Spine

SPINE Volume 42, Number 12, pp E740–E747

LITERATURE REVIEW

Intrathecal Morphine in Spine Surgery

A Meta-analysis of Randomized Controlled Trials

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Study Design. Meta-analysis of randomized controlled trials (RCTs).

Objective. The aim of this study was to evaluate the effectiveness of intrathecal morphine (ITM) in reducing postoperative pain and opioid analgesic consumption following spine surgery.

Summary of Background Data. The use of ITM following adult spine surgery is of particular interest because of the ease of access to the thecal sac and the potential to provide adequate analgesia at low doses. However, previous studies of ITM have been limited by small sample sizes and conflicting results.

Methods. A comprehensive search of PubMed, Web of Science, Clinicaltrials.gov, and the Cochrane Central Register of Controlled Trials for prospective RCTs was performed by two independent reviewers. Postoperative opioid consumption, pain scores, and complications were documented from the identified studies. Standard mean differences (SMDs) were applied to continuous outcomes and odds ratios were determined for dichotomous outcomes.

Results. Eight RCTs involving 393 subjects met inclusion criteria and were included in this meta-analysis. Patients receiving ITM (ITM group) as an adjunct to postoperative opioid analgesic were compared to patients receiving postoperative opioids only (control group). Postoperative morphine equivalent consumption was significantly lower during the first 24 hours postoperative in the ITM group ($P < 0.001$). Pain scores were similarly lower in the first 24 hours following spine surgery in those who received ITM ($P < 0.001$). In patients administered ITM, a greater percentage experienced pruritus ($P < 0.001$). Respiratory depression was solely encountered in the ITM group ($P = 0.25$). There were no significant differences between the ITM and control groups in terms of sedation ($P = 0.18$), nausea ($P = 0.67$), vomiting ($P = 0.62$), or length of stay ($P = 0.13$).

Conclusion. In patients undergoing spine surgery, use of ITM significantly reduced opioid analgesic consumption and Visual Analogue Schores pain scores compared to controls within the first 24 hours postoperatively. High-quality, follow-up RCTs with large sample sizes are recommended to determine the potential of supplementary ITM in spine surgery and complete the side effects profile.

Key words: analgesia, complications, intrathecal morphine, length of stay, meta-analysis, opioid consumption, perioperative care, postoperative pain, randomized controlled trial, spine surgery.

Level of Evidence: 1

Spine 2017;42:E740–E747

Intrathecal morphine (ITM) was first used to treat severe intractable pain in humans in 1979.[1] The primary advantage of ITM administration is the potential to confer adequate short-term analgesia at comparably low doses. In spine surgery, specifically, ITM is an attractive analgesic owing to accessibility of the thecal sac and reliability of the procedure.[2–4] Furthermore, several clinical trials of patients who underwent spine surgery have reported that ITM can effectively reduce postoperative analgesia consumption and postoperative pain, respectively.[5–6]

However, other studies have reported no difference in pain relief using adjunct intrathecal opioids with patient-controlled analgesia (PCA) compared to PCA alone.[7] In addition, existing trials of ITM have been limited by small sample sizes.[5–6] Furthermore, opioid-related side effects constitute a major deterrent to routine use of ITM. In fact, a recent meta-analysis found significantly greater incidence of respiratory depression, pruritus, and urinary retention in patients who received ITM following cardiac, thoracic, spine, abdominal, or hysterectomy surgery.[8]

This meta-analysis of ITM was performed to determine whether adjunct ITM could effectively reduce pain following spine surgery without drastically increasing the incidence of complications. The primary outcome was the

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Acknowledgment date: June 27, 2016. First revision date: August 24, 2016. Acceptance date: September 16, 2016.

The manuscript submitted does not contain information about medical device(s)/drug(s).

No funds were received in support of this work.

No relevant financial activities outside the submitted work.

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DOI: 10.1097/BRS.0000000000002198

difference in postoperative opioid consumption in the 24 hours following surgery. Secondary outcomes included differences in pain scores, length of stay, and adverse postoperative events.

MATERIALS AND METHODS

Search Strategy

A comprehensive search was designed and performed with the help of a medical librarian. The following databases were searched for prospective randomized controlled trials (RCTs): PubMed, Web of Science, Clinicaltrials.gov, and the Cochrane Central Register of Controlled Trials. The terms "intrathecal morphine," "spine surgery," and "postoperative pain," were used with word variations to produce search strategies tailored to each database. The retrieved results were last updated on February 23, 2015.

Inclusion and Exclusion Criteria

Articles that met the following criteria were incorporated into the meta-analysis: the article described a RCT; subjects were aged 18 years or older; subjects underwent spine surgery; subjects in at least one arm received ITM; opioid consumption was reported; pain scores were reported; adverse events were reported; anesthesia was administered. The exclusion criteria for this study were the following: intrathecal drug combinations were administered or intrathecal analgesic was combined with local anesthetic at the operation site; subjects were positive for a history of chronic opioid use; <10 subjects were included in treatment arm(s) of interest; the study did not incorporate the elements described by the inclusion criteria. Two reviewers (A.P. and I.A.) screened the list of studies independently using the predetermined inclusion and exclusion criteria. Agreement was quantified by Kappa scores. Discordant studies were reviewed by a third party (A.T.) to resolve the discrepancies. Each study included in the meta-analysis was evaluated with the Cochrane Collaboration risk of bias tool.

