

Optimizing the Dose of Intrathecal Morphine in Older Patients Undergoing Hip Arthroplasty

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Intrathecal (IT) morphine provides excellent postoperative analgesia but may result in many side effects, including postoperative nausea and vomiting, pruritus, and respiratory depression, particularly at larger doses. Older patients may be at particular risk. The optimal dose of spinal morphine in older patients undergoing hip arthroplasty is not known. We designed this prospective, randomized, controlled, double-blinded study to evaluate the analgesic efficacy and side effect profile of 50–200 μg of IT morphine in older patients undergoing elective hip arthroplasty. Sixty patients older than 65 years undergoing elective hip arthroplasty were enrolled. Patients were randomized to receive spinal anesthesia with 15 mg of bupivacaine and IT morphine in four groups: 1) 0 μg , 2) 50 μg , 3) 100 μg ,

and 4) 200 μg . IT morphine 100 and 200 μg produced effective pain relief and decreased the postoperative requirement for morphine compared with control. IT morphine 50 μg did not provide effective pain relief. Both 100 and 200 μg of IT morphine provided comparable levels of postoperative analgesia. There were no between-group differences in postoperative nausea and vomiting, sedation, respiratory depression, or urinary retention. Pruritus was significantly more frequent with 200 μg of IT morphine. In conclusion, 100 μg of IT morphine provided the best balance between analgesic efficacy and side effect profile in older patients undergoing hip arthroplasty.

(Anesth Analg 2003;97:1709–15)

The provision of high-quality postoperative analgesia after total hip arthroplasty in the older patient continues to present a challenge. Systemic opioids can cause sedation and respiratory depression, which may be especially undesirable in older patients with coexisting medical conditions, such as chronic obstructive pulmonary disease. Intrathecal (IT) opiates are a useful option in this patient group, with a marked opioid-sparing effect. IT morphine provides effective postoperative analgesia in patients undergoing major orthopedic procedures on the lower limb (1–4).

However, the use of IT morphine may be associated with a number of distressing (e.g., pruritus, urinary retention, nausea, and vomiting) (5–10) and potentially life-threatening (i.e., delayed respiratory depression) (5,9,11–13) adverse effects. Postoperative nausea and vomiting (PONV) after IT morphine may prove

particularly difficult to control (8), perhaps as a result of the potential for IT morphine to delay gastric emptying (7). The hydrophilic properties of morphine contribute both to the longevity of its analgesic action and to the risk of late respiratory depression when it is administered IT. Profound late respiratory depression was reported in a number of earlier studies, albeit after larger doses of spinal morphine than are currently used (9). However, the need for caution regarding respiratory side effects even with smaller doses (300 μg) of IT morphine has been emphasized (12,14). In addition, older patients may be particularly sensitive to the respiratory-depressant effects of IT morphine (15). These issues are of particular concern in the older patient undergoing total hip arthroplasty.

Smaller doses of IT morphine may provide effective analgesia while minimizing the incidence of side effects in the older patient population. IT morphine 200 μg (16) and 100 μg (17) provided superior analgesia compared with placebo in patients undergoing hip arthroplasty in recent studies. However, a significant incidence of side effects was reported with IT morphine 100 μg , including drowsiness, pruritus, nausea, and urinary retention (17). In a further study, 100 and 200 μg of IT morphine provided superior analgesia

Accepted for publication July 10, 2003.

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DOI: 10.1213/01.ANE.0000089965.75585.0D

compared with 25 and 50 μg (18). However, pain scores were low in all four groups studied, suggesting that significant analgesia may have been achieved with the doses less than 100 μg (18).

In summary, the optimal dosage of IT morphine that provides analgesic efficacy with minimal side effects in the older patient is not yet known. In particular, the potential for doses of IT morphine less than 200 μg to provide superior analgesia compared with placebo is not known. Furthermore, the potential for these smaller doses of IT morphine to reduce postoperative side effects is unclear. The aim of this study was to determine the analgesic efficacy and side effect profile of three smaller doses (50, 100, and 200 μg) of IT morphine compared with placebo in older patients undergoing elective hip arthroplasty.

