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Low dose spinal morphine and intravenous diclofenac for postoperative analgesia after total hip and knee arthroplasty

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Abbreviations:

ASA physical status	–	American society of anaesthesiologists physical status
CSF	–	cerebrospinal fluid
IT	–	intrathecal
NRS	–	numeric rating scale
NSAID	–	non-steroidal antiinflammatory drug
PONV	–	postoperative nausea and vomiting

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Abstract

Background and Aims: *Intrathecal (IT) morphine added to a spinal anaesthesia provides effective postoperative analgesia after hip and knee arthroplasty reducing the need for systemic opioids. To reduce the risk of side effects like pruritus, nausea/vomiting, and a more serious effect of respiratory depression, low dose IT morphine (0,1–0,3 mg) has been used. The aim of this prospective, randomized, double-blind study was to assess the analgesic efficacy of 0,2 mg IT morphine combined with postoperative i.v. diclofenac in the first 24 hours after hip and knee arthroplasty, the primary outcome measure being the number of patients without any additional opioid request. Side effects and possible complications of therapy and patient satisfaction with pain management were also recorded.*

Patients and Methods: *40 patients were randomized to receive spinal anaesthesia with levobupivacaine and 0,2 mL normal saline (control group) or 0,2 mg IT morphine. All patients received diclofenac 75 mg i.v. one and 10 hours postoperatively. Pain was assessed by numeric rating scale at 3,6,12 and 24 hours postoperatively and morphine 2 mg i.v. was given for inadequate analgesia. The third dose of diclofenac could be given 10–12 hours after the second dose for a pain score 3–4.*

Results: *IT morphine group had significantly lower postoperative pain scores at all measured time intervals and used significantly less i.v. morphine. 76,2% of patients in the IT morphine group did not require any additional i.v. morphine compared to 11,1% of the control group. This resulted in significantly higher patient satisfaction despite common occurence of mild pruritus. Postoperative nausea/vomiting were frequent in both groups with no cases of respiratory depression.*

Conclusions: *Low dose IT morphine added to regular postoperative i.v. diclofenac provides excellent analgesia after hip and knee arthroplasty and allows for a protocol without additional systemic opioids.*

INTRODUCTION

In recent years considerable attention has been paid to the treatment of postoperative pain with regard to the favourable effect of adequate analgesia on patient outcome. The provision of high quality analgesia after major orthopaedic surgery in older patients with comorbidities still presents a challenge. Intrathecal (IT) opiates, especially morphine, provide effective analgesia in patients undergoing total hip and knee arthroplasty in spinal anaesthesia *(1, 2)*. However, IT morphine may be

associated with dose related side effects like nausea and vomiting, pruritus, urinary retention and the most concerning adverse effect of delayed respiratory depression. In an attempt to reduce side effects and complications low doses of IT morphine ranging from 0,1–0,3 mg have been used with favourable results *(3–7)*. Even at low doses IT morphine produced effective pain relief in the first 24 postoperative hours with lower pain scores, decreased requirement for systemic opioids and high patient satisfaction. Some patients did not require any systemic opioids during 24 hours after surgery. Several dose ranging studies have looked into the lowest effective dose of IT morphine in patients undergoing total hip and knee replacement *(3, 4, 6–8)*. While 0,1 mg of IT morphine provides good analgesia after hip arthroplasty, knee arthroplasty requires doses of 0,2–0,3 mg for effective pain relief. In an attempt to improve postoperative analgesia several authors have used paracetamol, metamizol or nonsteroidal antiinflammatory drugs (NSAIDs) i.e. nonopioid analgesics in addition to IT and systemic opioids with further benefitial effects *(8–10)*. Multicentre study on orthopaedic patients *(9)* which used 0,1 mg and 0,2 mg of IT morphine and i.v. metamizol for postoperative pain management showed 40% of patients did not require any additional systemic opioids postoperatively.

The aim of this prospective, randomized, double-blind study was to assess the analgesic efficacy of low dose IT morphine (0,2 mg) combined with postoperative i.v. diclofenac in the first 24 hours after total hip and knee replacement. We also recorded side effects and possible complications of IT and systemic morphine use and patient satisfaction with pain management.

