen saturation immediately postoperative and at 6, 12, 18, 24, 36, 48, 60, and 72 hours postoperative. VAS

scores at rest were assessed at the same time points. A rescue analgesia of IV tramadol 100 mg was given if requested or if pain scores were ≥ 3. The time to first request of analgesia and total analgesic consumption in the first 72 hours postoperatively were recorded. The patient's level of sedation was assessed at the same time points using a modified Observer's Assessment of Alertness/Sedation (OAA/S) scale (where 6 = agitated to 0 = does not respond to deep stimulus).

The attending anesthesiologist, surgeon, and patient care giver or data collection personel were blinded to the patient assignment.

Postoperative adverse effects such as nausea, vomiting, hypotention, bradycardia, respiratory depression, mechanical ventilation, pruritus, and sedation were recorded and treated. Respiratory depression was defined as respiratory frequency of less than 10 bpm and hypotension was defined as decrease in systolic arterial pressure of at least 20 mmHg compared to preoperative baseline values. Patients were mechanically ventilated if they were sedated (score = 3), with respiratory rate < 8 br/pm or PaCo2 was > 50mmHg and naloxone was administered.

Statistical Analysis

The primary outcome measure was the total dose of analgesics consumed in the first 72 hours postoperative. Secondary outcome measures were time to first request of rescue analgesics, postoperative VAS scores, hemodynamics, and incidence of early postoperative side effects. Our power analysis was based on estimating a 20% reduction in analgesic requirements in a sample population of 300. A calculated sample size of 28 would have an 80% power of detecting a difference at a 0.05 level of significance using a confidence interval of 95%.

Analysis was performed using SPSS version 17 (Chicago, USA). Data were presented as mean ± SD, range, numbers, and percentages. ANOVA followed by post-hoc test were used for comparison of parametric data. Kruskal Wallis test was used to compare non-parametric data while Mann-Whitney was used to compare between 2 groups. Chi-square test was used for comparison between percentages and frequencies. $P < 0.05$ was considered significant.

Results

One hundred and eleven patients were screened for eligibility to participate in this study. Fifteen patients refused to participate in the study and 6 patients were inoperable and excluded from statistical analysis. Ninety patients subsequently consented and enrolled with no patient dropouts. These 90 patients were equally distributed in the 3 groups (n = 30 per group). There were no differences between groups in demographic characteristics regarding weight, height, BMI, and surgical time (Table 1).

The mean time to first request for rescue analgesia (Table 2) was significantly prolonged in Group II (ITM 0.5 mg) (22.13 ± 5.21 h, $P < 0.001$) and Group III (ITM 1

Table 1. *Patients demographics and clinical characteristics.*

Item	Group I ITM 0.2 mg n = 30	Group II ITM 0.5 mg n = 30	Group III ITM 1 mg n = 30	*P* value
Age (years)	50.86 ± 8.06 (35 – 64)	51.03 ± 7.76 (36 – 63)	49.46 ± 7.36 (36 – 60)	0.691
Weight (Kg)	73.83 ± 9.60 (55-89)	73.76 ± 9.10 (56 – 88)	74.93 ± 7.76 (60 – 88)	0.849
Height (cm)	166.63 ± 4.89 (157 – 175)	166.67 ± 5.83 (155 – 175)	166.93 ± 6.16 (15 5- 176)	0.975
BMI (kg/m2)	26.71 ± 4.22 (18.38 – 36.11)	26.62 ± 3.56 (19.38-31.93)	27.0 2 ± 3.69 (20.76 – 33.69)	0.914
ASA I/II/III	1/27/2	3/26/1	2/25/3	0.372
Operative procedure:				
-Pelvic excentration -Hemicolectomy -Sigmoidectomy -Cystectomy -Hystrectomy	3 8 10 5 4	2 9 11 4 4	2 7 12 6 3	0.352
Operative time (h)	2.78 ± 0.66	2.76 ± 0.55	2.75 ± 0.53	0.976

Data are expressed as mean ± SD, range and number. *P*: significance between groups.
ITM: intrathecal morphine.