Methods

After obtaining approval by the Hospital Ethics Committee and written informed patient consent, we studied 60 ASA physical status I-III patients older than 65 yr who were scheduled for elective hip arthroplasty in a prospective, randomized, double-blinded, controlled clinical trial. Exclusion criteria included nonsuitability for spinal anesthesia as deemed by the attending anesthesiologist, allergy to opioid analgesics or local anesthetics, or any medical condition resulting in ASA status more than III. All patients received spinal anesthesia. Patients were randomized to receive one of four IT doses of preservative-free morphine: 0 μg (control), 50 μg , 100 μg , and 200 μg .

All patients were visited the evening before surgery. No patient received premedication. Spinal anesthesia was performed, with the patient in the sitting position, at the L3-4 intervertebral space by using a 25-gauge Quincke needle. Patients were administered 15 mg of hyperbaric bupivacaine and 0, 50, 100, or 200 μg of preservative-free morphine into the IT space, depending on group allocation. A total volume of 4 mL was administered to each patient, with the balance of the IT injectate composed of 0.9% NaCl. The dose of IT morphine administered was not noted in the patients anesthesia record; however, this was documented in a sealed envelope attached to the patient's anesthesia record, which could be opened in case of an adverse event.

All patients received 40% oxygen via face mask for the duration of the procedure. Standard monitoring, including noninvasive blood pressure, electrocardiogram, and oxygen saturations, was used in all patients for the duration of surgery.

At the end of the procedure, all patients received diclofenac sodium 100 mg per rectum and were then transferred to a high-dependency unit (HDU) for 24 h after surgery. Rescue analgesia, which consisted of IM

morphine 10 mg and could be repeated in 6 h, was available on patient request. First-line treatment of PONV consisted of IM prochlorperazine 12.5 mg. If this proved ineffective, second-line therapy consisted of IV ondansetron 4 mg. Each administration was initiated by patient request, and a minimal interval of 1 h was required between the administration of first- and second-line drugs. Treatment for pruritus consisted of IM promethazine 20 mg every 6 h, and treatment in all cases was initiated on patient request. A response to promethazine was defined as a decrease in the severity of pruritus to a level considered tolerable by the patient (i.e., absent or mild pruritus). Naloxone was reserved for treatment of pruritus that was resistant to promethazine therapy.

Patients were continuously monitored for 24 h by the HDU nursing staff, who were unaware of the patient allocation. Assessment variables included severity of postoperative pain and the presence and severity of PONV, pruritus, sedation, and respiratory depression. Time zero was taken as the time of admission to the HDU, and each variable (severity of pain, PONV, pruritus, and sedation score) was recorded at 4-h intervals after admission for 24 h.

The primary outcome variable, the severity of pain in the first 24 h after surgery, was assessed by using a visual analog scale (VAS). In addition, the time to first request for supplemental analgesics and the total amount of supplemental analgesics administered were recorded.

The presence and severity of PONV was assessed by using an ordinal scale (0 = no nausea; 1 = mild; 2 = moderate; 3 = severe; 4 = vomiting). In addition, the time to first request for antiemetic therapy and the total amount of supplemental antiemetic administered were recorded. The presence and severity of pruritus was assessed by using an ordinal scale (0 = no itch; 1 = mild; 2 = moderate; 3 = severe). The time to first request for therapy for pruritus and the total amount of promethazine administered were recorded.

Respiratory rate and arterial oxygen saturation were assessed on a continuous basis over the 24-h postoperative period. The incidence of 1) respiratory depression, defined as respiratory rate <12 breaths/min, and 2) mild (Sao_2 <94% on room air), moderate (Sao_2 <90% on room air), and severe (Sao_2 <85% on room air) arterial hypoxemia were recorded.

Sedation was scored according to the following scale: 1, alert; 2, calm; 3, drowsy; 4, sleeping, easily arousable; and 5, sleeping, difficult to arouse. Significant sedation was defined as a sedation score of 5. The need for urethral catheterization (defined as an absence of spontaneous voiding 8 h after surgery and urine volume of >400 mL at catheterization) was recorded.