PATIENTS AND METHODS

The study protocol was approved by the Hospital Ethics Committee and informed consent was obtained from all patients before the study. 40 adult patients ASA physical status I–III scheduled for total hip or knee replacement surgery during spinal (intrathecal) anaesthesia were enrolled in the study in a prospective, randomized, double blinded manner. Exclusion criteria were as follows: any medical condition resulting in ASA status greater than 3, non-suitability for spinal anaesthesia as deemed by the anaesthesiologist providing care for the patient, history of adverse reaction or a contraindication to the administration of morphine, diclofenac or local anaesthetic agents and preoperative use of strong opioids.

No patient received a premedication. Spinal anaesthesia was performed with the patient in the sitting position at spinal levels L 3/4 or L 4/5. Patients were administered 13,5–15 mg of isobaric levobupivacaine (Chirocaine 5 mg/mL, Abbot, Italy) mixed with the study medication which was 0,2 mg of preservative-free morphine chloride (Morfinklorid Alkaloid 4 mg/mL, Alkaloid, Skopje, Republic of Macedonia) made up to 0,2 mL with normal saline in the morphine group or 0,2 mL of normal saline in the control group. The remainder of the intraoperative anaesthetic care was left to the discretion of the anaesthesiologist caring for the patient. All patients received indwelling urinary catheter preoperatively. Postoperatively patients were transfered to the high dependency unit for 24 hours where respiratory and haemodynamic parameters were monitored regularly. Standard monitoring included continuous ECG, respiratory rate, peripheral oxygen saturation (pulse oxymetry) monitoring and hourly, or more frequent, blood pressure measurements. All patients received oxygen via nasal canula at 3 L/min for the first 2 hours and later for oxygen saturation ≤ 93%, 75 mg of diclofenac sodium in 100 mL of saline infused over 30 minutes and 10 mg of metoclopramide i.v. at 1 and 10 hours postoperatively.

Assessment variables included the severity of pain, the presence and severity of postoperative nausea and vomiting (PONV), pruritus, sedation and respiratory depression. Each variable was recorded at the time of admission to the unit (time 0), at 3, 6, 12 and 24 hours postoperatively or more frequently if treatment was required. Pain severity was evaluated by using a numeric rating scale (NRS), previously explained to the patient. On NRS 0 denotes no pain and 10 denotes the most severe pain. The NRS was chosen for pain assessment, as it was found to be easier to use than the visual analogue scale in elderly patients, who frequently suffer visual and coordination difficulties. Patients with a NRS score ? 4 or patients who requested analgesic were administered 2 mg i.v. morphine bolus with a minimal interval of 15 minutes between each bolus. For pain with NRS score 3–4, 12 or more hours after the second dose of diclofenac, an additional 75 mg of diclofenac could be administered. 24 hours after the surgery patients were asked about their postoperative pain experience (worse then expected, as expected, less then expected).

The incidence and severity of PONV and pruritus were graded as follows: 0 = none; 1 = mild, no treatment requested by patient; 2 = moderate to severe, treatment requested by patient. First line treatment of PONV consisted of 6,5 mg of thiethylperazine, a phenothiazine, intravenously. Dexamethasone 8 mg i.v. was a second line therapy and if both proved unsuccessful, morphine was switched for another opioid (tramadol or meperidine). Treatment for pruritus consisted of 20 mg of chloropyramine, an antihistaminic, intravenously. Naloxone in increments of 0,04 mg was reserved for chloropyramine resistant pruritus. Sedation was scored on a scale 0–3 (0 = awake, 1 = dozing intermittently, 2 = mostly sleeping, 3 = difficult to waken). Significant sedation was defined as a sedation score of 3. Respiratory depression was defined as respiratory rate < 10 breaths per minute or oxygen saturation ≤ 93% on oxygen 3 L/min via nasal canula. For signifcant sedation and/or respiratory depression naloxone 0,1–0,4 mg i.v. was to be used.

The primary outcome variable was the number of patients without additional opioid request during the 24 hour study period. Secondary outcome measures included pain intensity 3,6,12 and 24 hours postoperatively, the total amount of supplemental morphine, the time to

first opioid request, the incidence of adverse effects and patient perception of postoperative pain management.

The sample size was estimated from the published studies of a similar design. Continuous numerical data were analysed for the normality of distribution (Kolmogorov-Smirnov test) and presented as mean ± S.D. Group comparisons were performed using Student's t-test. Categorical data were presented as raw data or as frequences and analysed with the χ^2-test. Statistical significance was defined as P value less than 0,05.

