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Efficacy and safety of intrathecal morphine for pain control after spinal surgery: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: This study aimed to assess the efficacy and safety of intrathecal (IT) morphine for postoperative pain control in adults undergoing spinal surgeries. We searched the electronic databases of PubMed, Embase, and CENTRAL up to 1st January 2021 for randomized controlled trials (RCTs) or controlled clinical trials (CCTs) comparing IT morphine with placebo or other analgesics. Twelve studies were included. Eleven were RCTs and one was a CCT. Our meta-analysis indicated a statistically significant reduction of pain scores with IT morphine at 2 hours, 4 hours, 6 hours, 8 hours, 12 hours, and 24 hours; but no significant difference at 48 hours. Meta-analysis indicated a statistically significant reduction in analgesic consumption with IT morphine as compared to control. Pooled analysis indicated that IT morphine had no statistically significant effect on length of hospital stay. Our analysis indicated no statistically significant difference in the risk of nausea, vomiting, sedation, respiratory depression, headache, and urinary retention between IT morphine and control groups. The incidence of pruritis was significantly increased in the IT morphine group. The certainty of the evidence was judged to be "moderate" for pain scores at 12 hours, 24 hours, and analgesic consumption. To conclude, our review indicates that IT morphine results in significantly better pain control in the first 24 hours after spinal surgery. The risk of pruritis is significantly increased with the use of IT morphine but not for other opioid-related adverse events. Future RCTs should focus on finding the most optimal dose of IT morphine for spinal surgeries.

Key Words:
Spinal surgery, Lumbar fusion, Lumbar surgery, Pain; Regional analgesia, Morphine.

Introduction

Postoperative pain management is an important component of any surgical procedure. Inadequate pain control is known to prolong hospital stay, increase patient dissatisfaction and also increase the risk of chronic pain[1,2]. In the case of spinal surgeries, pain management is extremely critical as severe postoperative pain can significantly limit patient mobility and delay rehabilitation[3].

With the refinement of surgical techniques and improved instrumentation, the number of patients undergoing spinal surgeries has increased exponentially in the past two decades[4,5]. Nevertheless, pain management with spinal surgeries can be challenging owing to the associated soft tissue dissection, instrumentation, removal of osseous structures, and prolonged operative time[6]. At present, opioids are the mainstay for pain control after spinal surgical procedures. However, parenterally administered opioids have significant adverse effects like nausea, vomiting, sedation, constipation, respiratory depression, and pruritis[7]. A safe and effective regional analgesic technique may therefore significantly reduce parenteral opioid use and improve patient outcomes after spinal surgeries[8].

Intrathecal (IT) morphine was first used for pain control in humans in 1979[9]. Since then IT morphine has been used for pain management in several surgical specialties[10-12]. Meylan et al[10] have reported improved pain control with IT morphine up to 24 hours after major surgery. However, analgesic consumption was shown to vary with the type of surgical procedure[10]. IT morphine

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can be an attractive regional anesthetic modality especially in the case of spine surgeries given the accessibility of the thecal sac[13]. Several studies[13,14] have reported outcomes of IT morphine in spinal surgeries but with mixed results. Also, there are concerns regarding opioid-related adverse events with the IT administration of morphine[10].

A recent meta-analysis[13] assessing the efficacy of IT morphine in pediatric spinal procedures has reported a potent analgesic effect of the drug in the immediate postoperative period. To the best of our knowledge, only one review has attempted to synthesize evidence on the efficacy of IT morphine for spinal surgeries in adults[14]. The study conducted its last literature search in 2015 and could include only eight trials. Thus, given the significant time interval, we hereby present results of an updated systematic review and meta-analysis assessing the efficacy and safety of IT morphine for postoperative pain control in adults undergoing spinal surgeries.

Materials and Methods

Search Strategy

The review was conducted following the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses)[15] and the Cochrane Handbook for Systematic Reviews of Intervention[16]. The review was not registered in PROSPERO. With the help of the librarian, we searched the electronic databases of PubMed, Embase, and CENTRAL. The search limits were from inception up to 1st January 2021. No language restriction was placed. We used the following keywords for the literature search: "morphine", "intrathecal", "spine surgery", "pain", "spinal surgery", "cervical surgery", "thoracolumbar", and "lumbar surgery". **Supplementary Table I** depicts the search strategy of the review. Two reviewers carried out the electronic search independent of each other. The primary search results were assessed initially by their titles and abstracts. We then identified relevant publications requiring full-text analysis. The full-texts of these selected articles were downloaded and were subjected to further review. The two reviewers independently assessed every article based on the inclusion and exclusion criteria. Any disagreements were resolved by discussion. In order to avoid missing out any other published studies, we also hand-searched the bibliography of included studies for any missed references.

Inclusion Criteria

We framed the inclusion criteria according to the PICOS (Population, Intervention, Comparison, Outcome, and Study design) guide. The following criteria were used for each domain:

Population: Adult patients (>18 years of age) undergoing any kind of spinal surgery with a sample size of at least 10 patients per arm.