On the basis of prior data from our clinical practice, sample size calculations were performed for the following primary end-point measurements: VAS pain score, morphine consumption, and incidence of PONV and pruritus. A maximum of 60 patients (15 per group) were required to detect a “clinically” significant difference in analgesic profile (decrease of 2.5 in mean VAS score and decrease of 5 mg in supplemental morphine consumption) and the incidence of PONV and pruritus (decrease in incidence from 75% to 25%) with a power of 80% and α set at 0.05.

Demographic data were analyzed with one-way analysis of variance (ANOVA) or χ^2 analysis, as applicable. For VAS data, group comparisons were performed at each time point by using one-way ANOVA with *post hoc* comparisons by using Student-Newman-Keuls analysis. Ordinal data were analyzed by using ANOVA on ranks; *post hoc* comparisons were performed by using the Mann-Whitney *U*-test with the Bonferroni correction for multiple comparisons. The incidence of pruritus was compared by using the χ^2 test for multiple variables.

Continuous data are presented as mean \pm SEM, ordinal data are presented as medians \pm quartiles (interquartile range), and categorical data are presented as raw data or as frequencies. The α level for all analyses was set as $P < 0.05$.

Results

A total of 60 patients were entered into the study. These were equally distributed among the groups, and there were no between-group demographic differences (Table 1). No patient was excluded after enrollment into the study.

Pain scores were significantly ($P < 0.05$) lower in the groups that received 100 and 200 μg of IT morphine compared with the control group at 8, 12, 16, and 20 h after surgery (Fig. 1). IT morphine 50 μg did not significantly decrease VAS scores compared with the control group except for one time point: at 8 h after surgery. The mean worst postoperative VAS scores reported in the control and 50- μg IT morphine groups were significantly ($P < 0.05$) higher than those reported with 100 and 200 μg of IT morphine (Table 2). In the groups that received 100 and 200 μg of IT morphine, there was no difference in mean postoperative VAS scores at any time point (Fig. 1) or in mean worst postoperative VAS scores (Table 2).

Mean supplemental morphine consumption over the first 24 postoperative hours was significantly ($P < 0.05$) larger in the control and 50- μg IT morphine groups compared with the groups that received 100 and 200 μg of IT morphine (Fig. 2). Mean morphine consumption was not significantly different between the control and 50- μg IT morphine groups or between

the groups that received 100 and 200 μg of IT morphine (Fig. 2). There was a significant ($P < 0.001$) between-group difference in the number of patients who required supplemental morphine (Table 2). The mean time to first request for rescue analgesia was significantly ($P < 0.02$) shorter in the control group compared with all other groups and was significantly ($P < 0.05$) shorter in the group that received 50 μg compared with 100 or 200 μg of IT morphine (Fig. 3). The time to first request for rescue analgesia was not significantly different between the groups that received 100 and 200 μg of IT morphine (Fig. 3).

There was no significant difference in the incidence or severity of PONV in the groups that received IT opiates compared with the control group (Fig. 4; Table 2). Specifically, there was no between-group difference in median PONV score at any time point (data not presented); time to first request for antiemetic therapy (Table 2); number of patients who required antiemetic therapy (Table 2); overall incidence of PONV (i.e., PONV score of 1 or more) (Fig. 4); or incidence of vomiting (i.e., PONV score of 4) (Table 2).

The overall incidence of pruritus was significantly ($P < 0.001$) more frequent in patients who received 200 μg of IT morphine compared with all other groups (Fig. 4). The number of patients who required antipruritic therapy in this group was significantly ($P < 0.01$) more than that in all other groups (Table 2). All patients responded to promethazine therapy, with 90% reporting complete relief of pruritus, and no patient required naloxone therapy.

There was no evidence of respiratory depression at any of the doses of IT morphine studied. Specifically, there was no difference in the number of episodes of respiratory depression (respiratory rate < 12 breaths/min) in the first 24 postoperative hours in any group (Table 2). There was no difference in the incidence of episodes of mild or moderate hypoxemia among the four groups, and all patients whose SpO_2 decreased to less than 94% responded to 40% oxygen via face mask (Fig. 4; Table 2). No patient in any group developed severe hypoxemia. There was no evidence of increased sedation at any of the doses of IT morphine studied compared with the control group (Table 2).

There was a nonsignificant trend toward an increased need for urethral catheterization in the groups that received IT opiates; no patient in the control group required catheterization (Fig. 4). Overall, 86% of all patients who required urethral catheterization were male.

