META-ANALYSIS OF INTRATHECAL MORPHINE FOR LUMBAR SPINE SURGERY

RESIDENT RESEARCH EXCHANGE DAY
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INTRODUCTION – WHY SPINE SURGERY?

- Readily accessible intrathecal sac
- Often severe post-op pain
- Practical and useful adjunct
- Some complex chronic pain patients
Opioid receptors first isolated in the spinal cord in 1976
  - First reported use of intrathecal morphine was in 1979 (Popping 2012, Wang 1979)

Intrathecal morphine widely used as part of neuraxial techniques alone or in conjunction with general anesthesia for post-operative analgesia
Multiple studies have reported efficacious use of intrathecal morphine for various surgeries.

Meta-analysis by Meylan 2009 suggested efficacy in abdominal, cardiac and thoracic surgeries.

Outcomes specific to intrathecal morphine for spine surgery undefined.
The aim of the current meta-analysis is to quantify the post-operative analgesic effect of various doses of intrathecal morphine for adult spine surgery based primarily on pain scores.
METHODS
METHODS – CRITERIA

- Thorough literature review including published papers and abstracts in all languages by 2 independent reviewers

- **Inclusion criteria:**
  - **Population:** Adults ≥ 18 yrs undergoing GA for spine surgery
  - **Intervention:** intrathecal morphine versus placebo
  - **Outcome:** Reported pain scores post-operatively
  - **Methodology:** RCT
METHODS

- Modified Jadad score then used to assess eligibility for inclusion into study

- Included:
  - Randomized?
  - Double-blinded?
  - Show completeness of follow-up?
  - Use of suitable techniques to create randomization sequence?
  - Describe an acceptable blinding method?
SOURCES OF HETEROGENEITY

- type of spine surgery
- time of intrathecal morphine administration
- doses of intrathecal morphine
- concurrent analgesic adjuncts
DATA ANALYSIS
DATA ANALYSIS

- **Primary Outcome**: VAS scores
- **Secondary Outcomes**:
  - pruritis
  - nausea
  - sedation
  - respiratory depression
  - urinary retention
  - post-dural puncture headache

