Efficacy of intrathecal morphine for postoperative pain management following open nephrectomy

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Abstract

Objective: To evaluate the efficacy and safety of intrathecal morphine (ITM) for postoperative pain control in patients with renal cell carcinoma undergoing open nephrectomy.

Methods: Forty-five patients scheduled for open nephrectomy were randomised to receive 300 µg ITM and intravenous patient-controlled analgesia (IV-PCA) ($n = 22$) or IV-PCA alone ($n = 23$) for postoperative analgesia. The numeric pain score (NPS), postoperative IV-PCA requirements and opioid-related complications including nausea, vomiting, dizziness, headache, and pruritus were compared between groups.

Results: NPS was significantly lower in the ITM group up to 24 h postoperatively. Upon coughing, NPS at 24 h postoperatively was 50 (interquartile range (IQR) 30–60) in the ITM group and 60 (45–70) in the IV-PCA group. Cumulative morphine consumption at 72 h postoperatively was significantly lower in the ITM group compared with the IV-PCA group (20 (9–33) mg vs. 31 (21–49) mg, respectively). Opioid-related complications were similar in both groups with the exception of pruritus (ITM, 77% vs. IV-PCA, 26%).

Conclusions: ITM was associated with greater analgesia without serious complications in patients undergoing open nephrectomy.

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Introduction

Nephrectomy is performed to treat malignant renal disease and for living kidney transplantation. Although the laparoscopic approach has become widely used,[1–3] open nephrectomy is still recommended and widely performed because of the difficulty, longer ischaemic time and higher incidence of ureteral complications associated with the minimally-invasive approach.[4] The extra-peritoneal loin incision for open nephrectomy can cause severe postoperative pain that may decrease quality of life.[3] A multi-modal approach has been attempted to accomplish effective pain control during the perioperative period. Wound infiltration with local anaesthetics,[5] use of adjuvant nonsteroidal anti-inflammatory drugs[6] and epidural analgesia[7,8] have been evaluated to achieve effective pain management and minimise the complications of opioid use.

A single dose of intrathecal morphine (ITM) combined with intravenous patient-controlled analgesia (IV-PCA) has advantages for perioperative pain control. This approach is associated with improved quality of analgesia and decreased systemic opioid use compared with IV-PCA alone or intrathecal local anesthetics without morphine, thus minimising the potential for renal toxicity, sedation and respiratory depression.[9–12] ITM has been effectively used in the control of postoperative pain due to prostatectomy,[13,14] transurethral resection of the prostate[15] and hepatectomy.[16] Although ITM has been investigated in many kinds of surgery, its effectiveness and safety has not yet been determined following open nephrectomy.

It was hypothesised that ITM combined with IV-PCA would improve the quality of perioperative pain control and decrease the side effects of systemic opioid use vs. IV-PCA alone. Therefore, the aim of this prospective, randomised study was to evaluate the efficacy and safety of a single injection of ITM combined with IV-PCA compared with IV-PCA alone in patients undergoing open nephrectomy.

Patients and methods

Study population

The study protocol was approved by the Institutional Review Board of Seoul National University Hospital (reference number: H1305-619-491). The study was registered at ClinicalTrials.Gov with the number NCT01997788 and performed according to the Helsinki Declaration. After providing written informed consent, patients with a primary diagnosis of renal cell carcinoma undergoing open nephrectomy between August 2013 and November 2013 were enroled into the study. Patients with American Society of Anesthesiology physical status I, II or III and aged between 18 and 80 years were included. Exclusion criteria were patients with renal dysfunction (creatinine clearance $< 70 \, ml/min$), coagulopathy, neurologic disorder, recent systemic infection, inability to use a PCA device, history of drug addiction or current treatment with opioids for chronic pain.

Study procedures and anaesthesia

Patients were randomised to receive ITM plus IV-PCA or IV-PCA alone using a computer-generated randomisation program. The randomisation was sequenced into blocks of four and six. Assignments were stored in concealed envelopes and were managed by the anaesthesia nurses who were not involved in patient care. Group assignment was provided to the investigator (H-CK) on the morning of surgery.