Discussion

This study demonstrates several important points. First, doses of 100 and 200 μg of IT morphine provide comparable and effective postoperative analgesia in

Table 1. Demographic Data and Intraoperative Factors

Variable	Control	IT morphine		
		50 μ g	100 μ g	200 μ g
No. patients	15	15	15	15
Age (yr)	73 \pm 2	72 \pm 2	73 \pm 2	70 \pm 2
Weight (kg)	76 \pm 2	77 \pm 2	75 \pm 2	76 \pm 2
Sex (M/F)	11/4	10/5	9/6	9/6
Duration of procedure (min)	82 \pm 23	85 \pm 34	79 \pm 28	84 \pm 23
Intraoperative blood loss (mL)	431 \pm 53	432 \pm 22	490 \pm 33	422 \pm 45
Intraoperative fluids administered (mL)	2200 \pm 400	2100 \pm 200	2400 \pm 400	2200 \pm 300

Data are mean \pm SEM.
IT = intrathecal.

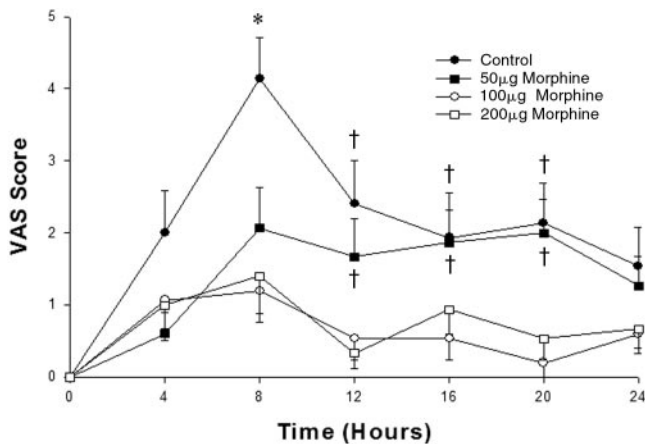


Figure 1. Mean postoperative visual analog scale (VAS) pain scores in each group, measured every 4 h for the first 24 postoperative hours. Mean VAS pain scores were significantly lower in the groups that received intrathecal (IT) morphine 100 and 200 μ g compared with the control group at 8, 12, 16, and 20 h after surgery. IT morphine 50 μ g did not decrease VAS scores compared with the control group except at 8 h after surgery. In the groups that received IT morphine 100 and 200 μ g, there was no difference in mean postoperative VAS scores at any time point. *Indicates a significantly ($P < 0.05$; *post hoc* Student-Newman-Keuls (SNK) test) higher VAS score compared with all other groups. †Indicates a significantly ($P < 0.05$; *post hoc* SNK test) higher VAS score compared with the 100- and 200- μ g IT morphine groups.

older patients undergoing elective hip arthroplasty. Second, 50 μ g of IT morphine did not provide effective analgesia compared with placebo and constitutes an inadequate dose of IT morphine in this patient group. Third, the incidence of respiratory depression and significant postoperative hypoxemia with this dose range of IT morphine is infrequent and appears not to be different from that seen in control patients. Fourth, 200 μ g of IT morphine appears to significantly increase the incidence of postoperative pruritus. Fifth, the use of 50–200 μ g of IT morphine did not significantly increase the incidence of PONV compared with placebo in these patients. This suggests that these smaller doses of IT morphine may reduce this distressing side effect. In summary, 100 μ g of IT morphine appears to provide the best balance between analgesic

efficacy and side effect profile in this older patient group.

Our study clearly demonstrates that, with the exception of a single postoperative time point, 50 μ g of IT morphine does not provide superior analgesia to that experienced by patients not receiving IT morphine. This suggests that 50 μ g of IT morphine constitutes an inadequate dose and, therefore, should not be used in this patient group. Furthermore, we have demonstrated that doses of 100 and 200 μ g of IT morphine provide comparable analgesic efficacy in older patients undergoing elective hip arthroplasty. In fact, both regimens provided excellent analgesia and had a small requirement for rescue analgesia in the first 24 hours after surgery. There was no difference in postoperative VAS scores at any time point between patients receiving 100 and 200 μ g of IT morphine. In addition, there was no difference in the duration of analgesia provided by these doses or in the need for or amount of supplemental analgesic therapy required.