- **Random effects model**:
  - Weighted mean differences (minimal heterogeneity)
    - Natural units
  - Standard mean differences (significant heterogeneity)
    - SD
RESULTS
<table>
<thead>
<tr>
<th>Author/Year</th>
<th># of Subjects</th>
<th>Type of Surgery</th>
<th>Amount of ITM (+ other ix)</th>
<th>Jadad Score</th>
<th>PCA/ Adjuncts used</th>
<th>Outcome/ Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almadni 2010</td>
<td>32</td>
<td>Elective lumbar spinal surgery</td>
<td>3.5 mcg/kg to max 350 mcg at end of OR</td>
<td>Uncertain</td>
<td>24 hr total PCA use: 40.8 mg vs 48 mg morphine</td>
<td></td>
</tr>
<tr>
<td>Techanivate 2003</td>
<td>40</td>
<td>Lumbar laminectomy with fusion, some with instrumentation. 2 or more levels</td>
<td>0.3 mg 30G before closure to surgical incision</td>
<td>5</td>
<td>PCA morphine 24h: 13.7 vs 41.3 mg 48h: 15.9 vs 27.1 mg</td>
<td>Pruritis 24h: 45 vs 5% 48: 45 vs 10%</td>
</tr>
<tr>
<td>Martin 1995</td>
<td>45</td>
<td>Lumbar surgery – unspecified</td>
<td>0.5 mg, unclear when during OR</td>
<td>uncertain</td>
<td></td>
<td>No Resp Depression</td>
</tr>
<tr>
<td>Yorukoglu 2005</td>
<td>40</td>
<td>Lumbar discectomy shorter than 3 hours with no instrumentation</td>
<td>0.1 mg 25 G after discectomy</td>
<td>4</td>
<td>IM meperidine and naproxen prn.</td>
<td></td>
</tr>
<tr>
<td>France 1997</td>
<td>68</td>
<td>Posterolateral lumbar fusion +/- decompression/ discectomy. Some with instrumentation.</td>
<td>11 mcg/kg 30 min prior to closure</td>
<td>3</td>
<td>Morphine PCA 24h: 7 vs 25 mg 24 – 36h: 24.1 vs 33.1 mg 24 – 48 h: 46.1 vs 37 mg</td>
<td></td>
</tr>
<tr>
<td>Ross 1991</td>
<td>64</td>
<td>Extradural lumbar spinal surgery (not specific on type, nor number of levels)</td>
<td>0.125, 0.25, 0.5 mg 27G 60- 90 min prior to PACU arrival</td>
<td>4</td>
<td>SC morphine: 24h: 4.4, 13.4, 26.1 vs 45.7 mg in control</td>
<td></td>
</tr>
<tr>
<td>O’Neill 1985</td>
<td>47</td>
<td>Lumbar spine procedures for prolapsed lumbar intervertebral disc, lumbar canal stenosis, extradural nerve root adhesions</td>
<td>1 mg, unclear when in OR</td>
<td>3</td>
<td>IM papaveretum 24h: 1.25 vs 2.3 doses of 15 – 20 mg</td>
<td>Increased pruritis incidence ITM group.</td>
</tr>
<tr>
<td>Ziegeler 2008</td>
<td>46</td>
<td>Posterior lumbar interbody fusion surgery (1 – 3 levels of lumbar/sacral)</td>
<td>27 G 0.4 mg prior to wound closure</td>
<td>5</td>
<td>PCA Pntramide unspecified</td>
<td>Earlier pruritis in ITM group (6 vs 20 hrs)</td>
</tr>
<tr>
<td>Urban 2002</td>
<td>65</td>
<td>Elective spinal surgery – multi level posterior instrumented spinal fusion. At least 3 levels instrumented/ fused.</td>
<td>0, 10 mcg/kg or 20 mcg/kg 25 G 2 – 3 h before surgery completion</td>
<td>2</td>
<td>PCA Morphine 0-6h: 13, 18 vs 25 mg 6-12h: 13, 19 vs 18 mg 12 – 24h: 43, 43, 40 mg</td>
<td>Pruritis –12*, 9*, 4</td>
</tr>
<tr>
<td>Johnson 1989</td>
<td>32</td>
<td>Lumbar fusions. Posterior, anterior approaches. Some with instrumentation. A few redos were included.</td>
<td>1.5 – 2.5 mg (by weight, but did not specify threshold) 30G needle at end of OR</td>
<td>2</td>
<td>PCA morphine 77.5 vs 89.6 mg</td>
<td></td>
</tr>
</tbody>
</table>
> 600 studies available containing search words in query.

\( \eta = 17 \) met inclusion criteria

- \( \eta = 2 \) did not report primary outcome
- \( \eta = 3 \) did not contain a placebo group
- \( \eta = 1 \) contained pediatric population
- \( \eta = 1 \) was a case report

\( \eta = 10 \) studies included

**Figure 1.** Flow diagram of study selection.
STUDY SELECTION

- **Study characteristics**
  - All 10 studies selected were RCTs
  - 9 English
  - 1 Spanish
  - Single-centered, international

- **Participants**
  - 520 total participants
  - 453 participants analyzed
  - Subgroup of 67 participants excluded as it did not meet our inclusion criteria

- **Intervention**
  - Low dose < 150 mcg intrathecal morphine
  - High dose > 150 mcg intrathecal morphine
**Figure 1: VAS Scores**

Significant WMD in VAS at:
- **0-6h**: -23
- **6-12h**: -12
- **12-18h**: -12

### Study Details

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Dose detail</th>
<th>%d status</th>
<th>WMD (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

*Note: Weights are from random effects analysis.*

* reported, sd as extracted from the original paper; imputed; sd was not reported in the original paper thus assumed with the maximum value 25.
FIGURE 2: VAS SCORES-FUNNEL PLOT