Table 2. *Time of first request of rescue analgesia and total tramadol consumption in the first 72 hours postoperative.*

Item	GROUP I ITM 0.2 mg n = 30	GROUP II ITM 0.5 mg n = 30	GROUP III ITM 1 mg n = 30	P1a	P1b	P1c
Time of first request (hr).	0.5 0 ± 0.66	22.13 ± 5.21	30.83 ± 4.89	0.001	0.001	0.03
Total analgesic consumption dose (mg)	770 ± 114.92	383.33 ± 91.28	300 ± 69.48	0.001	0.001	0.04

Data are expressed as mean± SD, P1a: significance between group I and II. P1b: significance between group I and III. P1c: significance between group II and III. ITM: intrathecal morphine.

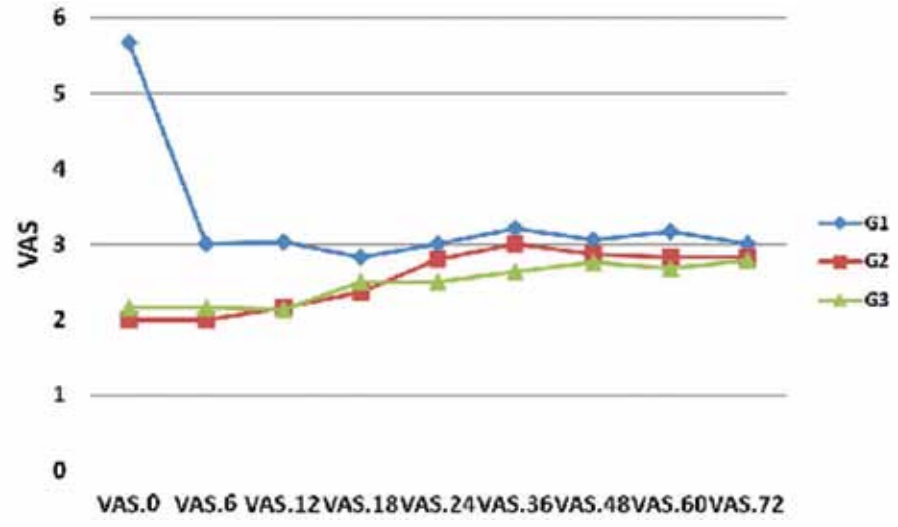

Fig. 1. *The Visual Analogue Scale scores.*

mg) (30.83 ± 4.89 h, $P < 0.001$), compared with Group I (ITM 0.2 mg) (0.50 ± 0.66 h). The mean tramadol consumption dose was significantly reduced in Group II (ITM 0.5 mg) (383.33 ± 91.28 mg, $P < 0.001$) and Group III (ITM 1 mg) (300 ± 69.48 mg, $P < 0.001$) compared with Group I (ITM 0.2 mg) (770 ± 114.92 mg). Compared with Group II (ITM 0.5 mg), patients in Group III (ITM 1 mg) showed longer request times ($P < 0.03$) and lower tramadol consumption ($P < 0.04$).

Lower postoperative pain scores were exhibited in patients in Group II (ITM 0.5 mg) ($P < 0.04$) and Group III (ITM 1 mg) ($P < 0.02$), compared with Group I (ITM 0.2 mg) (Fig. 1). After 24 hours postoperative, there were no significant changes in pain scores between Group II (ITM 0.5 mg) and Group I (ITM 0.2 mg). After 48 hours postoperative, there were no significant changes in pain scores between the 3 groups.

No significant differences were observed in the mean systolic and diastolic blood pressure values between groups. Although there was a trend towards lower mean SBP values in Group III (ITM 1 mg) at 12 and 18 hours postoperative (Figs. 2 and 3). Lower mean heart rate values were observed in Group III (ITM 1 mg) patients at 6 hours ($P < 0.01$) and 12 hours ($P < 0.03$) postoperative compared with Group I (ITM 0.2 mg) and Group II (ITM 0.5 mg) patients with a nonsignificant difference between the 3 groups in other time points (Fig. 4).

A lower nonsignificant ($P > 0.05$) decrease in respiratory rate mean values was observed in Group III (ITM 1 mg) patients compared with Group I (ITM 0.2 mg) and Group II (ITM 0.5 mg) patients (Fig. 5). There were no differences between groups in the mean oxygen saturation throughout the study (Fig. 6).