The finding that 100 μ g may be the optimal dose of IT morphine in older patients undergoing elective total hip arthroplasty is supported by previous studies (17,18). Slappendel et al. (18) demonstrated that 100 μ g provided similar-quality analgesia to 200 μ g and provided better-quality analgesia than 25 or 50 μ g of IT morphine. However, this study did not determine the extent of analgesia provided by 25 or 50 μ g of IT morphine because it did not include a placebo group. We have demonstrated for the first time in a study confined to older patients undergoing hip arthroplasty that 50 μ g of IT morphine does not provide better-quality analgesia compared with that seen in patients who did not receive IT morphine. This means that 100 μ g of IT morphine is likely to constitute the smaller effective dose in this patient group. The finding that 100 μ g of IT morphine provided similar-quality analgesia to 200 μ g of IT morphine in patients undergoing elective cesarean delivery suggests that it may constitute the optimal dose in a broad spectrum of patients (19).

Table 2. Postoperative Data

Variable	Control	IT morphine		
		50 μ g	100 μ g	200 μ g
No. patients who requested rescue analgesia	13/15*	9/15	4/15	3/15
Highest mean postoperative VAS pain score	5 \pm 0.4†	4 \pm 0.6†	2 \pm 0.5	3 \pm 0.5
Incidence of postoperative vomiting (total episodes of PONV score = 4)	0/15	2/15	1/15	3/15
Number of patients who requested antiemetic therapy	1/15	5/15	6/15	6/15
Time to first request for antiemetic therapy (min)	1390 \pm 50	1193 \pm 86	1144 \pm 92	1098 \pm 116
No. patients who requested antipruritic therapy	0/15	2/15	1/15	7/15*
Incidence of respiratory depression (total episodes of respiratory rate <12 breaths/min)	2/15	0/15	1/15	0/15
No. episodes of mild arterial hypoxemia (total episodes of SpO ₂ 90%–94%)	4/15	6/15	7/15	6/15
No. episodes of moderate arterial hypoxemia (total episodes of SpO ₂ 85%–90%)	0/15	0/15	0/15	2/15
No. episodes of severe arterial hypoxemia (total episodes of SpO ₂ <85%)	0/15	0/15	0/15	0/15
Median sedation score (interquartile range)	2 (1–4)	2 (1–4)	2 (1–4)	2 (1–4)
No. episodes of significant sedation (total episodes of sedation score = 5)	0/15	0/15	0/15	0/15

Data are presented as number of patients (from a maximum of 15) for each category unless otherwise stated. Data for time to request for supplemental analgesia and time to request for antiemetic therapy are presented as time in minutes \pm SEM. Sedation scores are presented as medians and interquartile ranges. VAS = Visual Analogue Scale; PONV = postoperative nausea & vomiting; IT = intrathecal.

* Indicates significant ($P < 0.05$) between group difference.

† Indicates significantly ($P < 0.05$) more than the 100- and 200- μ g IT morphine groups.

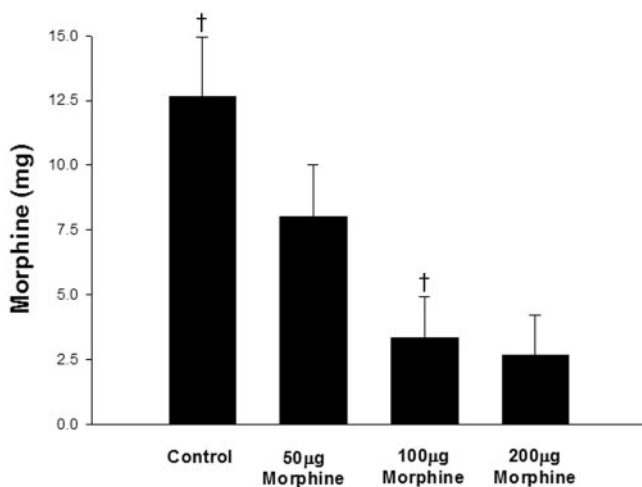


Figure 2. Mean requirement for supplemental morphine over the first 24 postoperative hours. Supplemental morphine consumption was significantly larger in the control and intrathecal (IT) morphine 50 μ g groups compared with the groups that received IT morphine 100 and 200 μ g. Mean morphine consumption was not significantly different between the control and 50- μ g IT morphine groups or between the groups that received 100 and 200 μ g of IT morphine. †Indicates a significantly ($P < 0.05$; *post hoc* Student-Newman-Keuls test) larger requirement compared with the 100- μ g and 200- μ g IT morphine groups.