Funnel Plots for VAS Scores

- **0-6 Hours**
- **6-12 Hours**
- **12-18 Hours**
- **18-24 Hours**

Sample size

Weighted Mean Difference

Funnel Plots for VAS Scores
**FIGURE 3: OVERALL SIDE EFFECTS**

<table>
<thead>
<tr>
<th>First author, dose (year)</th>
<th>OR (95% CI)</th>
<th>morphine</th>
<th>control</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pruritis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnson, 1.5-2.5mg (1989)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ross1, 0.25mg (1991)</td>
<td>6.52 (0.31, 138.23)</td>
<td>3/17</td>
<td>0/13</td>
<td>6.94</td>
</tr>
<tr>
<td>Ross2, 0.125mg (1991)</td>
<td>1.10 (0.02, 76.26)</td>
<td>1/14</td>
<td>3/46</td>
<td>3.63</td>
</tr>
<tr>
<td>Ross3, 0.5mg (1991)</td>
<td>0.21 (0.01, 8.21)</td>
<td>0/14</td>
<td>3/46</td>
<td>4.78</td>
</tr>
<tr>
<td>Martin-Laurani, 0.5mg (1995)</td>
<td>0.19 (0.01, 6.91)</td>
<td>0/14</td>
<td>4/48</td>
<td>4.98</td>
</tr>
<tr>
<td>Urban1, 10mcg/kg (2002)</td>
<td>8.69 (0.41, 184.28)</td>
<td>3/15</td>
<td>0/15</td>
<td>6.93</td>
</tr>
<tr>
<td>Urban2, 20mcg/kg (2002)</td>
<td>4.28 (0.73, 25.12)</td>
<td>9/19</td>
<td>2/11.5</td>
<td>20.64</td>
</tr>
<tr>
<td>Techanivate, 0.3mg (2003)</td>
<td>5.18 (0.92, 29.34)</td>
<td>12/23</td>
<td>2/11.5</td>
<td>21.61</td>
</tr>
<tr>
<td>Yourokogu, 0.1mg (2005)</td>
<td>16.55 (1.73, 139.65)</td>
<td>9/20</td>
<td>1/10</td>
<td>13.43</td>
</tr>
<tr>
<td>Ziegler, 0.4mg (2008)</td>
<td>1.00 (0.02, 52.15)</td>
<td>0/5</td>
<td>5/21</td>
<td>4.11</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.522)</td>
<td>3.99 (1.78, 8.91)</td>
<td>42/2180</td>
<td>7.5/129</td>
<td>100.00</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnson, 1.5-2.5mg (1989)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ross1, 0.25mg (1991)</td>
<td>11.88 (0.59, 237.55)</td>
<td>5/17</td>
<td>0/13</td>
<td>5.45</td>
</tr>
<tr>
<td>Ross2, 0.125mg (1991)</td>
<td>1.11 (0.05, 24.64)</td>
<td>2/14</td>
<td>6/46</td>
<td>5.15</td>
</tr>
<tr>
<td>Ross3, 0.5mg (1991)</td>
<td>0.51 (0.02, 15.23)</td>
<td>1/14</td>
<td>6/46</td>
<td>4.43</td>
</tr>
<tr>
<td>Martin-Laurani, 0.5mg (1995)</td>
<td>0.85 (0.05, 14.11)</td>
<td>2/14</td>
<td>8/48</td>
<td>5.98</td>
</tr>
<tr>
<td>Urban1, 10mcg/kg (2002)</td>
<td>21.00 (2.16, 204.61)</td>
<td>9/15</td>
<td>1/15</td>
<td>8.31</td>
</tr>
<tr>
<td>Urban2, 20mcg/kg (2002)</td>
<td>0.86 (0.10, 6.33)</td>
<td>3/19</td>
<td>2/11.5</td>
<td>10.21</td>
</tr>
<tr>
<td>Techanivate, 0.3mg (2003)</td>
<td>0.77 (0.10, 5.00)</td>
<td>3/23</td>
<td>2/11.5</td>
<td>10.29</td>
</tr>
<tr>
<td>Yourokogu, 0.1mg (2005)</td>
<td>0.54 (0.15, 1.92)</td>
<td>7/20</td>
<td>10/20</td>
<td>16.46</td>
</tr>
<tr>
<td>Ziegler, 0.4mg (2008)</td>
<td>0.44 (0.13, 1.67)</td>
<td>8/20</td>
<td>12/20</td>
<td>16.52</td>
</tr>
<tr>
<td>Subtotal (I-squared = 36.9%, p = 0.113)</td>
<td>2.49 (0.75, 8.34)</td>
<td>16/23</td>
<td>11/23</td>
<td>17.19</td>
</tr>
<tr>
<td><strong>Sedation</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Johnson, 1.5-2.5mg (1989)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ross1, 0.25mg (1991)</td>