Intervention: IT morphine

Comparison: Placebo or any other analgesic drug

Outcomes: Pain scores, analgesic consumption, length of hospital stay, adverse events (Reporting any one outcome)

Study design: Randomised controlled trials (RCTs) or controlled clinical trials (CCTs).

Exclusion criteria were: (1) Studies on pediatric patients (2) Studies using epidural morphine and not IT morphine (3) Studies evaluating the efficacy of continuous infiltration of morphine via a catheter and no single dose of IT morphine (4) Studies not reporting pain outcomes (5) Non-comparative studies, retrospective studies, animal studies, and review articles. (6) Studies with non-availability of full-texts.

Data Extraction and Quality Assessment

A data extraction sheet was prepared for extracting data from the included studies. Two reviewers extracted data independently. Data regarding the first author, publication year, study location, surgery type, sample size, mean age, male gender, study and control drug protocol, baseline analgesics, and study outcomes were extracted. The primary outcomes of interest for this review was to compare pain scores up to 48 hours after surgery and analgesic consumption in morphine equivalents between IT morphine and control group. Secondary outcomes were the length of hospital stay and adverse events between the two groups.

The Cochrane Collaboration's risk of bias assessment tool was used to assess study quality by two reviewers independently[16]. The following seven domains were used for quality assessment: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Studies were marked for each domain as high risk, low risk or unclear risk. Results were then depicted graphically. Any disagreements were resolved by discussion.

The certainty of the evidence of critical outcomes (pain scores at 12 hours, 24 hours, and analgesic consumption) was assessed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool using the GRADEpro GDT software [GRADEpro Guideline Development Tool. McMaster University, 2020 (developed by Evidence Prime, Inc.)].

Statistical Analysis

"Review Manager" (RevMan, version 5.3; Nordic Cochrane Centre [Cochrane Collaboration], Copenhagen, Denmark; 2014) was used for the meta-analysis. Pain scores at different time intervals, analgesic consumption, and length of hospital stay were summarized using Mean Difference (MD) with 95% confidence intervals (CI). We normalized pain scores to a 10-point scale for the meta-analysis. For studies reporting data only in graphical format, Engauge Digitizer Version 12.1 was used to extract data. Mean and standard deviation (SD) scores were required for meta-analysis of all continuous variables. In case SD was not reported by any study, it was imputed by pooling the variance from other trials using methods recommended by Furukawa et al[17] and Cochrane[16]. If the study reported only median and interquartile range, the data was converted into mean and SD using the method of Wan et al[18]. We also plotted the point estimates and 95% CI of pain scores at different time intervals in a graphical format to better understand the change in pain scores over time. Adverse events were summarized using risk ratios (RR) with 95% CI. The random-effects model was used for all the meta-analyses. Heterogeneity was assessed using the I^2 statistic. I^2 values of 25-50% represented low, values of 50-75% medium, and more than 75% represented substantial heterogeneity. We also performed a sensitivity analysis by sequentially excluding one study at a time to assess the influence of each trial on the overall results. The outcome of each study was excluded in the meta-analysis software itself to recalculate the effect size.

Results

The results of the literature search are screening of records are demonstrated in Figure 1. Twelve studies fulfilled the inclusion criteria of the review[19-30]. Details of the included studies are presented in Table I. Eleven of these studies were RCTs while one was a CCT[23]. The majority of the studies included a population of lumbar surgery patients while one was conducted on patients undergoing cervical laminoplasty. The smallest sample size was of Yen et al[26] with 32 patients while the largest study was of Dhaliwal et al[24] with 150 patients. There was a wide variation in the IT morphine dose ranging from 0.1 mg to 1 mg. Two studies compared IT morphine with diclofenac suppositories or intravenous (IV) morphine infusions[23,25]. The majority of studies used IV morphine as the baseline analgesic.

Pain Outcomes

Pain scores at different time intervals were pooled from the included studies. Results are presented in Figures 2 and 3. Our meta-analysis indicated statistically significant reduction of pain scores with IT morphine at 2 hours (MD: -1.76 95% CI: -3.01, -0.50 I^2=81% p=0.006), 4 hours (MD: -1.90 95% CI: -2.91, -0.88 I^2=79% p=0.0003), 6 hours (MD: -1.38 95% CI: -2.21, -0.55 I^2=87% p=0.001), 8 hours (MD: -1.36 95% CI: -2.40, -0.32 I^2=76% p=0.01), 12 hours (MD: -1.56 95% CI: -2.43, -0.68 I^2=91% p=0.0005), and