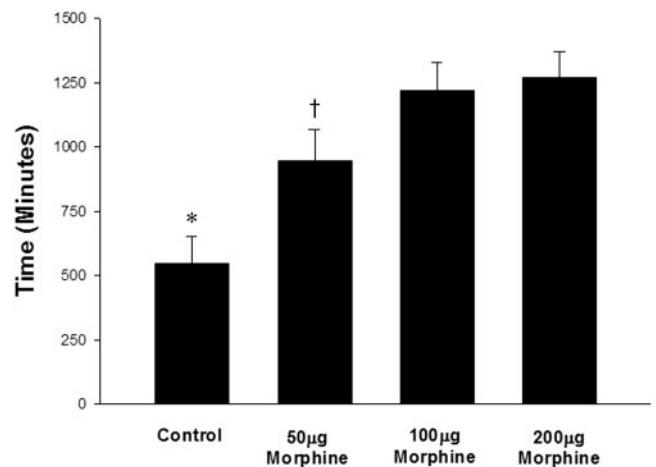


Figure 3. Mean time to first request for supplemental morphine in the first 24 postoperative hours. The mean time to first request for rescue analgesia was significantly shorter in the control group compared with all other groups. The time to first request for rescue analgesia was significantly shorter in the group that received intrathecal (IT) morphine 50 μ g compared with IT morphine 100 or 200 μ g. There was no difference in time to first request for rescue analgesia between the groups that received IT morphine 100 and 200 μ g. *Indicates a significantly ($P < 0.02$; *post hoc* Mann-Whitney U (MWU) test) shorter time compared with all other groups. †Indicates a significantly ($P < 0.05$; *post hoc* MWU test) shorter time compared with the 100- and 200- μ g IT morphine groups.

One of the major concerns raised regarding the use of IT morphine has been the incidence of PONV (5,8,9). In our study, there was a nonsignificant trend toward an increase in the incidence of PONV and a need for antiemetic therapy after the use of 50–200 μ g of IT morphine. Weber et al. (20) found that 200 μ g of

IT morphine did not contribute to the incidence of PONV in patients undergoing elective hip arthroplasty using spinal anesthesia, suggesting that PONV may be less problematic within this dose range in this patient group. However, in patients undergoing elective cesarean delivery, 100 μ g of IT morphine caused

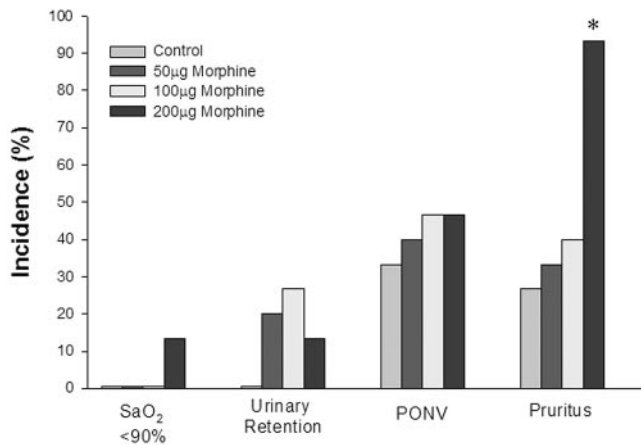


Figure 4. Incidence of side effects in the first 24 postoperative hours. There was a nonsignificant trend toward an increased incidence of hypoxemia in the intrathecal (IT) morphine 200 µg group and a trend to increased urinary retention requiring urethral catheterization in the groups that received IT opiates. There was no significant difference in the incidence of postoperative nausea and vomiting (PONV) (i.e., PONV score of 1 or more) in the groups that received IT opiates compared with the control group. The incidence of pruritus was significantly more frequent in patients who received IT morphine 200 µg compared with all other groups. *Indicates a significant (χ^2 ; $P < 0.001$) between-group difference in the incidence of pruritus.

less PONV than 200 µg of IT morphine, underlining the potential for smaller IT morphine doses to decrease PONV (19).