<td>0.13 (0.01, 2.99)</td>
<td>0/17</td>
<td>2/13</td>
<td>11.21</td>
</tr>
<tr>
<td>Ross2, 0.125mg (1991)</td>
<td>0.21 (0.01, 8.21)</td>
<td>0/14</td>
<td>3/46</td>
<td>8.09</td>
</tr>
<tr>
<td>Ross3, 0.5mg (1991)</td>
<td>0.21 (0.01, 8.21)</td>
<td>0/14</td>
<td>3/46</td>
<td>8.09</td>
</tr>
<tr>
<td>Techanivate, 0.3mg (2003)</td>
<td>0.85 (0.02, 38.70)</td>
<td>1/14</td>
<td>4/48</td>
<td>7.50</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.934)</td>
<td>0.43 (0.12, 1.57)</td>
<td>10/20</td>
<td>14/20</td>
<td>65.11</td>
</tr>
<tr>
<td><strong>Resp Depression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnson, 1.5-2.5mg (1989)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ross1, 0.25mg (1991)</td>
<td>0.77 (0.01, 41.44)</td>
<td>5/18</td>
<td>5/14</td>
<td>14.43</td>
</tr>
<tr>
<td>Ross2, 0.125mg (1991)</td>
<td>0.35 (0.01, 20.14)</td>
<td>5/15</td>
<td>5/56</td>
<td>13.97</td>
</tr>
<tr>
<td>Ross3, 0.5mg (1991)</td>
<td>1.13 (0.04, 32.59)</td>
<td>1/14</td>
<td>4/46</td>
<td>20.29</td>
</tr>
<tr>
<td>Martin-Laurani, 0.5mg (1995)</td>
<td>2.12 (0.09, 52.10)</td>
<td>2/10</td>
<td>4/48</td>
<td>22.33</td>
</tr>
<tr>
<td>Techanivate, 0.3mg (2003)</td>
<td>1.00 (0.02, 53.66)</td>
<td>5/16</td>
<td>5/16</td>
<td>14.43</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.993)</td>
<td>1.00 (0.02, 53.85)</td>
<td>5/21</td>
<td>5/21</td>
<td>14.54</td>
</tr>
<tr>
<td><strong>Urinary Retention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnson, 1.5-2.5mg (1989)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ross1, 0.25mg (1991)</td>
<td>2.45 (0.09, 65.26)</td>
<td>1/17</td>
<td>0/13</td>
<td>12.30</td>
</tr>
<tr>
<td>Ross2, 0.125mg (1991)</td>
<td>0.54 (0.05, 5.62)</td>
<td>6/12</td>
<td>2/64</td>
<td>16.95</td>
</tr>
<tr>
<td>Ross3, 0.5mg (1991)</td>
<td>0.11 (0.01, 1.43)</td>
<td>2/11</td>
<td>2/74</td>
<td>15.58</td>
</tr>
<tr>
<td>Martin-Laurani, 0.5mg (1995)</td>
<td>0.32 (0.03, 3.70)</td>
<td>4/10</td>
<td>2/74</td>
<td>16.39</td>
</tr>
<tr>
<td>Yourokogu, 0.1mg (2005)</td>
<td>28.00 (0.82, 277.96)</td>
<td>10/15</td>
<td>1/15</td>
<td>17.24</td>
</tr>
<tr>
<td>Ziegler, 0.4mg (2008)</td>
<td>0.53 (0.11, 2.60)</td>
<td>3/20</td>
<td>5/20</td>
<td>21.55</td>
</tr>
<tr>
<td>Subtotal (I-squared = 61.1%, p = 0.025)</td>
<td>0.91 (0.20, 4.24)</td>
<td>26/85</td>
<td>14/60</td>
<td>100.00</td>
</tr>
<tr>
<td><strong>PDPH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martin-Laurani, 0.5mg (1995)</td>
<td>1.00 (0.02, 53.66)</td>
<td>5/16</td>
<td>5/16</td>
<td>17.31</td>
</tr>
<tr>
<td>Techanivate, 0.3mg (2003)</td>
<td>1.00 (0.02, 52.85)</td>
<td>0/5</td>
<td>5/21</td>
<td>17.44</td>
</tr>
<tr>
<td>Ziegler, 0.4mg (2008)</td>
<td>1.00 (0.13, 7.78)</td>
<td>2/23</td>
<td>2/23</td>
<td>65.25</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 1.00)</td>
<td>1.00 (0.09, 5.24)</td>
<td>3/60</td>
<td>3/60</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**NOTE:** Weights are from random effects analysis.

