Chapter 6

Itching after intrathecal morphine
Incidence and treatment

This study has been submitted to the European Journal of Anesthesiology. Robert Slappendel, Eric W.G. Weber, Bart Benraad, Jacques van Limbeek, Ris Dirksen.
Itching after intrathecal morphine
Incidence and treatment

Introduction
Intrathecal opiates are often used for postoperative pain control in major orthopedic surgery of the lower limb (Domsky 1992, Kalso 1983, Grace 1996, Reay 1989). In our clinic, the intrathecal combination of a local anaesthetic and an opiate serves as an easy and cheap anaesthetic technique which produces both excellent surgical conditions and excellent postoperative pain relief. Moreover, the patients can ambulate quickly after surgery once the effect of the local anaesthetic has worn off, as opiates do not impair motor function.

Earlier studies used intrathecal morphine in doses up to 2.5 mg morphine, and many side effects were reported, including the dangerous late respiratory depression (Reay 1989, Jacobson 1988) and the more harmless but at times extremely bothersome side effects of postoperative nausea and vomiting, urinary retention and itching. The incidence of post operative nausea and vomiting, or urinary retention were unrelated to intrathecal morphine when doses of 0.2 mg are used (Weber 1998). In this study we evaluated whether the incidence and severity of itching can be minimised by adapting the low dose range of intrathecal morphine. Our questions were: 1) is itching a dose dependent phenomenon and is its incidence less after the lower doses of the range of 0.025 - 0.2 mg morphine intrathecally; 2) does systemically administered morphine contribute to the problem of itching; and, 3) how well can we control itching caused by low doses of intrathecal morphine by applying a standardised treatment using promethazine and - for intractable itch - naloxon.

Methods
The study was approved by the ethical committee of our hospital and written informed consent was obtained from all patients. Finally hundred forty three consecutive patients scheduled for total hip surgery by intrathecal anesthesia were included in the study after an informed consent.
All patients were premedicated with 5, 7.5, or 10 mg midazolam (approximately 0.1 mg/kg) orally one hour before intrathecal anesthesia. Intrathecal anesthesia was produced in each of these patients by administering 20 mg bupivacaine plus morphine solved in 4 mL intrathecally. Intrathecal puncture was performed in a sitting position. Patients were allocated and randomized to four groups in a double blind manner: Group I, 0.025 mg (0.00625 mg/mL), Group II, 0.05 mg (0.0125 mg/mL), Group III, 0.1 mg (0.025 mg/mL) and Group IV, 0.2 mg (0.05 mg/mL) morphine. The morphine dose was only known to the pharmacist. Adequate sedation was provided at patient request during the procedure: the anaesthesiologist administered 1 mg midazolam at the minimum interval of 5 minutes until the patient indicated that the desired sedation was settled. Non-invasive blood pressure, heart frequency (ECG), SpO\textsubscript{2}, and respiratory frequency were continuously monitored during anesthesia and at the intensive care unit during the first 24 h after surgery.

Itching In the postoperative period the presence of itching, and treatment for itching were noted every 3 hours by nurses at the intensive care ward. Itching was treated by a standardised protocol. In brief, the need for relief of itching was indicated by the patient. Thus, only on request of the patient, treatment of itching was initiated with a first dose of 25 mg promethazine intramuscularly. If itching had not diminished within 1 hour after this intramuscular injection, 0.12 mg naloxon was given subcutaneously. If itching diminished but returned after a period longer than one hour, intramuscular injection with promethazine was repeated once. If itching did not diminish after an subcutaneous injection of naloxon an continuous intravenous drip with naloxon was started at 5 µg/kg/h. The severity of itching was estimated from the requirement of treatment, and we recognised three categories: mild = only present after inquiry, moderate = need for promethazine, severe = need for naloxon.

Pain: In the post-operative period, all patients were treated with the analgesic nabumeton 30 mg/kg orally, 1 dose a day (1000 mg, 1500 mg or 2000 mg). Pain was evaluated using VAS scores (0 - 10; with 0 = no pain). If
pain was present morphine was administered intravenously in a patient controlled manner. The settings of the PCA (patient controlled analgesia) pump (BRAUN®, Melsungen, Germany): baseline 0.0 mg/hour, bolus dose 1.0 mg, bolus interval 5 minutes, maximum 30.0 mg per 4 hours.

