Abstract: Adding morphine to intrathecal bupivacaine provides sound analgesia, but is associated with side effects. The purpose of this study is to investigate if the contribution of intrathecal morphine to postoperative analgesia for total hip replacement outweighs its side effects in a modern multimodal setting.

From November 2012 till January 2013 patients undergoing total hip arthroplasty (THA) under spinal anesthesia received either plain bupivacaine (group B) or bupivacaine + 0.1 mg morphine (group M). VAS pain scores, PCA morphine consumption and side effects (nausea, vomiting, pruritus) were registered.

60 patients in group B were compared to 36 patients in group M. Overall morphine consumption and pain scores were low, although they were slightly but significantly lower in group M. Intrathecal morphine was associated with significantly more pruritus.

In this study, PCA morphine consumption and pain scores were low in THA with multimodal pain treatment, and the added analgesic value of intrathecal morphine did not outweigh the increased incidence of pruritus.

Key words: Anesthesia, spinal ; anesthesia, regional ; morphine ; pruritus ; total hip arthroplasty.

Over the years peri-operative pain management has changed with the introduction of pre-emptive analgesia and a multimodal approach to postoperative pain. In pre-emptive analgesia, analgesia is initiated before the surgical incision, aiming for inhibition of nociceptive systems before they are triggered (1). Multimodal analgesia consists of combining analgesics that act through different mechanisms so equal pain relief is achieved with a lower incidence of adverse effects (2). Gradually, these concepts have become more evident and have been implemented in guidelines (3, 4). Because adding pre-emptive multimodal pain treatment to existing pain treatment protocols is expected to reduce postoperative pain and side effects, we feel that some older pain regimens should be re-evaluated for their clinical relevance.

Intrathecally administered morphine, added to the local anesthetic bupivacaine, in total hip arthroplasty (THA) patients remained standard practice in our clinic after implementation of multimodal pre-emptive pain treatment. Intrathecal morphine provides profound analgesia and is used extensively to treat postoperative pain (5, 6), but it is also associated with side-effects such as nausea, vomiting, pruritus, urinary retention and respiratory depression (7). The rostral spread of morphine after intrathecal injection causes these supraspinally mediated side-effects (8). Intrathecally administrated morphine is not metabolized in the central nervous system. It remains in the cerebrospinal fluid for prolonged periods and slowly diffuses to the plasma compartment (9). The incidence of side effects increases with higher doses (7).

In the past, several studies have investigated the dose of intrathecal morphine at which pain relief is optimal with minimal side effects (10). Slappendel et al. found that the addition of low dose morphine (0.1 mg) to intrathecal bupivacaine provided excellent analgesia with an optimal side effect profile after orthopedic surgery (11). This was also demonstrated in older patients (12). However, since the evolution of pre-emptive multimodal analgesia, the added effect of intrathecal morphine may not outweigh side effects anymore.

The purpose of this study was to investigate if the contribution of intrathecal morphine to postoperative analgesia for total hip replacement outweighs its side effects in a multimodal setting.

Materials and Methods

Spinal anesthesia with or without morphine were both standard practice in our institution at the
time that the study started, with some anesthesiologists almost always using intrathecal morphine and some almost never. Since the purpose of this observational study was to compare the two current treatment regimes and translate the outcome into a new standard treatment, patients were not randomized and allocated, but the attending anesthesiologists were divided in two groups. One group of four anesthesiologists used spinal anesthesia combining plain bupivacaine with intrathecal morphine in all their patients scheduled for primary total hip arthroplasty, the other group of four anesthesiologists used spinal anesthesia with only plain bupivacaine. All anesthesiologists agreed not to deviate from the group to which they were assigned. The study was approved by our local institutional review board with the conclusion that given the conditions of the study, local institutional review board approval was sufficient and additional review by an ethics committee as specified in Dutch Law (wet medisch-wetenschappelijk onderzoek met mensen, WMO) was not mandatory.