Pruritus has been identified as a major side effect associated with IT opioids, and it may contribute significantly to patient discomfort (5). It has been proposed that this side effect is centrally mediated by μ -opioid receptors (21). Our study demonstrates that the overall incidence of pruritus was significantly increased in patients who received 200 µg of IT morphine compared with all other groups. In addition, the need for antipruritic therapy in this group, an index of the severity of the pruritus, was significantly more frequent with 200 µg of IT morphine. Conversely, pruritus did not appear to be a significant problem, in terms of incidence or need for antipruritic therapy, in patients who received 100 µg of IT morphine. This contrasts with the findings of Slappendel et al. (10), who found that the incidence of itching was dose related in the dose range of 25–200 µg of IT morphine. However, the rate of administration of antipruritic therapy was not related to IT morphine dose in this study (10). Therefore, the potential for doses of 25–200 µg of IT morphine to increase the incidence and/or severity of pruritus remains unclear. Our study clearly demonstrates an increase in both the incidence and severity of pruritus with 200 µg of IT morphine. Furthermore, our findings suggest that 100 µg of IT morphine may provide effective analgesia without increasing the incidence or severity of pruritus.

Many potential therapies have been described for treating spinal opioid-associated pruritus, including droperidol and subhypnotic doses of propofol, with variable efficacy reported (22,23). In this study, promethazine appeared to be an effective treatment for spinal morphine-associated pruritus.

Respiratory depression is a potentially serious side effect of IT morphine and is more likely in the older patient (15). Previous studies have demonstrated that, whereas larger doses of IT morphine result in profound and prolonged late respiratory depression, doses as small as 200 µg may result in significant respiratory depression (9). IT morphine has clearly been demonstrated to cause respiratory depression in this patient group (5). In our study, two patients who received 200 µg of IT morphine developed transient moderate hypoxemia that responded to the administration of 40% oxygen. No patient developed severe hypoxemia in this study, although we cannot exclude the possibility that the patients who developed moderate hypoxemia might have progressed to severe hypoxemia had they not received supplemental oxygen.

Sedation did not appear to be a problem at the doses of IT morphine used in this study. This study is the first to compare the sedative profile of a range of small doses of IT morphine with that in patients who did not receive IT morphine. There was tendency to an increased need for urethral catheterization in the groups that received IT morphine when compared with the control group, but this was not statistically significant. The incidence of urinary retention did not appear to be related to the dose of IT morphine administered. Male sex appeared to be a significant risk factor; 86% of all patients who required catheterization were male.

There are two limitations that must be considered when the clinical significance of this study is considered. First, the patient group selected was of ASA physical status I–III patients aged ≥ 65 years. However, there was no upper age limit, as reflected in an age range of 65–90 years. Caution should be exercised, however, in extrapolating these findings to extremes of old age or to patients of ASA physical status IV. A further limitation is that our study did not have sufficient power to detect between-group differences in the incidence of respiratory depression. This precludes definitive conclusions regarding the safety of these doses of IT morphine. This concern is further underlined by the finding that 200 µg of IT morphine causes respiratory depression in 1% of patients undergoing elective cesarean delivery (24). Nevertheless, the fact that no patient developed severe hypoxemia in this study supports previous findings (12,17,18) attesting to the relative safety of IT morphine in this dose range.

We conclude that the administration of 100 µg provides equally effective postoperative analgesia as 200 µg of IT morphine and has a superior side effect

profile in older patients undergoing total hip arthroplasty. IT morphine 100 μg appears to be well tolerated and safe in this patient group. In addition, 50 μg of IT morphine provides ineffective postoperative analgesia in these patients. We therefore recommend that 100 μg of IT morphine be used for postoperative analgesia in the older patient undergoing hip arthroplasty.

The authors wish to thank the nursing staff of the Special Care Unit, Merlin Park Regional Hospital, Galway, for their assistance in performing this study.

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