Other side effects. The presence or absence of other side effects (post operative nausea and vomiting (= PONV), urinary retention, sedation) was noted at a 3 h interval during the 24 h observation period. Also, medication to treat these side effects were registered at the same interval during the 24 h observation period.

Statistical analysis Pain scores were analysed using a one way ANOVA followed by Scheffé’s post hoc analysis. The incidence of PONV was analysed by Fisher's exact test. P value less than 0.05 was considered significant. Incidences of and the severity of itching was analysed by chi-square tests. The adjusted standardized residuals indicate the contribution of each cell of the table to the significance of the purposed differences. The duration of itching was calculated and analyzed by means of an anova with a Scheffé’s post hoc test.

Results
Demographic data are given in table 1. The four groups did not differ for age, length, weight or gender. Likewise other variables, e.g. preoperative use of beta blockers, peroperative blood loss, percentages of patient’s which got sedation during surgery, use of cementation, and blood pressure drop (> 25% decrease in MAP after cementation) showed no differences among the groups.

Itching Itching occurred in all groups. The overall incidence of itching was related to intrathecal morphine dose (figure 3) and time after surgery (figure 4). The overall incidences of itching were: 14.3%, 21.6%, 48.6% and 61.7% in group I, II, III, and IV respectively.
Table 1. Demographic data and intraoperative factors.

<table>
<thead>
<tr>
<th>Group</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrathecal morphine</td>
<td>0.025</td>
<td>0.05</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>n</td>
<td>35</td>
<td>37</td>
<td>37</td>
<td>34</td>
</tr>
<tr>
<td>Age in years</td>
<td>62.6 (12.8)</td>
<td>65.9 (8.9)</td>
<td>61.9 (15.2)</td>
<td>62.9 (11.3)</td>
</tr>
<tr>
<td>Length in cm</td>
<td>167.6 (7.8)</td>
<td>169.5 (8.2)</td>
<td>169.7 (7.4)</td>
<td>167.9 (8.6)</td>
</tr>
<tr>
<td>Weight in kg</td>
<td>69.5 (11.4)</td>
<td>73.5 (14.1)</td>
<td>74.9 (10.9)</td>
<td>74.2 (13.6)</td>
</tr>
<tr>
<td>Gender (m/ f)</td>
<td>12/ 23</td>
<td>10/ 27</td>
<td>10/ 27</td>
<td>7/ 27</td>
</tr>
</tbody>
</table>

Age, length, and weight are given as mean values, standard deviation in parentheses. n = number of patients, m = number of men, f = number of female. Standard deviation in parentheses.

Figure 3. Incidence and severity of itching

Incidence and severity of itching in four groups. Mild itching = only present after inquiry, moderate itching = need for promethazine, severe itching = need for naloxon). * indicates statistical differences between group III and IV versus group I and II. For details see text.
Incidence of itching related to time after surgery. * indicates statistical differences between group III and IV versus group I and II. For details see text.

The adjusted standardized residuals indicate a trend over group I to IV respectively varying from -3.1, -2.2, 1.8 to 3.3 in favor of itching (chi-square = 22.74; df = 3; p = 0.00005). The incidence of itching was related to time after surgery. Highest (time related) incidences of itching were found 6 to 9 hours after surgery (figure 4). The mean duration (hours) of itching in patients who itched was: 3.6, 3.4, 7.5, and 6.7 in group I, II, III, and IV respectively. A post hoc comparison between groups revealed that the duration of itching only differed between group I and II versus group III and IV respectively (F = 11.27; df (3,142); p = 0.0000). Both the need for treatment (figure 3) and the mean hours of itching (table 2) increased with the intrathecal morphine dose.
Table 2. Mean hours of itching

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>Itching (n)</th>
<th>Mean hours of itching</th>
<th>Total hours of itching</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I: 0.025 mg morphine</td>
<td>35</td>
<td>5</td>
<td>3.6</td>
</tr>
<tr>
<td>Group II: 0.05 mg morphine</td>
<td>37</td>
<td>8</td>
<td>3.4</td>
</tr>
<tr>
<td>Group III: 0.1 mg morphine</td>
<td>37</td>
<td>18</td>
<td>7.5</td>
</tr>
<tr>
<td>Group IV: 0.2 mg morphine</td>
<td>34</td>
<td>21</td>
<td>6.7</td>
</tr>
</tbody>
</table>

n = number of patients.