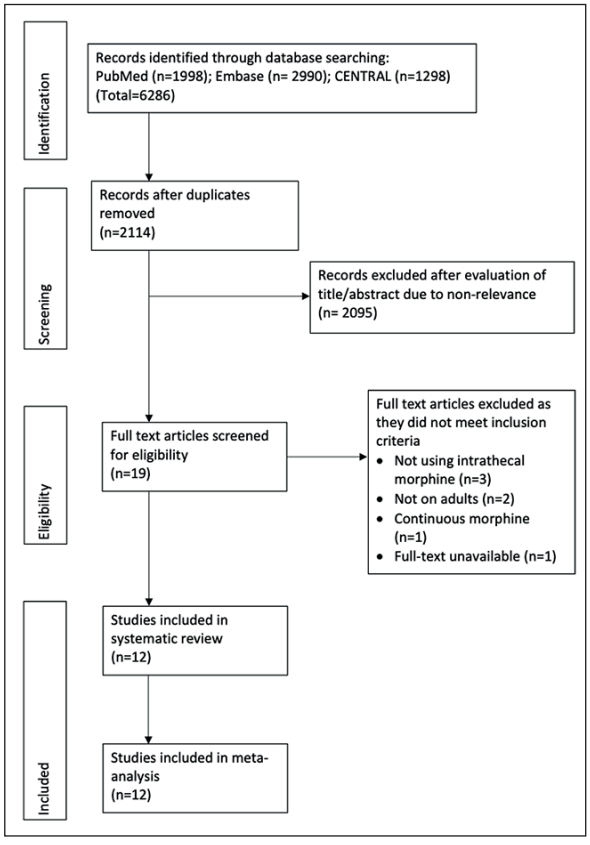

Figure 1. Study flowchart.

Table I. Characteristics of included studies.

Study	Location	Surgery type	Sample size	Mean age	Male gender (%)	Morphine dose	Comparative drug	Baseline analgesic
O'Neill 1985[21]	England	Lumbar surgery for prolapsed lumbar intervertebral disc, lumbar canal stenosis, or extradural nerve root adhesions	S: 24 C: 23	38.7 ± NR 40.7 ± NR	39.1 56.5	1 mg	No drug	IM Papaveretum 15-20 mg every 4-6 hours
Ross 1991[22]	USA	Lumbar surgery	S: 42 C: 14	53 ± 4.2 57.4 ± 4.1	61.9 57.1	0.125- 0.5 mg	Saline	SC morphine 0.005-0.15 mg/kg
France 1997[30]	USA	Posterolateral lumbar fusion with/without decompression/discectomy	S: 42 C: 26	48 ± 5 54 ± 3	NR NR	0.011 mg/kg	Saline	IV morphine PCA
Urban 2002[29]	USA	Elective multilevel posterior spinal instrumentation	S: 42 C: 23	47 ± 12.5 49 ± 15	40 21.7	0.01-0.02 mg/kg	No drug	IV morphine PCA
Techanivate 2003[19]	Thailand	Lumbar laminectomy	S: 20 C: 20	54.6 ± 9.1 52.8 ± 12.3	45 50	0.3 mg	Saline	IV morphine PCA
Yorukoglu 2005[27]	Turkey	Lumbar discectomy	S: 20 C: 20	41 ± 9 45 ± 11	50 40	0.1 mg	No drug	IM meperidine
Ziegeler 2008[28]	Germany	Posterior lumbar interbody fusion surgery	S: 23 C: 23	59.9 ± 10 56.7 ± 11	43.4 34.7	0.4 mg	Saline	IV piritramide PCA
Yen 2015[26]	Canada	Lumbar laminectomy with/without fusion	S: 18 C: 14	54.6 ± NR 54.8 ± NR	61.1 78.5	0.0035 mg/kg	Saline	IV morphine PCA
Hida 2016[23]	Japan	Cervical laminoplasty	S: 31 C: 32	61 ± 13 64 ± 10	74.2 53.1	0.3 mg	Diclofenac 50 mg suppository	NR
Morselli 2017[25]	Italy	Minimally invasive posterior lumbar fusion	S: 25 C: 25	52.1 ± NR 43.7 ± NR	NR	0.1 mg	IV morphine 0.006-0.008 mg/kg infusion (Total dose: 5 ± 2 mg)	None
Dhaliwal 2018[24]	Canada	Elective instrumented lumbar fusion	S: 74 C: 76	63.6 ± 11.1 60.4 ± 12.6	46 39	0.2 mg	Saline	IV morphine PCA
Wang 2020[20]	China	Elective lumbar laminectomy and dual-level fusions	S: 44 C: 43	66.4 ± 5.4 66.5 ± 7.5	47.7 51.2	0.2 mg	Saline	IV sufentanil PCA

S, study group; C, control group; IV, intravenous; IM, intramuscular; SC, subcutaneous; PCA, patient-controlled analgesia; NR, not reported.