Data Extraction

Data were extracted from the eligible studies by two authors (A.P. and A.T). Authors of each study were contacted for additional data, but no supplemental data were received. The following study characteristics were extracted: study authors, year published, sample size, primary postoperative analgesic, and mode of administration of analgesic. The following outcomes reported by at least three trials were analyzed: postoperative opioid consumption, pain scores, length of stay, and complications. Given that the analgesic effect of intrathecally injected morphine lasts for 18 to 24 hours,[9] opioid consumption and pain score data within the first postoperative day were selected for analysis. For studies that reported nonmorphine primary postoperative analgesics, opioid analgesics were converted to morphine equivalents for analysis.[10–11,13] Additionally, pain scores were averaged across the postoperative period to produce a composite score and normalized to a 0 to 10 scale before analysis.[10,13] The following complication data were recorded as dichotomous outcomes: pruritus, nausea, vomiting, sedation, and respiratory depression. In one trial, sedation was dichotomized before analysis despite being reported as a continuous outcome.[11]

Statistical Analysis

A total of eight studies were incorporated into the meta-analysis,[2–4,10–14] which was conducted with Review Manager 5.3.5 for Mac. The Cochrane Handbook was used as reference for the conduct of this meta-analysis.[15] Standardized mean difference (SMD) and 95% confidence interval (CI) were determined for continuous outcomes such as morphine equivalent consumption, pain scores, and length of stay. In studies that failed to report standard deviation, these values were imputed by calculating the pooled variance and performing a sensitivity analysis in accordance to the same meta-analysis method described by Furukawa *et al*.[16] Odds ratio (OR) and 95% CI were calculated for the following dichotomous outcomes: pruritus, nausea, vomiting, sedation, and respiratory depression. Heterogeneity between the trials was measured using χ^2 ($P < 0.10$) and I^2 test (I^2 >50%). If an outcome was associated with substantial heterogeneity, the random-effects model was used to determine the overall effect; if not, the fixed-effects model was used. The significance level for the overall effect was set at $\alpha = 0.05$.

RESULTS

Search Results

The comprehensive search returned a total of 3049 articles from PubMed (n = 980), Web of Science (n = 1209), Clinicaltrials.gov (n = 127), and the Cochrane Central Register of Controlled Trials (n = 733). After 985 duplicates were excluded, 2064 articles were screened independently by two investigators by reviewing titles and abstracts. A total of 21 articles were determined to be potentially eligible ($\kappa = 0.6$). The full-text review yielded eight studies ($\kappa = 0.9$), which were incorporated into the meta-analysis (Figure 1). Risk of bias can be viewed in Figure 2. Study characteristics were recorded in Table 1.[2–4,10–14] Morphine Equivalent Consumption, Postoperative Pain, and Length of Stay are recorded in Table 2.

Within the first 24 hours following spine surgery, morphine equivalent consumption was statistically lower in the cohort that received ITM (SMD −0.93; 95% CI −1.32 to −0.53; $P < 0.001$; Figure 3). In addition, the patients in the ITM group experienced, on average, less pain within the first postoperative day compared to their counterparts (SMD −0.47; 95% CI −0.69 to −0.25; $P < 0.001$; Figure 4). Although patients that received ITM remained in the hospital for fewer days compared to control, this difference was not statistically significant (SMD −0.69; 95% CI −1.58 to 0.20; $P = 0.13$; Figure 5). Funnel plots were used to indicate symmetry about the standard error (Figure 6A).