Patients who experienced itching used significantly less systemic morphine (n = 52; 11.7 (± 11.7) mg morphine) than those patients who did not have itching at all (n=91; 18.0 mg (± 14.3) morphine, t = 2.71; df = 139; p = 0.008). In our population of patients we found no relation between age, gender, weight and the incidence of itching.

Pain

As can be depicted from the VAS scores given in figure 5, excellent pain relief was present in the post operative period for all patients in all groups. The mean use of systemic morphine administered by PCA infusion pump was in group I to IV respectively: 23.7 mg; 17.8 mg; 10.9 mg; and, 9.9 mg. A statistical difference is present between group III and IV versus group I, p<0.01. No correlation was found between VAS scores and itching.
Figure 5. VAS pain scores

Other side effects
Respiratory depression (defined as breathing frequency below 10 per min and arterial blood gas showing acidosis and hypercarbia) did not occur in all groups. Incidences of PONV were 34.3%, 45.9%, 37.8% and 41.2% in group I, II, III, and IV respectively. The incidence of urinary retention (defined as absence of spontaneous voidance of urine at 7 hours after surgery and the bladder content at catheterisation of > 400 mL) was 74.2%, 92.0%, 67.6% and 70.6% in group I, II, III and IV respectively. There were no differences among the four groups for these two side effects and there was no correlation between PONV, incidence and degree of sedation or urinary retention with itching.

Discussion
This study shows clearly, that intrathecal injection of morphine in human beings results in itching and the incidence of this effect increased in a dose dependent fashion in the dose range of 0.025 - 0.2 mg intrathecal morphine. Itching responded well to the antihistaminic drug promethazine in the dose of 25 mg intramuscularly.
In our study the incidence of itching is found to increase in a dose related fashion. The incidence of itching after intrathecal morphine in our study
Itching

(14.7 to 61.3%) was similar to that earlier reported in the elderly orthopedic patient (Jacobson 1988, Weber 1998). The incidence of itching after intrathecal bupivacaine alone (without added morphine) was 1% in an earlier study in 100 patients (Weber 1998). Even higher incidences and a greater intensity of itching were found in young women after elective caesarean section (Alhashemi 1997, Cardosos 1998, Milner 1996). However, we have not found a relation between gender or age to the incidence of itching in the population studied. The incidence of itching was not found to relate to the dose in the study of Milner who compared 0.1 and 0.2 mg intrathecal morphine after elective caesarean section (Milner 1996). Yet, our findings are based on inquiry every three hours, which seems to be the best way to establish the incidence of itching (Pinckaers 1980, Dirksen 1980).

Highest incidences of itching were found 6 to 9 hours after surgery (figure IV), i.e. 7.5 to 10.5 hours after intrathecal injection. The kinetics of the liquor flow (Partain 1978) and the delay between moment of injection and itch are consistent, which suggests that supraspinal centrally located morphine receptors mediate itching. In accordance with this notion are data of animal studies (Thomas 1993, Tohda 1997) which implied opioid receptors in the medullary dorsal horn in an itch-like phenomenon. Noteworthy, centrally induced itch is always sensed in the skin, and thereby itch is caused by systemic administration of morphine. Here, itching has an incidence of approximately 1% (Weber 1998), and it may relate to morphine’s ability to cause release of histamine (Hermens 1985).

We do not expect that the administration of an antihistaminic drug is causal therapy for centrally induced itching. Nevertheless, it was highly successful in most patients. Only in one patient in group IV 25 mg promethazine was insufficient on its own and naloxon was needed. Several drugs (e.g. droperidol, propofol, diphenhydramine) have been used without success in clinical studies (Alhashemi 1997, Horta 1996, Warwick 1997). Nalbuphine (Alhashemi 1997) effectively relieved itching by intrathecal morphine, but resulted in higher pain VAS scores. Ondansetron is only used in case reports to treat itching (Larijani 1996).

We conclude that even after low doses of intrathecal morphine the incidence of itching is high and typically dose related to intrathecal
morphine. When necessary it is easy to treat by administration of promethazine 25 mg intramuscularly.

Figure 1. Standard operating procedure for the evaluation of itch.
Figure 2. Flowchart for itch evaluation and the four steps of treatment.

itch evaluation

Yes

treat

step 1
promethazine 25 mg i.m.

step 2
promethazine 25 mg i.m.

step 3
naloxon 0.12 mg s.c.

step 4
naloxon 0.12 mg s.c. + 5 µg/kg/hr

wait