Efficacy and respiratory effects of low-dose spinal morphine for postoperative analgesia following knee arthroplasty

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A randomized, double-blind study of 38 patients undergoing total knee replacement was undertaken to compare the efficacy and respiratory effects of low-dose spinal morphine and patient-controlled i.v. morphine against patient-controlled i.v. morphine alone. Patients received either morphine 0.3 mg or saline 0.3 ml with 0.5% heavy spinal bupivacaine 2–2.5 ml. Respiratory effects were measured continuously for 14 h postoperatively with an Edentec 3711 respiratory monitor. There was an improvement in pain relief in the intrathecal morphine group, with significantly lower median VAS pain scores on movement at 4 h (0 (median 0–1.5) vs 5 (1.25–7.75) P < 0.01), 12 h (2 (1–5) vs 6 (3–8) P < 0.01) and 24 h (3 (1–5) vs 5 (3–7) P < 0.05) postoperatively, despite using significantly less patient-controlled morphine (20 mg (10.25–26.25) vs 38.5 mg (27–51) P < 0.01) in the first 24 h. There was a small but statistically significant reduction in the median oxygen saturation (SpO₂) in the intrathecal morphine group 97 (95–99)% compared with the placebo group 99 (97–99)% (P < 0.05). Although marked disturbances in respiratory pattern were observed in both groups, none of the patients in the study had severe hypoxaemia (SpO₂ < 85% > 6 min h⁻¹) and there was no significant difference in the incidence of mild (SpO₂ < 94% > 12 min h⁻¹) or moderate (SpO₂ < 90% > 12 min h⁻¹) hypoxaemia or the incidence of episodes of apnoea or hypopnoea in the two groups.


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Intrathecal opioids have been shown to provide effective analgesia in a variety of surgical settings since the introduction of the technique into clinical practice in 1979. The advantage of spinally administered opioids is that prolonged analgesia can be provided using a single injection at the time of surgery without the need for cumbersome and expensive pumps in the postoperative period. However, the use of this technique has been limited by a high incidence of opioid-related side effects including nausea, pruritus and urinary retention, and the fear of respiratory depression, which may be delayed in onset. In an attempt to limit major and minor opioid side effects, the use of low-dose spinal opioids has been advocated. When using low doses there are concerns about the appropriate choice of rescue analgesia if patients have ineffective pain relief. Although studies using intrathecal opioids have demonstrated improved analgesia, there have been a limited number of studies that assess their respiratory effects.

The aim of this study was to investigate whether the combination of low-dose (0.3 mg) intrathecal morphine and patient-controlled i.v. morphine provides more effective analgesia than patient-controlled i.v. morphine alone in patients undergoing knee arthroplasty. A secondary aim was to investigate the respiratory effects of the combination of intrathecal morphine and patient-controlled i.v. morphine as rescue analgesia.

Methods

After obtaining Hospital Ethics Committee approval and informed patient consent, we studied 38 ASA 1 or 2 patients scheduled for unilateral knee arthroplasty, in a prospective, randomized, double-blind, placebo-controlled study.

Patients undergoing knee arthroplasty were chosen for this study because audit from our acute pain team has consistently shown that these patients have high analgesic requirements and require early mobilization.

Patients in whom either non-steroidal anti-inflammatory drugs or spinal anaesthesia were contraindicated were excluded from the study.

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The anaesthetic management of all patients was standardized. Spinal anaesthesia was undertaken using a mixture of 0.5% heavy bupivacaine 2–2.5 ml plus a pharmacy-prepared solution of morphine or saline, which was allocated on a double-blind randomized basis by pharmacy, using a computer-generated random number system. The randomization was stratified to ensure that morning and afternoon cases were divided equally between the two groups.

Patients received either morphine 0.3 mg (0.3 ml from a 2-ml ampoule of 1 mg ml⁻¹ preservative-free morphine), or normal saline 0.3 ml (0.3 ml from a 2 ml 0.9% sodium chloride solution) in addition to the bupivacaine in their spinal anaesthetic. General anaesthesia was induced in unpremedicated patients with propofol (1–3 mg kg⁻¹) and fentanyl (0–1 μg kg⁻¹) at the anaesthetist’s discretion. Maintenance of anaesthesia was provided with oxygen, nitrous oxide and enflurane in patients breathing spontaneously through a laryngeal mask airway.

In addition to the spinal injection, postoperative anaesthesia consisted of diclofenac 50 mg every 8 h (PO or PR). Patients were allowed to self-administer i.v. morphine via a patient-controlled analgesia system (Graseby 9300 model) in 1 mg boluses with a 5-min lockout period. Metoclopramide was routinely prescribed for postoperative nausea and vomiting. All patients were given oxygen by nasal cannulae at 2 litres min⁻¹, if at any time their oxygen saturation was noted to be 94% or below.