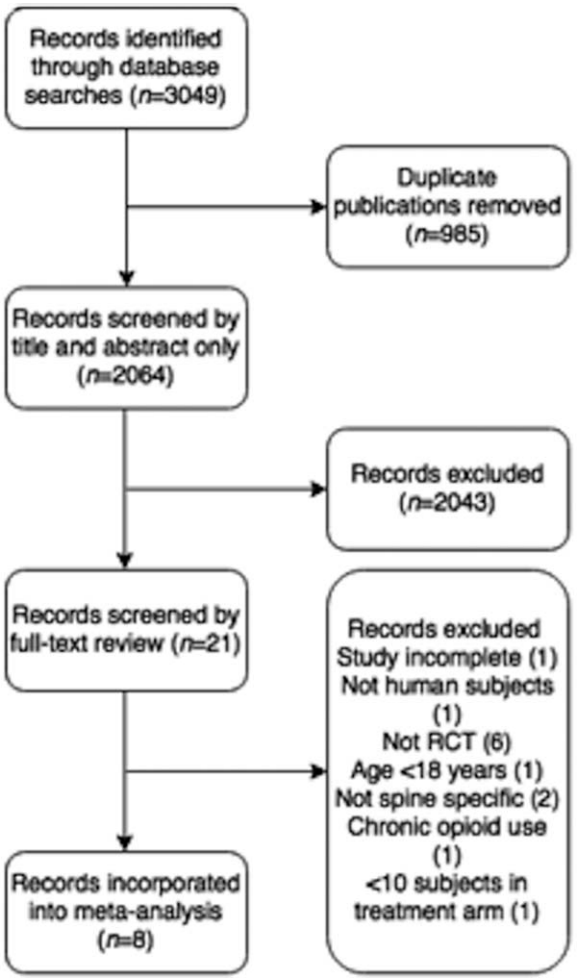


Figure 1. Flow diagram.

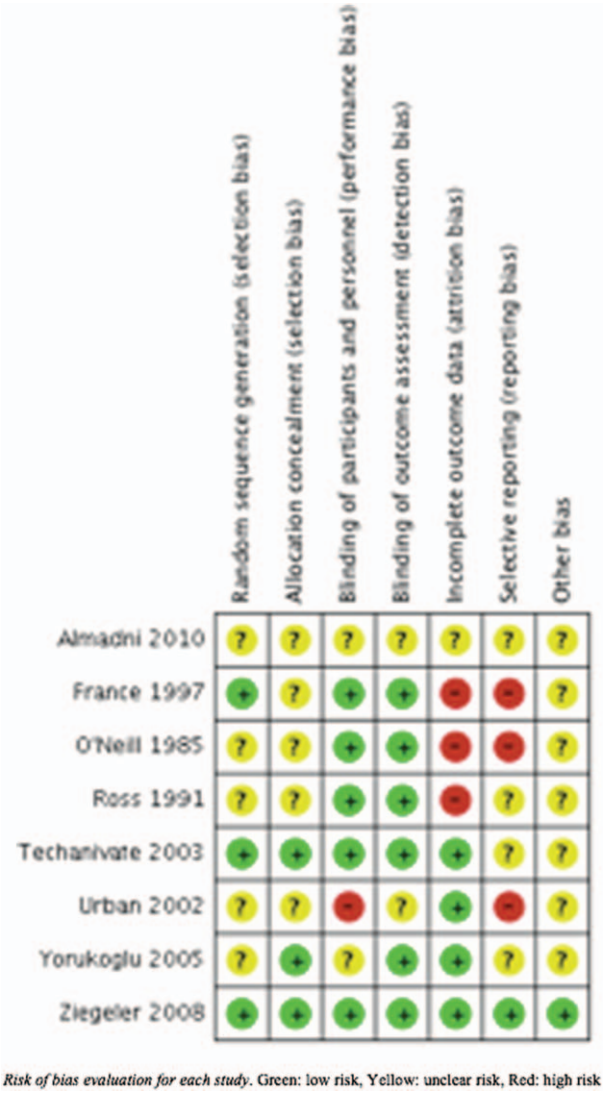


Figure 2. Risk of bias was evaluated for each study included in the meta-analysis.

Postoperative Complications

The incidence of pruritus was determined to be statistically greater in patients who received ITM (OR 4.09; 95% CI 1.84–9.11; $P < 0.001$; Figure 7; Table 3). Neither nausea (OR 0.86; 95% CI 0.44–1.68; $P = 0.67$; Figure 8) nor vomiting (OR 1.22; CI 0.55 to 2.70; $P = 0.62$; Figure 9) was experienced in amounts that would be considered statistically significant when comparing the intrathecal and control groups. Sedation occurred more commonly in the control group, although this was not considered significant (OR 0.54; 95% CI 0.22–1.32; $P = 0.18$; Figure 10). Respiratory depression was more commonly encountered in the ITM group (OR 3.48; 95% CI 0.41–29.32; $P = 0.25$; Figure 11). For each complication, symmetry about the standard error was displayed with funnel plots in Figure 6B. Several adverse events were not analyzed because of being reported by fewer than three studies: urinary retention, constipation, and symptoms of cerebrospinal fluid leak. Urinary retention and constipation were more commonly encountered in the ITM group[12] and there were no signification differences between groups in terms of symptoms of cerebrospinal fluid (CSF) leak such as postdural puncture headache (PDPH).[3,13]

DISCUSSION

Currently, no clinical consensus exists regarding whether supplementary ITM can effectively reduce postoperative pain without additional side effects. In an effort to address this ambiguity, this meta-analysis was completed to address

TABLE 1. Characteristics of the Studies Incorporated in the Meta-analysis

First Author (Year)	Sample Size: ITM (Control)	Primary Analgesic (Mode of Administration)
France *et al* (1997)[2]	42 (26)	Morphine (IV-PCA)
O'Neill *et al* (1985)[10]	24 (22)	Papaveretum* (IM)
Ross *et al* (1991)[12]	42 (14)	Morphine (SC)
Urban *et al* (2002)[4]	42 (23)	Morphine (IV-PCA)
Techanivate *et al* (2003)[3]	20 (20)	Morphine (IV-PCA)
Yörükoglu *et al* (2005)[11]	20 (20)	Meperidine* (IM)
Ziegeler *et al* (2008)[13]	23 (23)	Piritramide* (IV-PCA)
Almadni and Yen (2010)[14]	18 (14)	Morphine (IV-PCA)