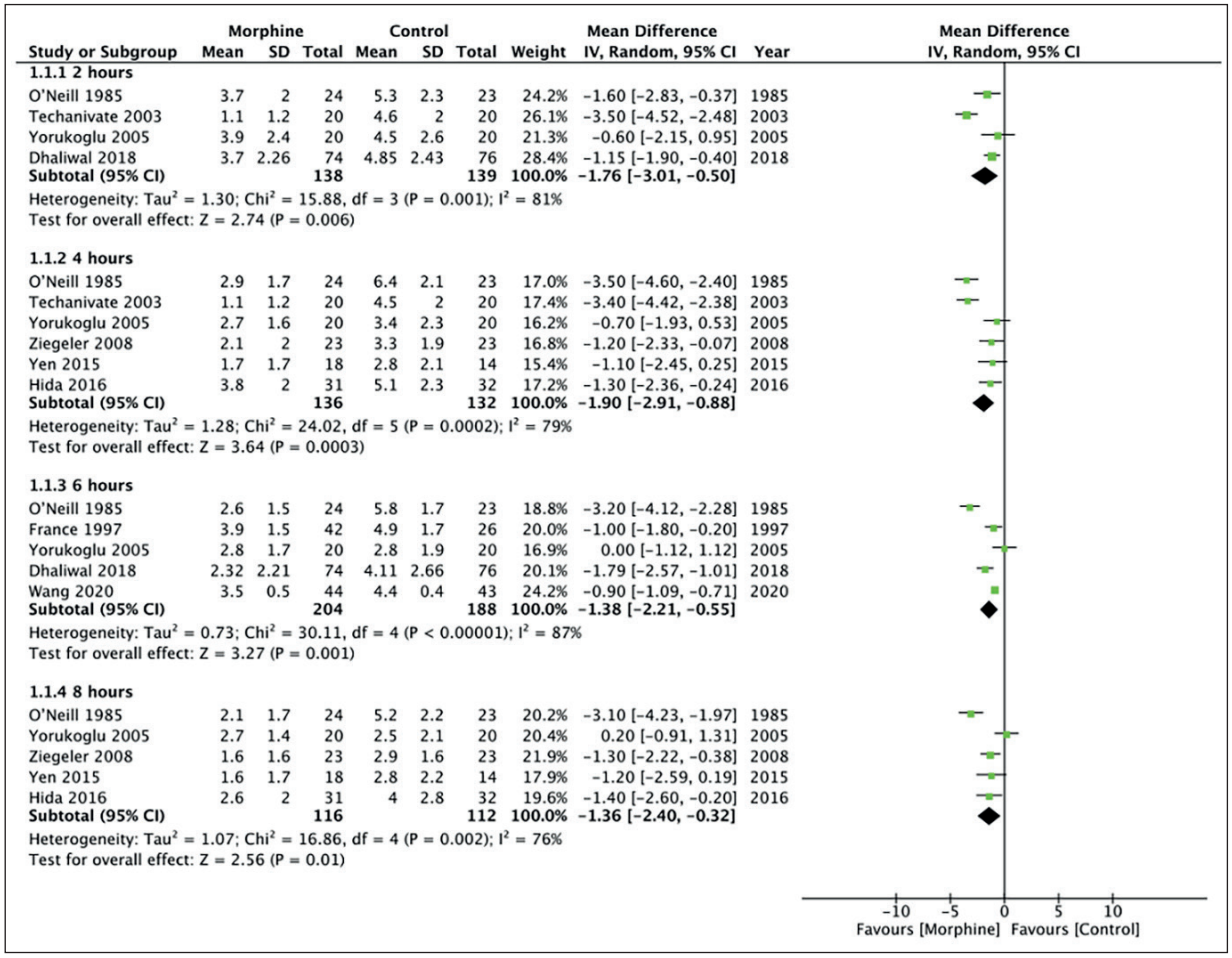

Figure 2. Meta-analysis of pain scores at 2 hours, 4 hours, 6 hours, and 8 hours.

24 hours (MD: -0.92 95% CI: -1.45, -0.40 I^2=87% p=0.0006). However, there was no significant difference in pain scores at 48 hours (MD: -0.37 95% CI: -1.13, 0.39 I^2=81% p=0.34). Change in pain scores are graphically depicted in Figure 4. The figure indicates that the maximum effect of IT morphine was noted at 4 hours followed by a reduction in effect at 48 hours.

Nine studies reported data on analgesic consumption. Meta-analysis indicated a statistically significant reduction in analgesic consumption in morphine equivalents with IT morphine as compared to control (MD: -15.59 95% CI: -22.64, -8.54 I^2=95% p<0.0001) (Figure 5).

Length of Hospital Stay and Adverse Events

Five studies reported data on length of hospital stay. Pooled analysis indicated that IT morphine had no statistically significant effect on length of hospital stay (MD: -0.56 95% CI: -1.33, 0.20 I^2=95% p=0.15) (Figure 6).