Six patients (20%) in Group II (ITM 0.5 mg) and 8 (26.7%) in Group III (ITM 1 mg) exhibited pruritus compared with 2 (6.66%) in Group I (ITM 0.2 mg) ($P < 0.01$). Respiratory depression developed in one patient (3.3%) in Group III (ITM 1 mg). She was 65 years old, frail, ASA III, with cancer of the ovary and had undergone an abdominal hysterectomy with bilateral oophorectomy. The patient showed delayed return of spontaneous

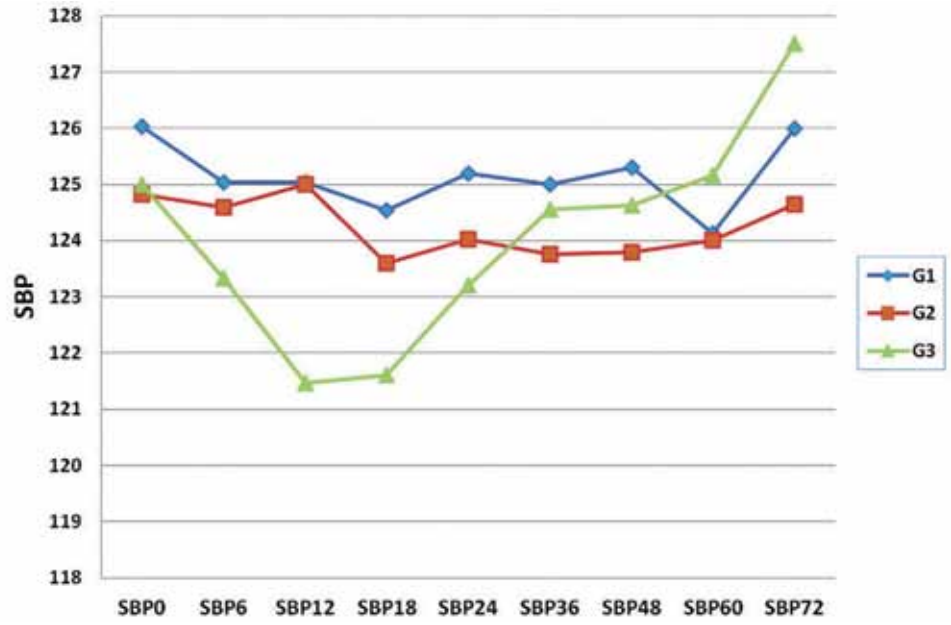

Fig. 2. Changes in the mean systolic blood pressure (SBP) with time.