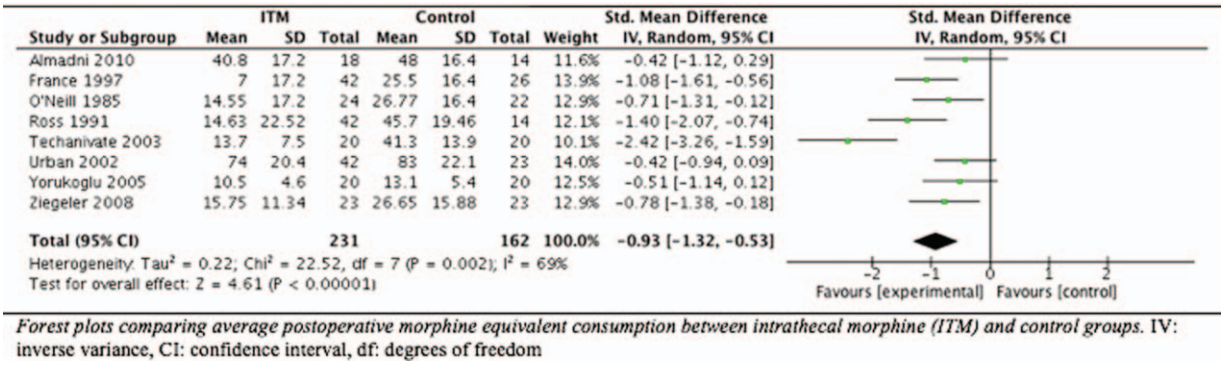
IM indicates intramuscular; ITM, intrathecal morphine; IV, intravenous; PCA, patient-controlled analgesia; SC, subcutaneous.

**Converted to morphine equivalents.*

TABLE 2. Postoperative Morphine Equivalent Consumption, Postoperative Pain Scores, and Length of Stay

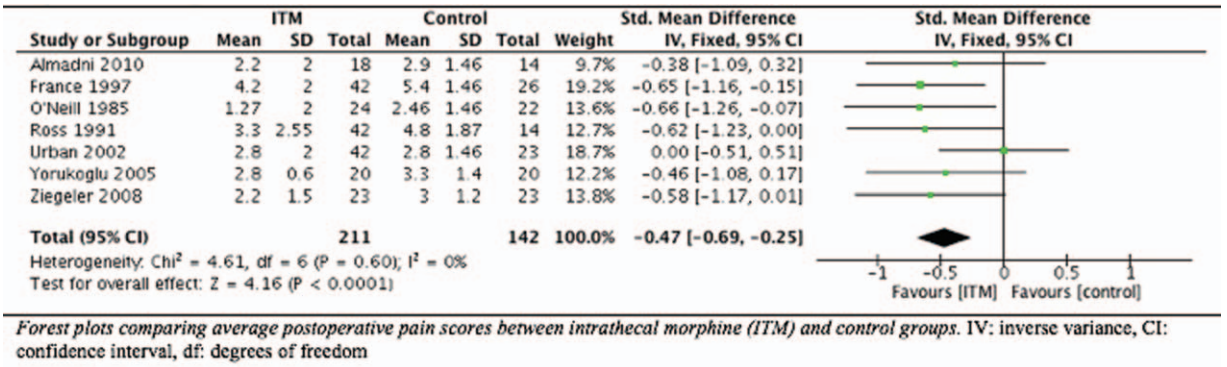
Outcome	# of Studies	Sample Size ITM (Control)	Analysis Model	SMD (95% CI)	*P* Hetero	*P* Effect
Morphine equivalents*	8	231 (162)	Random effects	−0.93 (−1.32 to −0.53)	0.002	<0.001
Pain scores*	7	211 (142)	Fixed effects	−0.47 (−0.69 to −0.25)	0.60	<0.001
Length of stay	3	107 (63)	Random effects	−0.69 (−1.58 to 0.20)	<0.001	0.13

CI indicates confidence interval; ITM, intrathecal morphine; SMD, standard mean difference.
**Missing standard deviation data imputed.*