Pooled analysis of adverse events between IT morphine and control group is depicted in **Supplementary Figure 1**. The incidence of respiratory depression in IT morphine group was 1.8% (6/331). Our analysis indicated no statistically significant difference in the risk of nausea (RR 0.86 95% CI: 0.57, 1.31 I^2=25% p=0.48), vomiting (RR 1.14 95% CI: 0.57, 2.27 I^2=18% p=0.71), sedation (RR 0.74 95% CI: 0.46, 1.17 I^2=0% p=0.20), respiratory depression (RR 3.27 95% CI: 0.42, 25.67 I^2=0% p=0.26), headache (RR 1.56 95% CI: 0.32, 7.64 I^2=0% p=0.58), and urinary retention (RR 0.67 95% CI: 0.43, 1.05 I^2=34% p=0.08) between IT morphine and control groups. However, the incidence of pruritis was significantly increased in the IT morphine group as compared to control (RR 3.08 95% CI: 1.62, 5.84 I^2=0% p=0.0006).

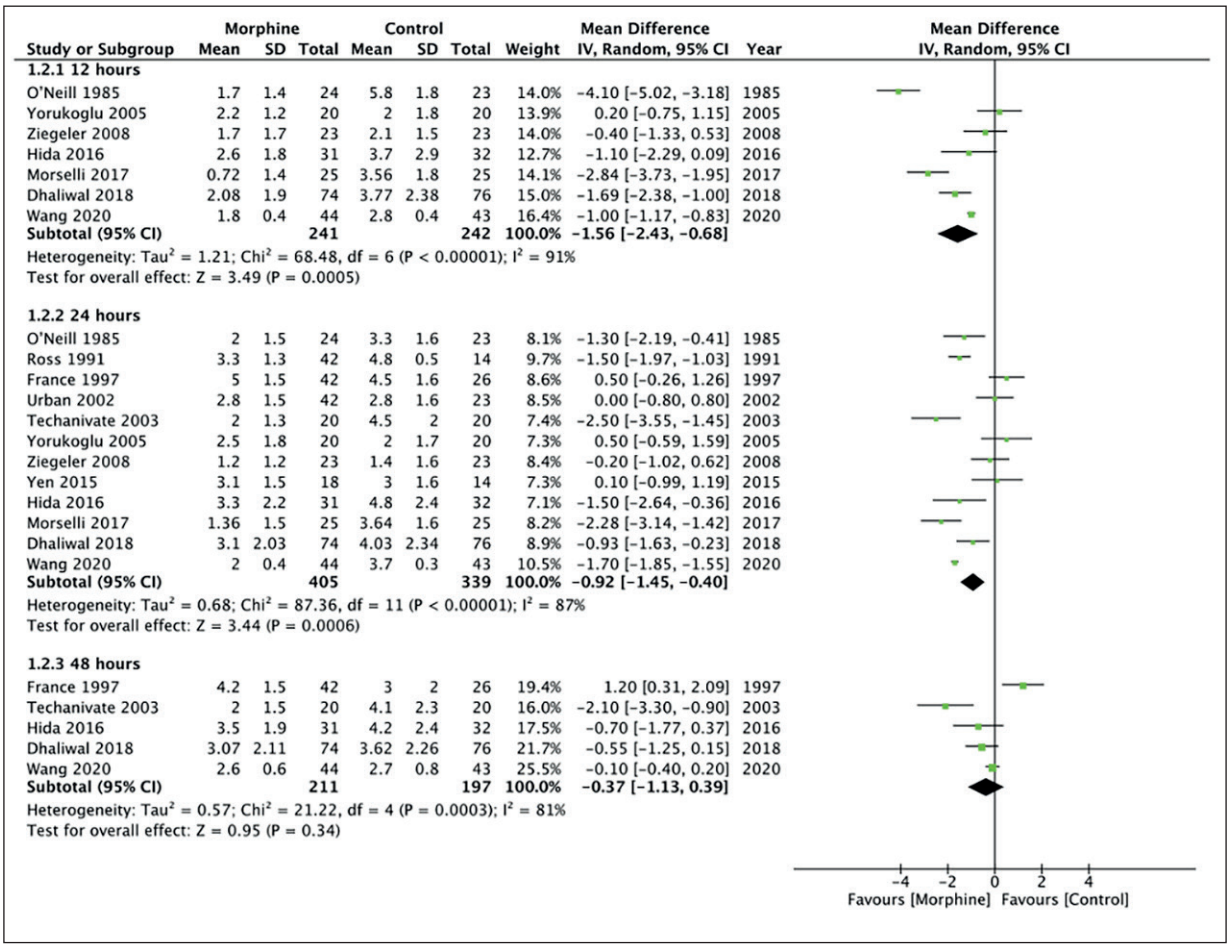

Figure 3. Meta-analysis of pain scores at 12 hours, 24 hours, and 48 hours.

Sensitivity Analysis

No change in the direction and significance of the results was seen for any outcome on the exclusion of any study (data not shown). However, when the study of Dhaliwal et al[24] was excluded from the analysis of urinary retention, our analysis revealed a significantly lower risk of urinary retention in the IT morphine group as compared to the control group (RR 0.48 95% CI: 0.27, 0.86 I^2=0% p=0.01).