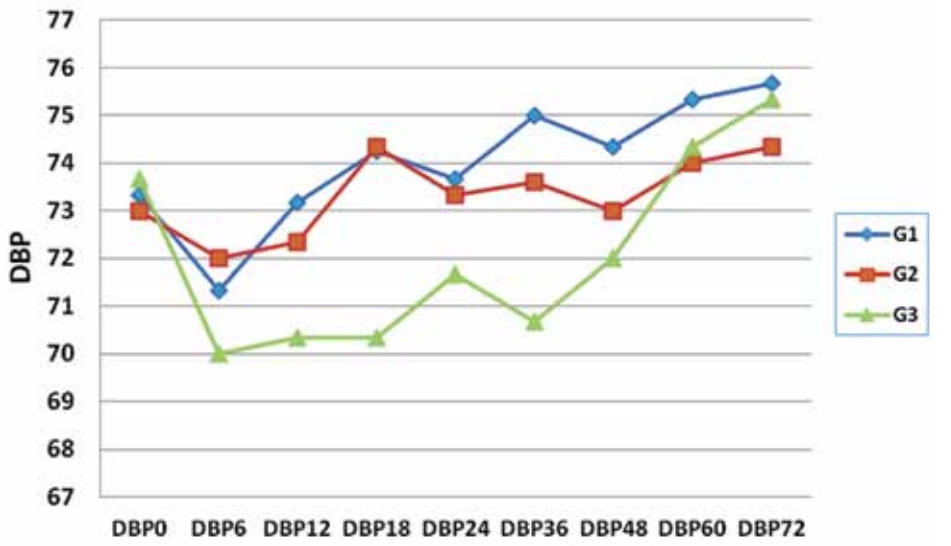

Fig. 3. *Changes in the mean diastolic blood pressure (DBP) with time.*

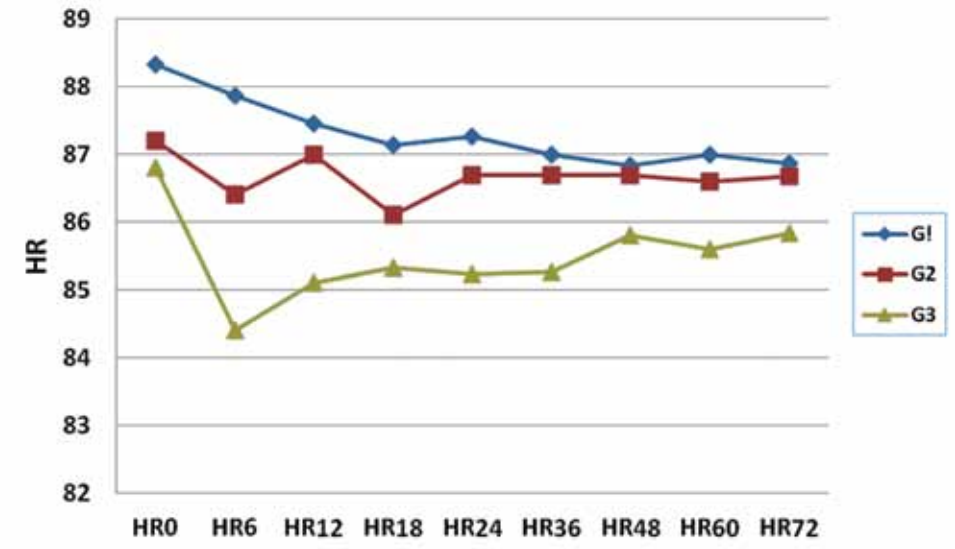

Fig. 4. *Changes in the mean heart rate (HR) with time.*

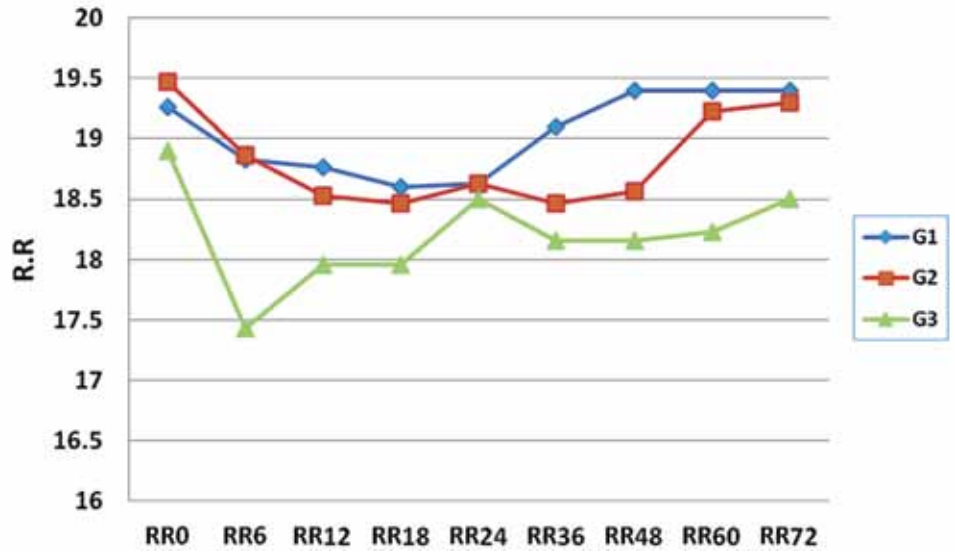

Fig. 5. *Changes in the mean respiratory rate (RR) with time.*

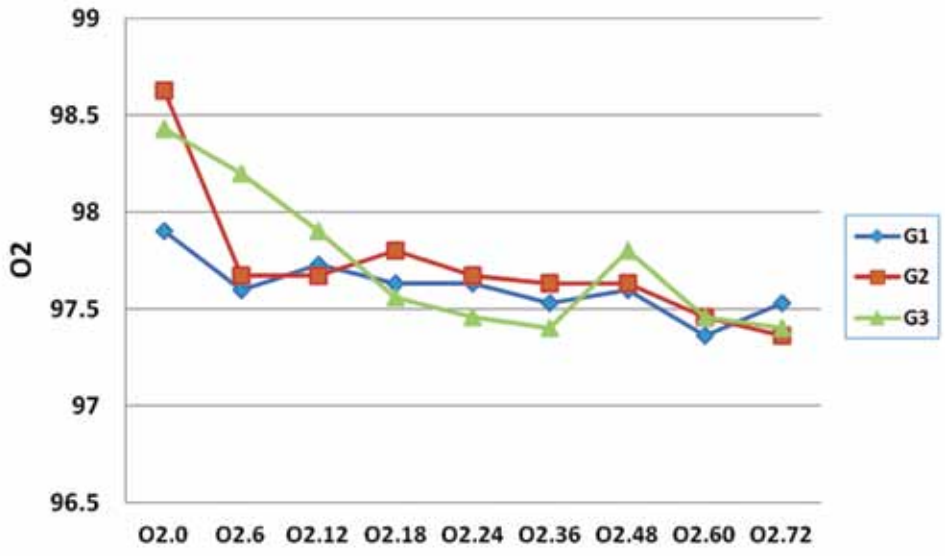

Fig. 6. *Changes in the mean oxygen saturation (SaO2%) with time.*

Table 3. *Postoperative side effects.*

Side effect	GROUP I ITM 0.2 mg N = 30	GROUP II ITM 0.5 mg N = 30	GROUP III ITM 1 mg N = 30	*P* value
Nausea	11 (36.7%)	7 (23.3%)	6 (20%)	0.303
Vomiting	12 (40%)	5 (16.7%)	8 (26.7%)	0.129
Pruritus	2 (6.66%)	6 (20%)	8 (26.7%)	0.01
Hypotension	-------	---------	--------	-------
Bradycardia	--------	--------	---------	-------
Respiratory depression			1 (3.33%)	--------
Mechanical ventilation	--------	------	1 (3.33%)	-------
Sedation	-------	-------	------	-------

Data are expressed as number and percentages. *P*: significance between groups. ITM: intrathecal morphine.

muscle activity and IV naloxone 0.4 mg was administered immediately postoperative. No intergroup statistical differences were observed for other studied side effects (Table 3).

Discussion

This study evaluated the effect of ITM without local anesthesia in 3 different doses (0.2, 0.5, and 1 mg) in adult cancer patients undergoing major abdominal surgery under general anesthesia. The major findings were that patients who received 1 mg ITM showed lower postoperative tramadol requirements and lower VAS scores in the first 48 hours postoperative, with a nonsignificant difference between doses afterwards.