**Significant OR with morphine:**
- **Pruritis:** 3.9
- **Sedation:** 0.35
FIGURE 4: SIDE EFFECT PROFILE-FUNNEL PLOT

Funnel Plots for Overall Side Effects

- Pruritis
- Nausea
- Sedation
- Resp Depression
- Urinary Retention
- PDPH
DISCUSSION
ITM beneficial when compared to placebo as suggested by lower VAS scores up to 18 hours post-op.

Effectiveness beyond 24 hours cannot be established.

Unable to establish ideal ITM dosing
DISCUSSION – SECONDARY OUTCOMES

- Increased incidence of pruritis in ITM group
- Trend toward decreased sedation with ITM
- Combining high and low dose groups produced no change in outcome
- Meta-analysis showed that there were no major increases in the incidence of respiratory depression, urinary retention, nausea/vomiting
Major concern w/ ITM is risk of delayed respiratory depression

Based on this meta-analysis, difficult to draw conclusions regarding risk of respiratory depression due to:

- Limited number of pts
  - Only 6 total pts identified as having respiratory depression
- Variability amongst studies in defining respiratory depression
  - 2 studies defined changes in PaCO2
  - 3 studies NOT defined
  - 5 studies resp rate variable (RR 8-12)
    - Treatment guidelines inconsistent amongst studies
STUDY LIMITATIONS

- Small sample size
- High variability use of analgesic regimens and adjuncts
- Inconsistent side effect profile reporting
- Lack of consistent blinding of outcome assessors
- Difficult to standardize type of spine surgery
CONCLUSIONS

- ITM efficacy well known for post-op analgesia in multiple patient populations.
- This review demonstrated that ITM was effective in reduced pain scores for up to 18 hours after spine surgery
  - Consistent with current body of evidence supports the superiority of ITM in the first 24 hours post-op
- However, comes at the cost of increasing the incidence of pruritis
- ITM shows a decreased risk of sedation (re: respiratory depression)
QUESTIONS?
REFERENCES (1)


Employed as it was assumed that the included studies were a random sample of population of studies investigating intrathecal morphine

- Weighted mean differences (minimal heterogeneity)
  - Natural units
- Standard mean differences (significant heterogeneity)
  - SD
Duration of data collection ranged from 20 hours to 10 days.

Data analysis grouped into 6 hour time frames for VAS scores.

Maximum time frame of 24 hours for VAS scores.

VAS scores standardized to 100 point scale.

Limited number of studies with low does ITM.

Low and high dose results pooled.

Nausea and vomiting pooled.
RESULTS

- Primary outcomes
  - ITM group had significantly lower VAS scores at 0-6, 6-12, and 12-18 hours (95% CI) compared to placebo
  - no significant difference in the VAS at 18-24h

- Secondary outcomes
  - ITM group had significantly higher incidence of pruritis
  - ITM group had significantly lower incidence of sedation
  - No significant difference between control and ITM for nausea, respiratory depression, urinary retention or PDPH.
Results confirm that ITM efficacious for postoperative analgesia but at a cost of increased pruritis
- Consistent w/ other studies by Meylan et al., Gehling et al., and Popping et al.

Our results also reveal that ITM does not increase the incidence of respiratory depression which contrasts those findings by Meylan et al. and Popping et al.
- Even with MA sample may be too small to rule out an effect on respiratory depression

Large variability exists in literature due to underpowered studies