RESULTS

Forty patients were enrolled in the study and were randomly assigned to IT morphine (21 patients) or control group (19 patients). No patient was excluded after entering the study, only the data for 24 hour morphine consumption from one patient in the control group were not included in the analysis, because the patient had severe PONV with i.v. morphine use and was switched to i.v. tramadol. There were no significant differences in demographic characteristics, ASA (American Association of Anaesthesiologists) status or the type of operation i.e. hip or knee surgery between the groups (Table 1).

Pain assessment by NRS at rest at different time intervals after arrival to the unit is presented in Table 2. The NRS scores were significantly lower in the IT morphine group at 3, 6, 12 and 24 postoperative hours with P ≤ 0,001. The mean worst postoperative NRS scores reported in the control group were significantly higher (P < 0,001) then those reported in the IT morphine group. Maximal pain scores in control patients (NRS 6,08 ± 1,86) were unacceptably high and probably reflect the delay in patient's request for analgesia and the delay in nurse administering the analgesic compared to patient-controlled analgesia. The 24 hour use of supplemental morphine was significantly lower (P < 0,001) in the IT morphine group then in the control group with a longer time to the first request for supplemental morphine (Table 3). In the IT morphine group 76,2 % of patients did not require any systemic opioid in the first 24 postoperative hours compared to only 2 patients (11%) in the control group, the difference being significant with P = 0,021. This correlated well with much higher proportion of patients (81%) experiencing less pain than they had expected compared to the control group (21,1%), P = 0,007. The incidence and severity of PONV were not different between the groups, while pruritus was significantly more frequent in the IT morphine group (Table 4). However, in all patients pruritus was mild and did not require treatment. The possible effect of IT morphine on urinary retention could not be analysed as all patients had urinary catheters placed preoperatively. None of the

TABLE 1

Patient and surgery characteristics.

	Control	IT morphine	P value
No. patients (% of total)	19 (47.5%)	21 (52.5%)	
Age (years)	67.74 ± 6.32	68.05 ± 8.8	n.s.
Sex (M:F)	7:12	9:12	n.s.
Weight (kg)	85.95 ± 12.8	85.8 ± 12.91	n.s.
Height (cm)	164.89 ± 7.42	166.66 ± 10.73	n.s.
ASA grade			
2	15 (37.5%)	17 (42.5%)	n.s.
3	4 (10%)	4 (10%)	n.s.
Surgery			
Hip replacement	12 (30%)	15 (37.5%)	n.s.
Knee replacement	7 (17.5%)	6 (15%)	n.s.

Values are mean ± S.D. or number (proportion); IT = intrathecal; n.s. = non-significant

TABLE 2

Pain assessment by numeric rating scale (NRS) at rest at different times after surgery.

Time (hours)	Control (n = 19)	IT morphine (n = 21)	P value
3	3.79 ± 2.21	0.93 ± 1.68	P < 0.001
6	4.2 ± 2.32	1.29 ± 1.42	P < 0.001
12	3.6 ± 2.21	1.50 ± 1.45	P = 0.001
24	4.21 ± 1.52	1.48 ± 1.6	P < 0.001
Max NRS	6.08 ± 1.86	2.79 ± 1.71	P < 0.001

Values are expressed as mean ± S.D.; IT = intrathecal

TABLE 3

Data regarding postoperative morphine requirement and overall patient assessment of pain in the first 24 hours.

	Control (n = 19)	IT morphine (n = 21)	P value
Morphine consumption (mg)	6.28 ± 3.96	0.67 ± 1.32	P < 0.001
Patients without opioid request (% of the group)	2 (11.1%)	16 (76.2%)	P < 0.021
Time to morphine request* (hours)	4.93 ± 7.06	19.7 ± 7.98	P < 0.001
Pain assessment			
Less than expected	4 (21.1%)	17 (81%)	P = 0.007
As expected	9 (47.4%)	4 (19%)	P = 0.267
Worse than expected	6 (31.6%)	0	P = 0.031

Values are mean ± S.D. or number (proportion); IT = intrathecal
* If no morphine was given in 24 hours, the time was recorded as 24 hours

TABLE 4

Incidence of side effects in the first 24 postoperative hours.