All patients undergoing primary total hip arthroplasty under spinal anesthesia in our hospital from November 2012 till February 2013 were enrolled, with the exception of patients with a contra-indication for opiates. All patients received written study information at the day of the surgery. Patients could decline participation before the study started and during data collection.

Patients were premedicated with 1000 mg paracetamol, 90 mg etoricoxib and 7.5 mg midazolam or 10 mg oxazepam. Upon arrival in the anesthetic room, intravenous access was established and routine monitoring (heart rate, arterial oxygen saturation and non-invasive intermittent blood pressure measurement) was instituted. Patients were placed in the sitting position and lumbar puncture was performed with a 27G spinal needle. After obtaining a free flow of cerebrospinal fluid, spinal anesthesia was established with plain bupivacaine 0.5% 2-4 mL with (group M) or without (group B) 0.1 mg morphine. Subsequently, the patient was placed in the supine horizontal position and a urinary catheter was inserted. Before entering the operating room spread of sensory block (loss of cold sensation) was tested to ensure adequate anesthesia. Upon patient request sedation was given during the operation using propofol (range 10-40 mg/kg/hour). Post-operatively, patients received 1000 mg paracetamol four times daily and 90 mg etoricoxib once daily. Upon arrival in the recovery room, patients were connected to a patient controlled analgesia (PCA) device set to deliver 1 mg morphine bolus upon patient request with a lockout time of 5 minutes and a maximum of 32 mg morphine per 4 hours (or a 4 hour maximum of 28 mg if the patient’s body weight was < 70 kg).

Both patients and observers collecting postoperative data were unaware of the intrathecal dose the patient had received. Every six hours patients were asked to score their pain by means of a visual analogue scale (VAS). They indicated their average pain score since the operation,last time interviewed and the absolute worst pain felt since their operation. The highest score given for the worst pain experienced was designated maximal pain VAS score. Patients were also asked about possible side effects : nausea, vomiting and pruritus. If they received anti-emetics (dexamethasone, ondansetron, metoclopramide or droperidol) or additional opiates besides PCA, the type, dosage, route and time of administration were registered. PCA morphine was continued for 24 h postoperatively. Morphine consumption, and number of requested and administered boluses were read-out after discontinuation.

The primary outcome parameter was average morphine consumption per hour after the first request of a morphine bolus. Secondary outcome parameters were VAS-scores, time to first request (TTFR), overall morphine consumption and side effects.

Statistical analysis was performed using SPSS version 20 for Windows (SPSS Inc., Chicago, IL). Differences between treatment groups were analyzed using Fisher’s Exact Test for dichotomous data or Mann Whitney U test for continuous variables. For continuous data the Hodges-Lehmann method was used to calculate a confidence interval around the median. P < 0.05 was considered statistically significant. “Time To First Request” (TTFR) of PCA morphine after spinal injection (t = 0) was calculated in minutes. PCA morphine consumption per hour after TTFR was calculated using the following formula: morphine consumption (mg/hour) = morphine consumption (mg)/(1440 – TTFR (min))/60.

**Results**

Onehundredsixtyfour patients were enrolled in this study. Details on the trial flow can be found in the STROBE flow diagram (Fig. 1). For final analysis data were available of 60 patients in group B and 36 patients in group M. No conversion to general anesthesia occurred and no patients declined to participate. All anesthesiologists kept to their allocated
14 patients were lost to follow up because of logistic problems. Logistic problems were: no prescription for PCA-morphine (1 patient in group B, 3 patients in group M), preliminary discontinuation of the PCA on the ward by the nurse and subsequent loss of PCA data from the device (3 patients in group B, 4 patients in group M) and incomplete NRS-scores (1 patient in group B and 2 patients in group M). Patients that received PCA dipidolor instead of morphine were excluded from analysis because of the different side effect profile.

Fig. 1. — STROBE flow diagram of the study
**DISCUSSION**

In this trial we studied the effect on postoperative pain of 0.1 mg intrathecal morphine added to intrathecal bupivacaine in a pre-emptive, multimodal perioperative pain strategy for primary total hip arthroplasty. Intrathecal morphine lowered PCA morphine consumption and pain scores and significantly, but pain scores in both groups were low and the difference was clinically irrelevant. The use of intrathecal morphine was associated with an increased risk of pruritus.