The use of a visual analogue scale was described at the preoperative visit and the effectiveness of analgesia was measured by visual analogue pain scores on movement (VASm 0–10) at 4, 12 and 24 h. Patients were also asked to give a verbal rating score for satisfaction with the quality of analgesia (poor, fair, adequate, good, excellent), and pain severity (absent, mild, discomforting, distressing, excruciating) for the 24-h period. In addition, the PCA 24 h morphine consumption was recorded.

Respiration was monitored continuously using the Edentec model 3711 digital recorder (Edentec 3711, Nellcor, Eden Prairie, MN, USA) for 1 h preoperatively for a baseline reading, and then for 13–14 h after the patient had returned to the orthopaedic ward postoperatively. This digital recorder comprises a lightweight portable recorder, with non-invasive probes attached to the subject, continuously measuring nasal airflow, chest impedance and pulse oximetry. Chest impedance and heart rate were recorded by attaching two electrodes to each side of the chest (mid axillary line at T4–5). Chest wall movement was measured by passing a constant current through the chest giving a measure of impedance. Nasal airflow was measured by a thermistor attached between the upper lip and nose.

All Edentec respiratory data were downloaded onto a desktop computer. Each tracing was assessed in 10-min epochs by two of the authors (P.C., D.C.) in a blinded fashion. These data were edited to exclude obvious artefact recordings, which included non-physiological hypoxaemia, interference due to patient movement and/or disconnection from the recorder. The edited data were then analysed using an ETS 2.0 software program.

An apnoea event starts when the airflow stays between +5% and −5% of baseline for at least 10 s, and ends when the airflow is greater than 5% or less than −5%. A hypopnoea event starts when the trace amplitude is less than 50% of the average amplitude over the previous 2 min and stays at or below this level for at least 10 s. The event ends as soon as the amplitude increases above 50% of the average amplitude.⁸ Frequencies of events were calculated per hour of recording. Studies with less than 4 h of recorded data were regarded as technically unsatisfactory and rejected. The respiratory distress index (RDI) is the sum of apnoea and hypopnoea events per hour. An RDI greater than 30 is said to be diagnostic of sleep apnoea/hypopnoea syndrome requiring treatment.⁸

Hypoxaemia was classified by previously defined criteria⁹ as mild when the SPO₂ was <94% >12 min h⁻¹, moderate when the SPO₂ <90% >12 min h⁻¹ and severe when the SPO₂ <85% >6 min h⁻¹. The mean saturations and the percentage time spent below a saturation of 95% during the study period for each patient were also recorded.

Measurement of oxygen saturation, sedation scoring (0=None, patient alert; 1=mild, occasionally drowsy, easy to arouse; 2=moderate, frequently drowsy, easy to arouse; 3=severe; somnolent, difficult to arouse), respiratory rate and visual analogue score for pain were recorded on the ward at hourly intervals for the first 4 h and then every 4 h thereafter. The incidence of nausea or pruritus requiring treatment was noted.

Previously collected audit data on patients who had received a spinal anaesthetic with bupivacaine alone and a morphine PCA following knee arthroplasty had shown that the mean morphine consumption was 40 (SD 16) mg. Assuming a clinically significant reduction in morphine consumption of 20 mg, it was calculated¹⁰ that 30 patients (15 pairs) would be required to have a 90% power of detecting a 50% reduction in 24 h morphine consumption at a significance level of 0.05.

Data were analysed by using the SPSS statistics package (version 8). Mann–Whitney and chi-squared tests were used for the non-parametric data, and an unpaired Student’s t-test for the patient characteristics. A value of P<0.05 was regarded as statistically significant.

Results

Thirty-eight patients completed the study. Two patients were excluded as an incorrect dose of intrathecal drug was administered to one and premedication was given to the second. Due to software problems with the Edentec monitor and patient non-compliance, a further four patients had incomplete respiratory data for analysis, but their data on morphine consumption were included.
Patient characteristics were similar between the two groups. Mean (sd) age, body weight and height were 70.3 (9.9) yr, 82.3 (15.7) kg and 1.7 (0.1) m, and 71.3 (7.6) yr, 80.5 (14.3) kg and 1.7 (0.1) m in the intrathecal morphine and intrathecal saline groups, respectively.

The preoperative baseline respiratory monitoring showed median saturations (interquartile range) of 98.5 (96–99)% in the morphine group and 98.5 (97–99)% in the control group.

Patients in the intrathecal morphine group had significantly lower VASm pain scores on movement at 4, 12 and 24 h (Fig. 1), and used a significantly lower dose of patient-controlled i.v. morphine in the first 24 h after surgery (Fig. 2).