In a meta-analysis of 27 studies (8) (15 concerning cardiothoracic, 9 abdominal, and 3 spinal surgeries) with a total of 645 patients who received doses between 100 and 4000 µg, it was demonstrated that among those given ITM, VAS at rest, on a scale of 10 cm, was 2 cm lower at 4 hours and 1 cm lower at 12 and 24 hours and this effect was more pronounced with movement; the relative improvement being more than 2 cm throughout the period of monitoring. This lower VAS score was significantly better than

the outcome with other analgesic techniques such as intraoperative low dose ketamine (scores fell by 0.4 cm), postoperative NSAIDs (scores fell by 1 cm), and even continuous epidural infusion technique with local anesthetics (scores fell by 1 cm) (9). In the current study, a superior analgesic effect was recorded in patients who received 1 mg ITM compared with 0.2 and 0.5 mg. In contrast, in this review, the authors did not detect a linear relationship between the dose administered and the degree of analgesia reached or any of the adverse effects and they could not recommend a minimum effective dose. The authors also concluded that we still do not know the optimal dose of ITM when used alone.

In the present study, ITM was not combined with local anesthesia, therefore, a synergistic effect of ITM and local anesthesia, as suggested by Eberle and Norris (10), can be excluded.

In the absence of clear dosing guidelines, intrathecal opioids (ITOs) were labeled as having a disturbingly high frequency of respiratory depression and it was believed that lower doses still provided adequate postoperative analgesia (11). Chadwick and Ready (12) studied the analgesic effect of 0.3 mg to 0.5 mg ITM after caesarean section and reported that 78% of the patients experienced more than 20 hours of sufficient analgesia. These findings differ from our study and may be explained by the combined use of ITM and local anesthesia in obstetrics and labor analgesia and the less invasiveness of these operations compared with major abdominal cancer dissection surgeries tested in our study.