As two of the included trials[23,25] had compared IT morphine with other analgesics (IV morphine and diclofenac suppository), we also excluded both these studies from all our analyses to re-check the pooled outcomes. However, we did not find any change in the results after the exclusion of these studies (data not shown).

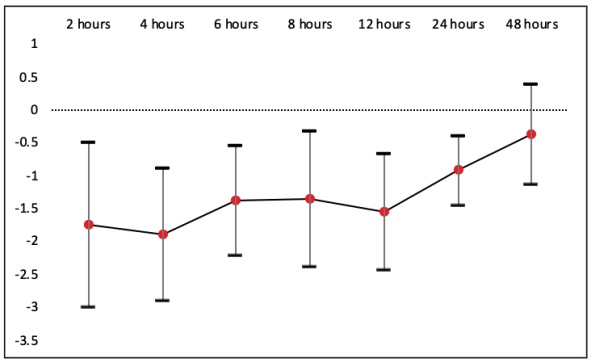

Figure 4. Graphical depiction of effect size of pain scores over different time intervals. Orange circles represent effect size while vertical lines represent 95% confidence intervals.

Quality of Included Studies and Certainty of the Evidence

The risk of bias analysis as per the author's judgment is presented in Figure 7. Assessment of evidence based on GRADE for critical outcomes is depicted in **Supplementary Figure 2**. The certainty of the evidence was judged to be "moderate" for pain scores at 12 hours, 24 hours, and analgesic consumption in morphine equivalents.

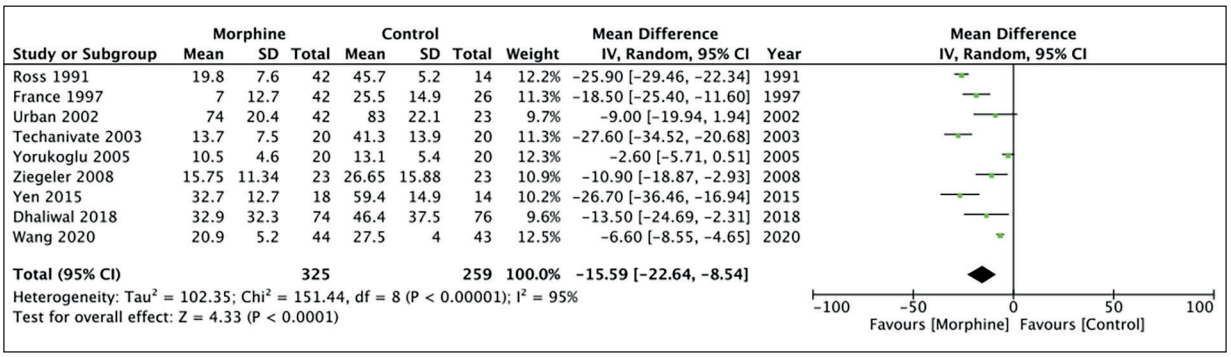

Figure 5. Meta-analysis of analgesic consumption in morphine equivalents.

Discussion

To date, IT morphine has been used for pain relief after a wide range of surgical procedures like cesarean section, hysterectomy, hip arthroplasty, knee arthroplasty, cardiac surgeries, and abdominal surgeries[10-12]. Despite its widespread use, only a few clinical trials have assessed its efficacy for pain control after spinal surgeries. Given the limited number of studies in the earlier systematic review[14], we conducted an updated literature search and added four more studies to present up-to-date results on the efficacy and safety of IT morphine for pain control after spinal surgeries.

On pooled analysis of pain scores across a wide range of time intervals, we found that IT morphine was associated with a statistically significant reduction of pain scores from 2 hours to 24 hours postoperatively. The pooled effect was the highest at 4 hours with a gradual reduction to a non-significant difference at 48 hours. Our results concur with the previous meta-analysis of Pendi et al[14]. In a pooled analysis of seven studies, they had reported significantly better pain reduction with IT morphine after spinal surgeries [Standardized mean difference (SMD): -0.47 95% CI -0.69, -0.25 I^2=0% p<0.001)]. However, only average postoperative pain scores were pooled in their study, while our review presents an hour-wise pooled analysis of data from a maximum of 12 trials. Quantification of the analgesic effect of IT morphine allows for comparison with other analgesic modalities used in spinal surgeries. The pooled effect size of pain scores in our analysis varied from the lowest of -0.37 (24 hours) to -1.9 (4 hours) which means IT morphine can result in a reduction of up to ~ 2 points on a 10cm Visual Analog Scale (VAS). In comparison, a meta-analysis[31] on the use of supplemental ketamine after spinal surgery has reported a maximum pain reduction by -1.27 points (on a 10-point VAS) while infiltration of local anesthetic before wound closure in spinal surgeries can reduce pain only by -0.87 points that too only in the first postoperative hour[32].