Average pain scores in the first 24 hours postoperative were slightly lower in group M. Compared to group B, patients in group M showed a decrease of 0.6 cm on the average pain VAS score (0-10) and a decrease of 1.6 cm on the maximum pain VAS score. However, average pain scores and maximum pain scores were low in both groups and therefore the decrease lacks clinical relevance. We believe that an average pain score of 2.3 cm on a 10 cm VAS (group B) is an acceptable score after hip arthroplasty and is in itself no reason for adjusting the pain regimen.

Overall 24 hour PCA morphine consumption in both groups was also low, with a small reduction of morphine consumption in group M of 8.9 mg. Correcting for TTFR showed a median consumption of morphine of 0.54 ± 0.64 mg/hr in group M vs 0.72 ± 0.48 mg/hr in group B, a difference that, although statistically significant, has no clinical relevance in our opinion.

We found a significantly higher incidence of pruritus in group M (36.1% vs 6.7%, p = 0.001). We found no difference in the incidence of PONV between groups, however, patients in group M received significantly more anti-emetics peroperatively (66.7% in group M vs 16.7% in group B, p < 0.001). Data on TTFR, morphine consumption, and side effects are summarized in Table 2.

Patient satisfaction was equally high in both groups, with an average score of 8.3 out of 10.
Effects. The incidence and intensity of pruritus associated with intrathecal morphine is dose dependent (7, 10). Despite the relatively low dose of intrathecal morphine in our study, we found a significant difference in the incidence of pruritus (36.1% in group M vs 6.7% in group B).

We did not investigate the incidence of urinary retention and respiratory depression; however, it has been well documented that intrathecal morphine is associated with an increase in the incidence of both (7, 13).

Although rare, delayed respiratory depression is the most feared side effect of intrathecal opiates (14). We did not observe late respiratory depression, but one patient in group M suffered from early respiratory depression and ongoing sedation immediately after surgery. This patient had received 45 mg propofol and 2 mg midazolam during surgery for sedation. The patient was admitted to the Post Anesthesia Care Unit (PACU) for monitoring and oxygen therapy until her somnolence and respiratory depression resolved. This patient was on psychiatric medication (pimozide, pericazaine, clonazepam and venlafaxine); together with the intraoperative sedative medication this may explain her postoperative sedation and respiratory depression.

Although the literature shows that intrathecal morphine is associated with an increased incidence of PONV (6, 7, 10), we found no difference in the incidence of PONV between the two groups in our study. The use of anti-emetics during surgery was left at the discretion of the attending anesthesiologist; in our study, patients in group M received significantly more perioperative anti-emetics compared to patients in group B. We believe that this may explain why we found no difference in the incidence of PONV.

Our study has several limitations. We did not use a randomized double-blind design and different preferences of the anesthesiologists regarding total dose of local anesthetic and the use of anti-emetics constitutes a bias. However, since the purpose of our study was to investigate the additional effect of intrathecal morphine on postoperative pain relief in the clinical setting and both patients and research
assistants were unaware of the assigned treatment, we believe that the absence of randomization does not affect the validity of our findings.

Finally, a practical disadvantage of the addition of morphine to bupivacaine is that pre-mixed ampoules are no longer commercially available, and mixtures need to be prepared individually prior to injection with the inherent risk of dosage mistakes and compromising sterility.

In conclusion, 0.1 mg morphine added to plain bupivacaine 0.5% slightly lowers morphine consumption in a statistically significant but clinically irrelevant fashion. With small amounts of PCA morphine, acceptable pain scores were reached in both groups but with a much higher incidence of pruritus associated with the use of intrathecal morphine. In our opinion, the addition of intrathecal morphine to bupivacaine in patients undergoing THA does not outweigh the disadvantage of the increased incidence of pruritus, since our multimodal pain regimen without intrathecal morphine also results in low PCA morphine consumption, low pain scores and high satisfaction scores.

References