	Control (n = 19)	IT morphine (n = 21)	P value
PONV*			
Mild (score 1)	6 (15%)	6 (15%)	n.s.
Moderate to severe (score 2)	2 (5%)	3 (7.5%)	n.s.
Pruritus*			
Mild (score1)	9 (22.5%)	1 (2.5%)	P = 0.021
Moderate to severe (score 2)	0	0	
Resp. depression	0	0	
Significant sedation* (score 3)	0	0	

Values are number (proportion); IT = intrathecal; PONV = postoperative nausea and vomiting; n.s. = non-significant
* grading PONV, pruritus and sedation as described in methods

patients in the IT morphine or control group developed respiratory depession or excessive sedation. There were no other complications possibly related to the treatment protocol and all patients were transfered to the regular ward after 24 hours.

DISCUSSION

The main finding of the present study was that low dose IT morphine (0,2 mg) added to regular postoperative administration of NSAID diclofenac provided excellent analgesia in the first 24 hours after total hip and knee arthroplasty in spinal anaesthesia without significant adverse affects. Effective postoperative analgesia manifested itself in a high proportion of patients (76,2%) not requiring any additional opioids during the 24 hour study period and in high patient satisfaction with their pain management as they experienced less pain then they had expected.

Intrathecal morphine was introduced into clinical practice in 1979 *(11)* and has been shown to provide effective and long lasting analgesia after a variety of surgical procedures. Although in some institutions IT opioids, typically morphine, are applied as a single-dose injection in patients undergoing major surgery under general anaesthesia *(12),* more commonly they are added to intrathecally injected local anaesthetics in patients undergoing surgery in spinal anaesthesia like Caesarean section, orthopaedic surgery, urological and gynaecological surgery *(13–15)*.

Morphine is a highly hydrophilic opioid and applied intrathecally it enters the spinal cord slowly producing persistently high cerebrospinal fluid (CSF) concentrations. This contributes to the longevity of its analgesic action, but also to the risk of late respiratory depression due to cephalad migration in the CSF. CSF opioid concentrations, analgesia and respiratory depression are dose dependent and profound respiratory depression has been reported in the earlier studies which used larger doses of IT morphine i.e. more than 1 mg *(16)*. Jacobson *et al. (16)* suggested that the peak onset of respiratory depression was 5–10 hours after the injection. Also, respiratory depression has been reported more commonly in studies which used IT opioids to provide analgesia after major surgery under general anaesthetic.

In an attempt to decrease the risk of respiratory depression and other side effects of which pruritus seems to be dose dependent, several dose ranging studies have looked into the lowest effective dose of IT morphine after

certain types of surgeries. The studies have shown that even low dose IT morphine (0,1–0,3 mg) significantly reduced acute pain after total hip and knee arthroplasty manifested by lower pain scores, decreased requirement for systemic opioids via patient-controlled analgesia and an increase in the time until first opioid request *(3–8)*. Similarly, in our study patients who received 0,2 mg IT morphine with spinal anaesthetic had significantly lower pain scores at all measured time intervals and used significantly less systemic opioid during the study period. However, when using low dose IT morphine there are concerns about the appropriate choice of rescue analgesia if patients have ineffective pain relief because systemic opioids can increase the risk of respiratory depression. Some authors have used the concept of multimodal analgesia and regular doses of nonopioid analgesics like paracetamol, metamizol or NSAIDs in addition to IT morphine to improve the quality of analgesia and possibly avoid the use of systemic opioids *(8–10, 17)*. The studies differed in the study population i.e. the type of surgery and nonopioid analgesic used, but all have shown the beneficial effect of combining IT morphine with nonopioid analgesics. In the study in which they compared 0,2 mg and 0,5 mg IT morphine for postoperative analgesia after knee replacement, Bowrey *et al. (8)* used oral paracetamol 1 g four times daily and diclofenac 50 mg three times daily. The efficacy of this protocol is questionable considering high frequency of PONV in this and other studies on IT morphine. In a more recent multicentric study on orthopaedic patients receiving metamizol 1 g i.v. on a regular basis, Gehling and *al. (9)* showed that 0,2 mg IT morphine significantly reduced the number of patients requiring systemic opioids in the first 24 hours (31%) compared to 0,1 mg IT morphine (51%) or control group (76%). They concluded that in patients receiving analgesia with a combination of IT morphine and systemic nonopioid analgesia, the use of patient-controlled analgesia device could be avoided. We used NSAID diclofenac 75 mg administered intravenously in two doses, with possibly the third dose 10–12 hours after the second dose for NRS score 3–4. This provided highly effecient analgesia with 76,2% of patients not requiring any additional opioid and 81% of patients being very satisfied with their pain management as they experienced less pain in the early postoperative period than they had expected.