Postoperative analgesic consumption or the opioid-sparing effect of an anesthetic modality can be considered as a surrogate marker of its analgesic efficacy[10]. Our analysis revealed that patients receiving IT morphine had significantly reduced analgesic consumption in the first 24 hours after surgery and the resultant morphine

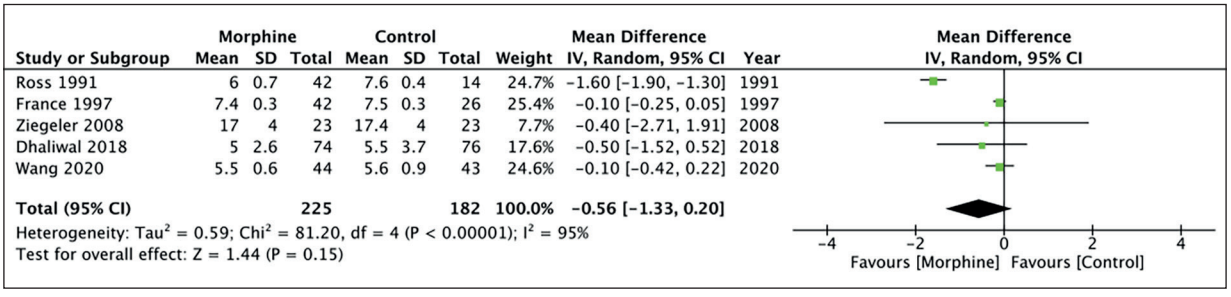

Figure 6. Meta-analysis of length of hospital stay in days.

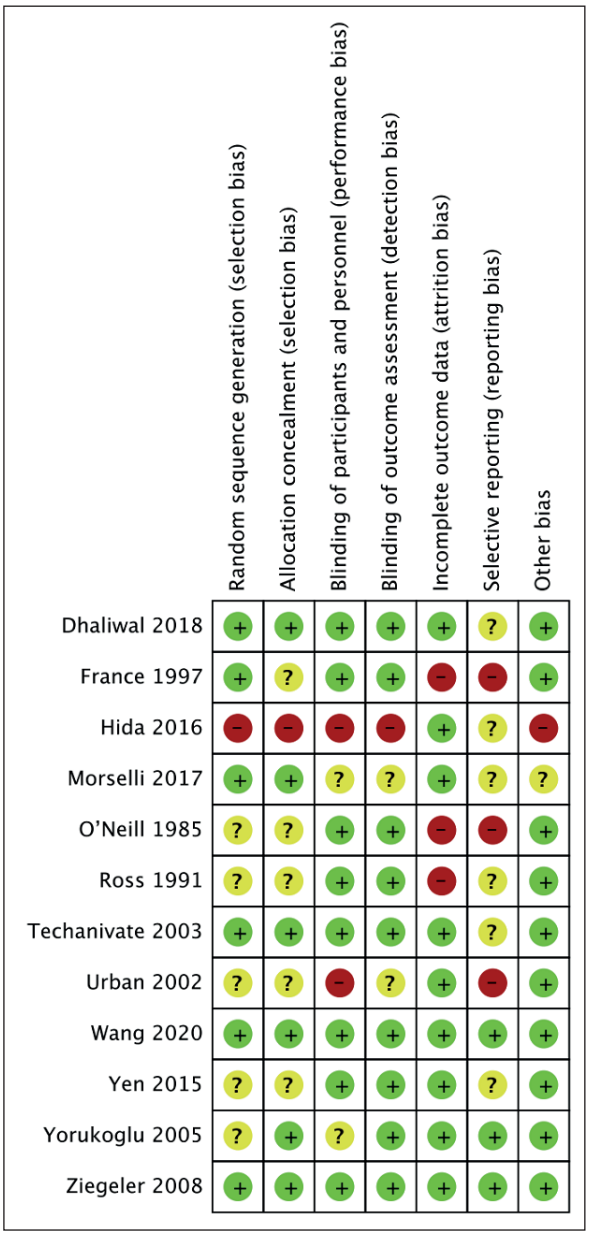

Figure 7. Risk of bias analysis.

spared was 15.59 mg. Our results are similar to the study of Meylan et al[10] wherein the use of IT morphine for various surgical procedures was associated with morphine sparing effect of 16.9 mg (95% CI: -23.7, -10.1). Similarly, Musa et al[13] in their analysis of pediatric spinal surgical patients have found that IT morphine significantly reduces analgesic consumption and increases the time-to-first analgesic request. Time-to-first analgesic request, however, could not be analyzed in our review owing to the unavailability of data from the included trials.