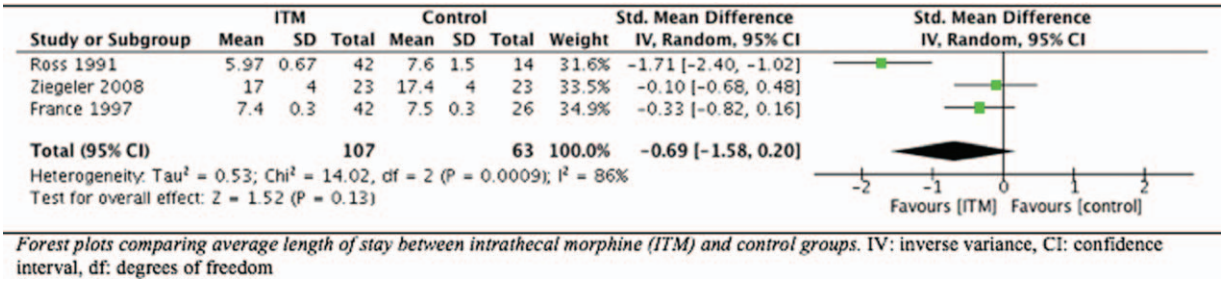
Forest plots comparing average postoperative morphine equivalent consumption between intrathecal morphine (ITM) and control groups. IV: inverse variance, CI: confidence interval, df: degrees of freedom

Figure 3. Morphine equivalent consumption.



Forest plots comparing average postoperative pain scores between intrathecal morphine (ITM) and control groups. IV: inverse variance, CI: confidence interval, df: degrees of freedom

Figure 4. Postoperative pain scores.



Forest plots comparing average length of stay between intrathecal morphine (ITM) and control groups. IV: inverse variance, CI: confidence interval, df: degrees of freedom

Figure 5. Length of stay.

the patient-centered clinical outcomes, particularly, postoperative opioid consumption, pain scores, length of stay at the facility, and adverse events.

Our results suggest that ITM exhibited an overall opioid-sparing effect because patients who received ITM consumed fewer opioids during the first 24 hours following surgery. Also, in the first 24 hours following surgery, the ITM group was associated with significantly lower pain scores. These results provide evidence that adjunctive ITM alleviates pain during the initial 24 hours following spine