Although more patients in the intrathecal morphine group scored the severity of their pain as mild or absent and more patients in this group required treatment for emesis, these differences were not statistically significant. There was no significant difference between the two groups in the incidence of pruritus or their verbal rating of satisfaction (Table 1).

When comparing the apnoea and hypopnoea episodes, there was no significant difference between the two groups in the median RDI or in the incidence of those with a respiratory distress index >30 (Table 2). Patients in both groups had disordered respiratory patterns with episodes of central and obstructive apnoea.

The median values of the mean saturations in the postoperative period between the two groups were compared and were significantly lower in the intrathecal morphine group compared with the intrathecal saline group.

Using previously defined criteria, 5/17 patients in the intrathecal morphine group could be classified as mildly hypoxaemic and 1/17 as moderately hypoxaemic during the study period. In the saline group, 3/15 subjects showed mild hypoxaemia. However, this difference was not statistically significant. No patients had severe hypoxaemia using these criteria.

Although patients in the intrathecal morphine group spent a median of 10% of their time with a saturation below 95% compared with a median of 3% in the placebo group, this was not statistically significant.

Discussion

This study has achieved the primary aim of demonstrating that, following knee arthroplasty, intrathecal morphine 0.3 mg followed by patient-controlled i.v. morphine, improves postoperative analgesia and reduces i.v. morphine consumption compared with patient-controlled i.v. morphine alone. This confirms earlier studies on the quality of analgesia after Caesarean section and hip surgery.

Whilst this combination of intrathecal and patient-controlled i.v. morphine provides effective analgesia, there are concerns in clinical practice about the safety of intrathecal opioids particularly if systemic opioids are used for rescue analgesia. A 17-nation European survey revealed that, except for the UK, morphine was the most commonly used of the long-acting opioids. This initial study used morphine because it has been extensively used, and whatever degree of respiratory depression was seen with intrathecal morphine, respiratory depression would be less
likely to occur when low doses of more lipid-soluble opioids are administered by the intrathecal route.\textsuperscript{7,17}

Due to the dose-dependent nature of respiratory depression,\textsuperscript{5} a dose of morphine 0.3 mg was used, based on an earlier dose–response study that showed that this is an effective dose with the fewest side effects.\textsuperscript{4} However, more recent studies have shown that lower doses (0.1 mg) are effective for analgesia after Caesarean section\textsuperscript{12} and hip replacement surgery.\textsuperscript{14}

There have been many reports of respiratory depression following spinal opioids.\textsuperscript{7} Previous studies looking at the respiratory effects of intrathecal opioids have used a combination of pulse oximetry, sedation scoring, respiratory rate and invasive arterial blood–gas analysis.\textsuperscript{5,7,18}

The availability of relatively simple to use, bedside respiratory monitors allows us to continuously study the ventilatory pattern and oxygenation of patients receiving intrathecal opioids. Although it is often assumed that bedside monitors such as the Edentec are less accurate than conventional sleep studies with polysomnography, this equipment has recently been used to validate the detection of respiratory disturbances in patients with sleep apnoea/hypopnoea syndrome\textsuperscript{8} and to investigate patients recovering from major abdominal surgery.\textsuperscript{19}

Our study demonstrated that respiratory disturbances occurred in both groups. The pattern of respiratory dysfunction was similar to that previously described following the use of i.v. morphine,\textsuperscript{20,21} and included obstructive and central apnoeas.

Although patients in the morphine group spent three times as long with a saturation below 95% and twice as many were classified as ‘hypoxaemic patients’; that is they spent greater than 20% of their time with mild or moderate hypoxaemia (85–94%),\textsuperscript{9} these differences were not statistically significant. The only statistical difference was between the median oxygen saturations in the two groups. In view of the risks of postoperative hypoxaemia\textsuperscript{22} and its potential effects on postoperative morbidity, it was deemed necessary to give patients in this study supplementary oxygen if their oxygen saturations fell below 94%. Because oxygen was not administered to all the study patients, the small but statistically significant difference between the mean saturations (97% and 99%) may not be of clinical significance.

None of the patients in the study met the pre-defined criteria\textsuperscript{9} for severe hypoxaemia, that is, spending more than 10% of their time with a saturation below 85%. The only patient in the study who approached this level was a patient in the spinal morphine group who spent 90% of their time with saturation below 95% including 4% of their time below 85%. This would be regarded by most clinicians as a significant level of hypoxaemia.

Because of the low incidence of respiratory depression, a much larger study would be needed to detect or exclude a significantly increased risk with low-dose spinal morphine. Further studies are required into the efficacy and duration of action of more lipid-soluble opioids which are likely to be associated with a lower incidence of respiratory depression.

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References