Important to note is that there was significant heterogeneity in all our meta-analyses except for the pooled analysis of adverse events. Other than the differences in surgical procedures and patient population, a major source of heterogeneity, according to us, was the dosage of IT morphine used in the included trials which varied from 0.1 mg to 1 mg. While the optimal dose of IT morphine depends on the type of surgery[32], the dose-response curve of the drug with IT administration is known to be associated with ceiling analgesic effect as doses >0.5 mg provide limited additional pain relief while significantly increasing adverse effects[24]. Notably, high doses were used only in the earlier studies (pre-2003) while most post-2003 studies used doses ranging from 0.1-0.4 mg. Only a few studies have assessed the optimal dose of IT morphine for spinal surgery[29,33]. Boezaart et al[33] in an RCT published in 1999 compared 0.2 mg, 0.3 mg, and 0.4 mg of IT morphine for pain control after lumbar spinal fusion. The authors reported significantly higher pain with 0.2 mg IT morphine at 12 hours post-surgery and equivalent analgesic effect of 0.3 mg and 0.4 mg morphine. Since respiratory depression was significantly higher with 0.4 mg compared to the other doses, 0.3 mg IT morphine was recommended as the optimal dose. A limitation of the study was the relatively small sample size of the groups (20 patients each). Because of the scarce data available, future RCTs should focus on comparing different doses of IT morphine in a large sample size to provide robust evidence on the same.

The safety of the drug is of paramount importance in clinical practice. One of the major concerns with the use of IT morphine amongst clinicians is the risk of respiratory depression[12]. Morphine being less hydrophobic than other opioids stays for a longer time in the cerebrospinal fluid and may cause delayed-onset respiratory depression[13]. Of the total 331 patients receiving IT morphine in the included studies, only six patients experienced respiratory depression with a pooled incidence of 1.8%. Our incidence is similar to that reported by Meylan et al[10] at 1.2%. However, it is important to note that the definition of respiratory depression was not coherent amongst the included studies with some defining it as <12 breaths/minute[19,22] or <8 breaths/minute[30], and the majority not providing a definition at all. Furthermore, since none of the trials were designed to study the risk of respiratory depression, some cases may have been missed. The

pooled RR in our analysis was estimated to be 3.27 (95% CI: 0.42, 25.67) and considering the wide confidence intervals, clinicians should be careful of this complication.

Of the many other opioid-related complications, our analysis indicated a significantly increased risk of only pruritis with IT morphine. The incidence of pruritis with IT morphine as reported in the literature varies from 20%[34] to as high as 59.5%[35]. Pruritis is an opioid-specific adverse event due to the action of the drug on M-receptors of mast cells located in the skin. This causes granulation and histamine release leading to skin rashes and itching[34]. A significantly higher risk of pruritis with IT morphine has been reported by previous reviews as well[10-12]. Notably, our analysis demonstrated no increased risk of nausea, vomiting, sedation, and urinary retention with the use of IT morphine. Furthermore, headache due to injection procedure was also not significantly increased in the study group. Only a limited number of studies evaluated the effect of the intervention on length of hospital stay. Pooled analysis indicated that IT morphine does not affect the duration of hospital stay.

The limitations of our review need to be mentioned. Foremost, there was significant heterogeneity in our analysis. As mentioned earlier, this may have been due to differences in the types of surgery, the complexity of the surgery, patient populations, drug dose, and baseline analgesic protocol. Furthermore, the studies were conducted over a wide timeline ranging from 1985 to 2020, during which several advances in surgical techniques and instrumentation have taken place. Secondly, the comparator group and the type of baseline analgesia were not coherent in the included trials. In two trials[23,25], IT morphine was compared with a different analgesic. However, since in all other trials IT morphine was used as an "adjuvant" to another baseline analgesic and all control group patients received a different analgesic, we chose to include these two studies[23,25] in our meta-analysis. Nevertheless, sensitivity analysis with the exclusion of these trials failed to change the direction of the effect size. Thirdly, there was bias related to allocation concealment and blinding in some of the included trials. Pain outcomes and analgesic consumption in the postoperative period may have been affected by this in the included studies. The overall certainty of the evidence was therefore downgraded by us and was deemed to be moderate.

To conclude, our review of only RCTs indicates that IT morphine results in significantly better pain control in the first 24 hours after spinal surgery. Pain scores and analgesic consumption is significantly reduced with the use of IT morphine. The analgesic effect, however, does not seem to persist at 48 hours wherein there was no difference in pain scores between IT morphine and control. The risk of pruritis is significantly increased with the use of IT morphine. There was no statistically significant increase in other opioid-related adverse events with the use of IT morphine. Our findings have important clinical implications and encourage the use of IT morphine for better pain control after spinal surgeries especially in the first 24 hours. Future RCTs should focus on finding the most optimal dose of IT morphine for spinal surgeries.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authors' Contribution

Conceptualization, J.W.; Methodology, H.S., W.S., Huaping.S. and T.T.; Validation, J.S.; Formal analysis, J.W.; Investigation, H.S., W.S., Huaping.S. and T.T.; Data curation, H.S., W.S., Huaping.S. and T.T.; Writing—Original draft preparation, J.W.; Writing—Review and editing, J.S.

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