However, in Myelan et al's (8) meta-analysis of randomized trials assessing the benefits and risks of ITM without local anesthetics, the opioid-sparing effects of ITOs for abdominal surgery were consistently apparent. In an editorial, Stoeling (13) encouraged the anesthesia community to consider ITOs as the preferable route for opioid-based analgesia and to develop a new attitude towards this underused modality. In a retrospective study of nearly 6,000 patients who received ITOs for postoperative pain (3), the morphine doses ranged from 0.2 mg to 0.8 mg. Patients were very satisfied with the pain control, and the side effects were easily managed with a 3% incidence of respiratory depression. The duration of the observed analgesia lasted more than 23 hours when high-dose ITM was used, which confirmed the observation from our study and from previous studies (14).

Respiratory depression with deep sedation is a rare but fatal complication of opioid administration. Intrathecal opioid induced respiratory depression is divided into 2 types: early respiratory depression which occurs within 2 hours after opioid administration and delayed respiratory depression which occurs more than 2 hours after opioid administration (15). Early respiratory depression due to ITM administration has never been reported. In contrast, all reports of clinically relevant delayed respiratory depression have evolved from the administration of morphine either intrathecally or epidurally (5). Delayed respiratory depression usually occurs 6 – 12 hours following intrathecal or epidural morphine administration (16) and can be readily reversed with the administration of a mu antagonist (Naloxone), or a Kappa agonist/mu antagonist (Nalbuphine) (17-19).

The risk factors for development of respiratory depression include increasing age and ASA class, the concomitant use of long-acting sedatives, positive pressure ventilation, and co-existing respiratory disease (20).

In this study, among patients who received high dose ITM (Group III ITM 1 mg, n = 30), one frail patient (ASA class III) (3.3%) showed atypical presentation of early respiratory depression. She had delayed return of spontaneous muscle activity and received IV naloxone immediately postoperative. Eschertzhuber et al (21) studied the quality of analgesia and the incidence of side effects of a low-dose regime (morphine 5μg/kg plus sufentanil 1μg/kg) of intrathecal opioids compared with those of a high-dose regime (morphine 15 μg/kg plus sufentanil 1 μg/kg) in scoliosis surgery in children and adolescents. In accordance with our results, they found no respiratory depression with the high-dose regimen, however time until extubation was significantly longer when compared with the low-dose regimen, which should be considered in planning postoperative management (21). And consequently all patients receiving neuraxial opioids should be monitored for adequate ventilation (e.g., respiratory rate, depth of respiration), oxygenation (e.g., pulse oximetry when appropriate), and level of consciousness (22). However, this study (14 per group) and ours (30 per group) were of small sample sizes.

The main target in this study was to prolong the duration of postoperative analgesia as much as possible through using a single high dose ITM, taking into consideration the possibility of respiratory depression as a side effect. Liposome-encapsulated preparations of morphine have been documented to produce substantial blood concentrations for 6 days after a single subcutaneous injection in mice (23). Similar prepara-

tions have been documented to produce appreciable blood concentrations and analgesic effects after epidural administration in rats and dogs (24,25). Epidural administration of liposome-encapsulated morphine (DepoDur) is well tolerated by human patients (26) and clinical trials of its efficacy in human patients are currently underway.

Further studies are needed to examine whether the beneficial structural and pharmacokinetic properties of multivesicular liposome formulations will translate into improved clinical outcomes, either because of decreased drug toxicity or increased drug efficacy.

Study Limitations

This study of small sample size was powered to investigate analgesic efficacy. Small pain studies are likely to find results by random chance (27). They are unlikely to identify the rare but clinically relevant adverse effects, e.g. respiratory depression, or to show differences in the incidence of such side effects.

Conclusion

In summary, a high dose of 1 mg ITM provided superior analgesia for 48 hours postoperative compared with 0.2 mg and 0.5 mg ITM with a nonsignificant difference in the incidence of side effects. Further studies of larger sample sizes are recommended to confirm these findings. To administer high-dose ITM in surgical patients, careful patient selection and strict postoperative monitoring are recommended.

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