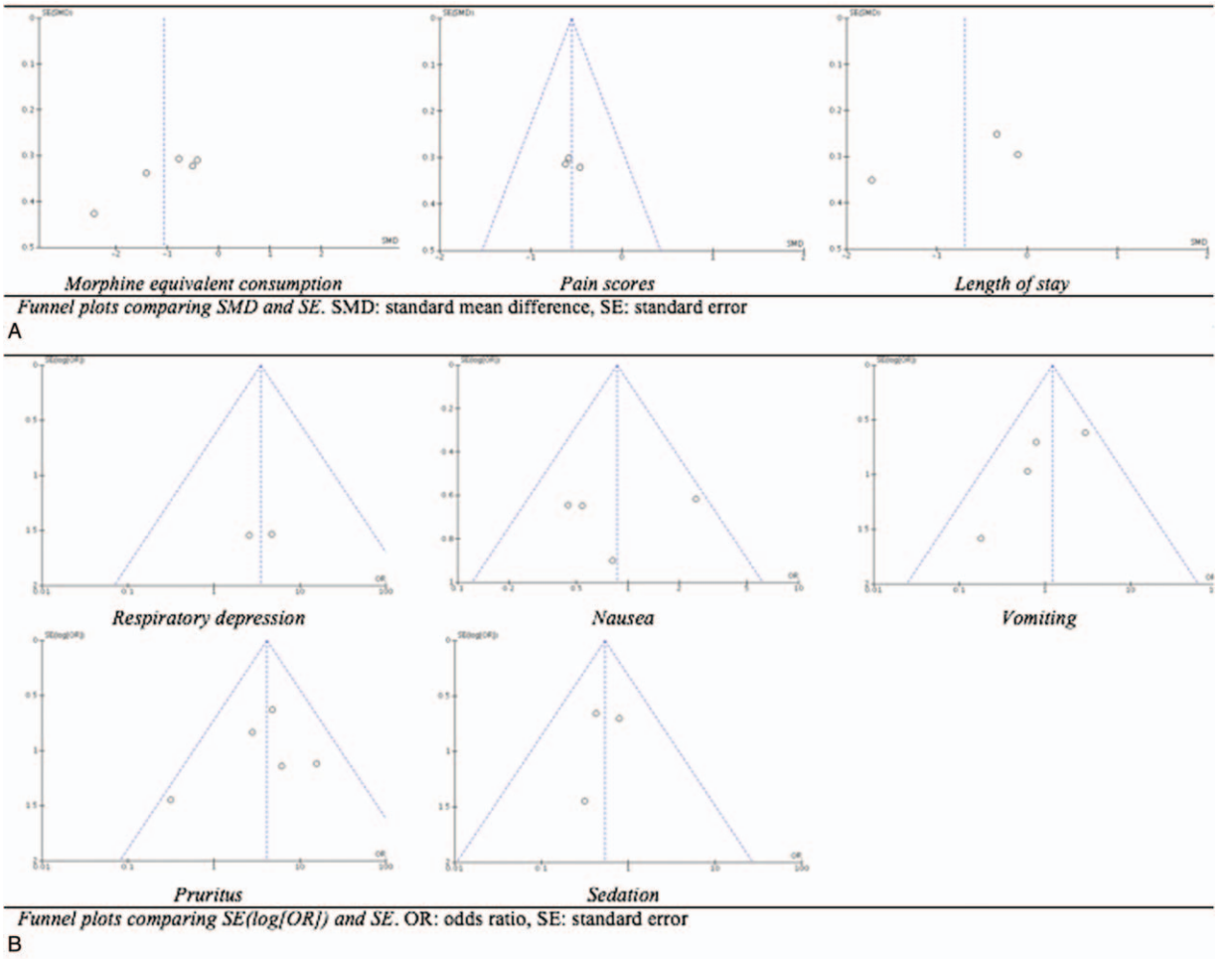


Figure 6. (**A**) Funnel plots of morphine equivalent consumption, pain scores, and length of stay. (**B**) Funnel plots of complications.

surgery and may be preferred to alternative opioid pain management options in patients undergoing spinal surgery. Although supplemental ITM was associated with a shorter length of stay, this difference was not statistically significant. Given that the average length of stay was between 10.1 and 10.8 days and the reported duration of ITM is only 18 to 24 hours,[9] the effects of ITM were apparent only over the initial postoperative period and did not significantly affect how long a patient remained at the facility.

In regards to postoperative side effects of opioid usage, pruritus was experienced significantly more often in the ITM group. These findings are corroborated by several large-scale studies, which have reported pruritus as the most commonly encountered adverse event after intrathecal injections in a variety of surgical operations.[17–18] Because subjects experienced significantly more pruritus if administered ITM, efforts to prevent, screen for, and treat pruritus may need to be focused on patients that are given adjunct ITM.

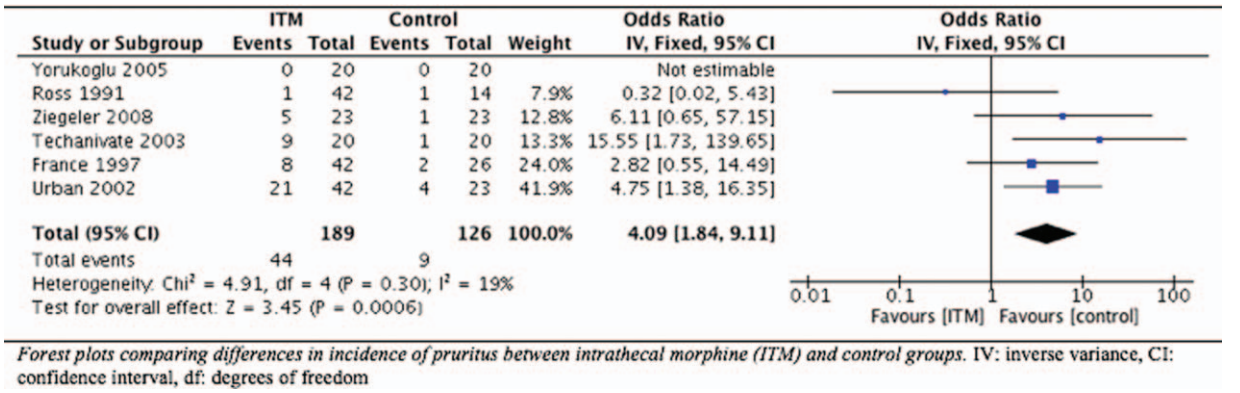
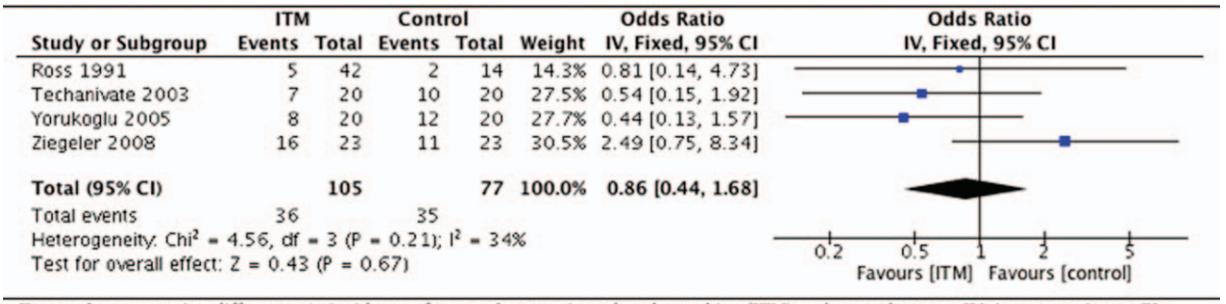


Figure 7. Pruritus.