The most frequent side effects of opioid therapy are nausea/vomiting and pruritus. The incidence and severity of nausea/vomiting in our study did not differ significantly between the IT morphine and the control group which received systemic opioids. This is consistent with the results from other studies on orthopaedic patients *(3, 4, 9, 16),* although the doses of systemic opioids used were often higher then we have observed. The most commonly employed antiemetics were phenothiazines followed by ondansetron. In a meta analysis of 28 randomized controlled studies on IT morphine with spinal anaesthesia, Gehling and Tryba *(13)* found a moderate and clinically relevant increase in nausea/vomiting, pruritus and urinary retention with IT morphine. Considering the incidence of nausea/vomiting and pruritus, they recommended prophylaxis for these side effects. Ondansetron, a serotonin receptor antagonist seems to be a good choice because apart from being antiemetic, in some studies it has been used successfully for the prevention and treatment of opioid induced pruritus *(18–20)*. Pruritus is a well recognized side effect of opioid therapy with the prevalence depending mainly on the method of administration, but also on the opioid used and the patient population. The risk is much higher when opioids are given epidurally or intraspinally compared to systemic administration. In patients undergoing major orthopaedic surgery the reported prevalence of pruritus is 30–60 % and it seems to be dose dependent *(3, 4, 6, 8, 12, 13, 16, 18)*. Neuraxial opioid-induced pruritus is mediated centrally via ì-opioid receptors most likely in the dorsal horn of the medulla, and naloxone is effective in prevention and treatment of pruritus. Although antihistamines are said not to be useful for this type of pruritus, they have been used as the first choice therapy in a number of studies on orthopaedic patients *(4, 7, 8, 12)*. Similarly, we have found that the incidence of pruritus was significantly higher in the IT morphine group (42,85%) compared to the control group *(5, 3)*. However, in all patients the symptoms were mild, not bothersome and no patient requested the treatment. Beneficial effect of rectal diclofenac on pruritus in patients receiving IT morphine has been shown in one study, and diclofenac use could have contributed to low grade pruritus in our study *(17)*.

We have not observed a case of respiratory depression or excessive sedation defined as described in the methods, but the present study does not have the power to detect such a rare events. Also, there is no clear definition of respiratory depression. In most studies it is defined as low respiratory frequency (respiratory rate less than 12, 10 or 8 per minute), more rarely as hypercapnia or decreased peripheral oxygen saturation. A depressed level of consciousness may be even a more reliable sign of respiratory depression *(14, 21)*. The reported incidence of respiratory depression in more recent surveys and meta analyses varies from 3% down to less than 0,3%, the lower incidencies beeing not higher than with systemic administration of opioids via patient-controlled analgesia or i.m. injections *(12–14)*. In earlier mentioned meta analysis in which respiratory depression was defined as low respiratory frequency, Gehling and Tryba *(13)* have found that with IT morphine doses less than 0,3 mg there were no more episodes of respiratory depression than in placebo patients receiving systemic opioids. They concluded that there were no data to support the need for extended monitoring of patients receiving low dose spinal morphine. However, allocation of patients after IT morphine administration to regular surgical wards requires established guidelines and protocols for postoperative monitoring and management of these patients.

CONCLUSION

Low dose IT morphine (0,2 mg) in combination with regular postoperative administration of diclofenac i.v. provides excellent analgesia in the first 24 hours after total hip and knee replacement surgery without major adverse effects. The protocol we have used resulted in significantly lower postoperative pain scores in the IT morphine group with the majority of patients (76,2%) not requiring any additional opioid. Mild pruritus was commonly associated with IT morphine use, while nausea was a frequent side effect in both IT morphine and control group. Postoperative allocation and the need for monitoring the patients receiving IT opioids is still a matter of debate. The current opinion is that patients receiving low dose IT morphine without other indication for ICU can be safely nursed on regular surgical wards provided that the printed guidelines and protocols for management of these patients exist. Avoiding systemic opioid use while still providing effective postoperative analgesia by combining IT opioids with NSAIDs could additionally increase patient safety.

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