TABLE 3. Postoperative Complications

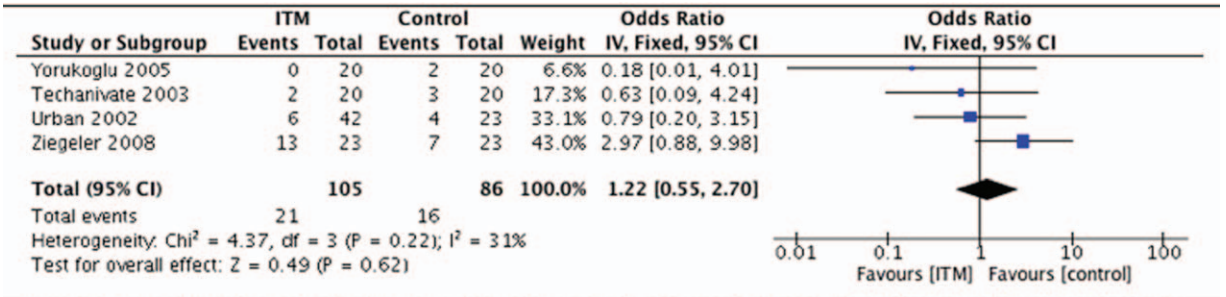
Outcome	# of Studies	Events (ITM Total)	Events (Control Total)	Analysis Model	OR (95% CI)	*P* Hetero	*P* Effect
Pruritus	6	44 (189)	9 (126)	Fixed effects	4.09 (1.84–9.11)	0.30	<0.001
Nausea	4	36 (105)	35 (77)	Fixed effects	0.86 (0.44–1.68)	0.21	0.67
Vomiting	4	21 (105)	16 (86)	Fixed effects	1.22 (0.55–2.70)	0.22	0.62
Sedation	4	17 (124)	19 (77)	Fixed effects	0.54 (0.22–1.32)	0.76	0.18
Respiratory depression	8	6 (231)	0 (162)	Fixed effects	3.48 (0.41–29.32)	0.78	0.25

CI indicates confidence interval; ITM, intrathecal morphine; OR, odds ratio.



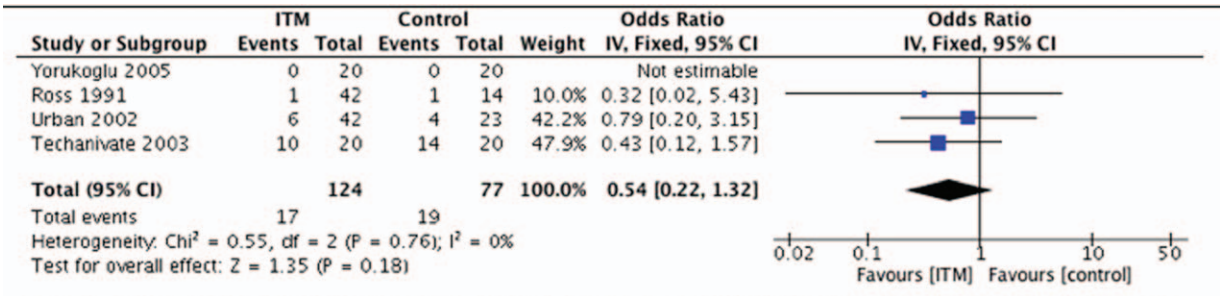
Forest plots comparing differences in incidence of nausea between intrathecal morphine (ITM) and control groups. IV: inverse variance, CI: confidence interval, df: degrees of freedom

Figure 8. Nausea.



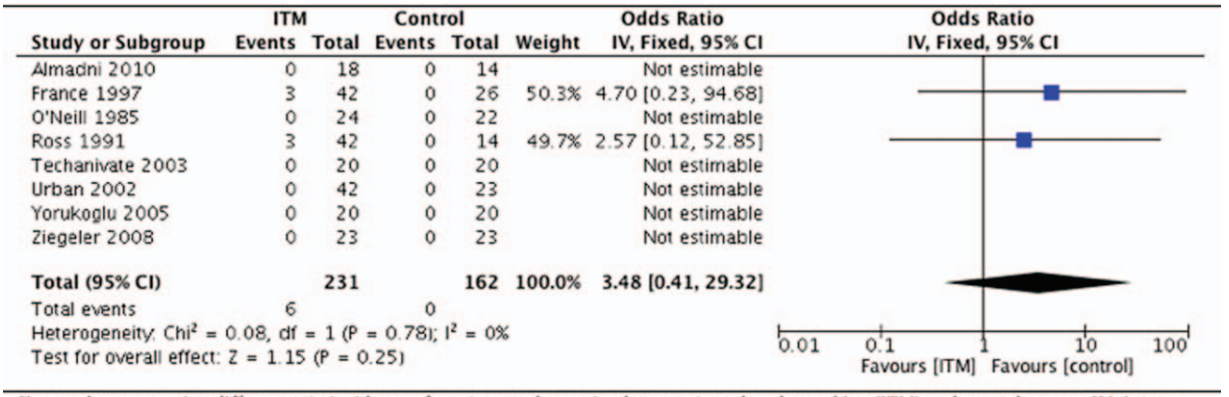
Forest plots comparing differences in incidence of vomiting between intrathecal morphine (ITM) and control groups. IV: inverse variance, CI: confidence interval, df: degrees of freedom

Figure 9. Vomiting.



Forest plots comparing differences in incidence of sedation between intrathecal morphine (ITM) and control groups. IV: inverse variance, CI: confidence interval, df: degrees of freedom

Figure 10. Sedation.



Forest plots comparing differences in incidence of respiratory depression between intrathecal morphine (ITM) and control groups. IV: inverse variance, CI: confidence interval, df: degrees of freedom

Figure 11. Respiratory depression.

For example, Naloxone has been recommended as a treatment for commonplace opioid-induced pruritus (OIP).[19]

Delayed-onset respiratory depression has been associated with ITM because of the hydrophilic nature of morphine, which exhibits a characteristic gradual spread through the cerebrospinal fluid after injection.[9] Yet, incidence was only 2.6% in the ITM group and no cases of respiratory depression were reported in the control group.[2–4,10–14] Nevertheless, an OR of 3.48 in the ITM group has clinical relevance. It should be noted, however, that the criteria used to define respiratory depression varied between studies: <12 breaths per minutes,[3,12] <8 breaths per minute[2], or $PaCO_2$ >50 mm[4]. Furthermore, several of the studies included in the meta-analysis did not explicitly define respiratory depression.[10–11,14] Because of this variation, there is uncertainty regarding the true risks of respiratory complications following administration of ITM.[20]

Several clinically-relevant adverse events following opioid use could not be assessed in this analysis. For example, urinary retention has been known to occur after spine surgery, in patients who received intrathecal opioids.[6,11–12,21] Incidence of urinary retention could not be incorporated because four of the included RCTs did not report urinary retention explicitly[4,10,13–14] and two included patients that were catheterized routinely following surgery.[2–3] As a result, the risk of urinary retention remains unknown in this study. In addition, injections into the intrathecal space carry risks of PDPH or cerebrospinal fluid leaks. Neither of the aforementioned outcomes were analyzed because PDPH was only reported in two trials,[3,13] and symptoms of dural leakage covered in one.[13]

The conclusions of this meta-analysis are moderated by the significant heterogeneity between trials, particularly in terms of opioid consumption, which was the primary outcome of this study. Owing to differences in the choice of postoperative opioid for pain management, the primary postoperative analgesic was normalized to morphine equivalents for the sake of comparison. Alternative opioids included papaveretum,[10] meperidine,[11] and piritramide.[13] Additionally, the dosage of ITM varied considerably between trials. O'Neill *et al*[10] administered 1 mg of ITM compared to 0.1 mg for Yörükoglu *et al*'s,[11] 0.3 mg for Techanivate *et al*'s,[3] and 0.4 mg for Ziegeler *et al*'s study.[13] Ross *et al*[12] injected 0.125 mg, 0.25 mg, or 0.5 mg in separate treatment arms. Weight-adjusted dosing regiments were employed by France *et al*[2] (0.011 mg/kg), Urban *et al*[4] (10–20 μg/kg), and Almadni and Yen[14] (3.5 μg/kg). Trials also differed in terms of control groups, most of which were administered placebo,[2–3,12–14] although others were not.[4,10] Despite the low heterogeneity between trials in terms of pain scores, scores were averaged across the first 24-hour postoperative period and normalized to a 10-point scale before being analyzed. In fact, several trials reported average pain scores at multiple time points within the 24-hour period[2–3,10–11,13–14] in contrast to studies that reported only a single average pain score for the first postoperative 24 hours.[4,12]

Other factors affecting heterogeneity between studies may be that trials were conducted as long ago as 1985 and as recently as 2010, corresponding to several decades during which technology and knowledge relating to spine surgery have changed markedly. Moreover, surgeries took place in a variety of countries and comprised both minor surgeries such as laminectomies and major operations such as instrumented fusions of three or more levels. Differences in terms of the type of surgery, surgical technique, and the population studied may have contributed to the significant heterogeneity between the studies incorporated in the meta-analysis.

In conclusion, the use of ITM as an adjunct therapy to control postoperative pain after spine surgery has been shown to reduce pain scores and opioid consumption during the first postoperative day. However, in the ITM group, pruritus was encountered statistically significantly more often and a greater incidence of respiratory depression may be clinically significant. Although complications such as PONV and sedation were not statistically more common in the experimental or control groups, the risks of certain adverse effects such as incidence of urinary retention, cerebrospinal fluid leaks, and others remain incompletely understood. Future high-quality trials are needed to investigate the use of ITM particularly with regards to the incidence of urinary retention, constipation, and CSF leak.

➢ Key Points

- ❑ Adjunctive ITM reduces postoperative pain and opioid consumption in the 24 hours following spine surgery.
- ❑ Pruritus was experienced more commonly by patients who received ITM compared to control.
- ❑ There were no differences between patients administered ITM and the control group in terms of incidence of nausea, vomiting, sedation, or respiratory depression.
- ❑ There was also no significant difference in length of stay.

Acknowledgments

Authors thank Robert Edward Johnson MLIS for search strategy, and M. Ali Khan, MD, for critical review.

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