Patients arrived in the operating room without premedication. Routine monitoring was started using a noninvasive arterial blood pressure, pulse oximetry and three-lead electrocardiogram. Intravenous access was established using an 18-G catheter.

Patients in the ITM group received a spinal injection of 300 µg morphine before induction of anaesthesia.[10,17,18] Morphine was diluted in saline (100 µg/ml) and 3 ml of this solution was administered intrathecally. Spinal injection was performed using a 27-G Sprotte spinal needle at the level of the L3–4 or L4–5 intervertebral space. Patients in the IV-PCA group did not receive ITM.

Anaesthesia protocols were standardised for all study patients. General anaesthesia was induced using a bolus injection of 2 mg/kg propofol and target controlled continuous infusion of 4 ng/ml remifentanil (Orchestra® Base Primea, Fresenius Kabi, Brezins, France). Tracheal intubation was facilitated by intravenous 0.8 mg/kg rocuronium. Anaesthesia was maintained with desflurane in an oxygen-air mixture adjusted to maintain a bispectral index of 40–60. Remifentanil was infused continuously and controlled by the attending anaesthesiologist.

After induction of anaesthesia, patients were placed in a lateral flank position for open nephrectomy. The attending surgeon performed a subcostal incision from the 12th rib to the suprapubic area, varying in length from 10–14 cm. The kidney was approached extraperitoneally without rib resection.

Postoperative pain management

At the end of surgery, all patients received IV-PCA for postoperative pain management. The IV-PCA device (AutoMed 3200, Acemedical, Seoul, Korea) was connected to the patient upon closure of the fascia. The IV-PCA solution contained 100 mg morphine in normal saline and a total volume of 100 ml (1 mg/ml); the programme consisted of a 1 ml bolus injection of the IV-PCA solution with a lockout time of 5 min without continuous infusion. One bolus of IV-PCA solution (1 mg morphine) was administered by the attending anaesthesiologist to reduce postoperative pain at

emergence. After extubation of the endotracheal tube, patients were transferred to the postoperative care unit. The total amount of remifentanil used during surgery and the time from the end of surgery to extubation was recorded.

The numeric pain score (NPS; 0 = no pain, 100 = worst pain imaginable) was recorded at 3, 6, 12, 24, 48 and 72 h after surgery, and was evaluated at rest and on coughing with patients in a sitting position. Cumulative morphine consumption by IV-PCA was assessed at 3, 6, 12, 24, 48 and 72 h postoperatively. When the NPS was > 50, an additional bolus of PCA was administered. Patients received 25 mg meperidine as a rescue pain treatment at the discretion of the treating physician when pain management by additional morphine was considered ineffective. This dose was half that of the usual dose (50 mg) due to the risk of renal dysfunction after nephrectomy.[19] Frequency and dose of rescue therapy were recorded.

Side effects including nausea, vomiting, dizziness, headache, and pruritus were assessed using a three-point-scale (0 = none, 1 = mild, 2 = moderate and 3 = severe) at 3, 6, 12, 24, 48 and 72 h postoperatively. These side effects were treated when requested by the patient. Sedation was assessed on a five-point-scale (1 = completely awake with eyes open, 2 = drowsy, 3 = dozing, 4 = mostly sleeping and 5 = not responding). Respiratory depression was defined by at least one of the following variables: respiratory rate $< 8 \, min^{-1}$, $SpO_2 < 90\%$ or $PaCO_2 > 70 \, mmHg$ and was assessed using a two-point-scale (0 = no, 1 = yes). If patients were not responding or respiratory depression was detected, naloxone was administered. Management of side effects was performed by physicians and nurses who were blinded to the patient assignments and all treatments were recorded. Postoperative variables including NPS, rescue therapy and opioid-related complications were recorded

by the investigator who was blinded to patient assignments.

Statistical analyses

The primary outcome measure of this study was the NPS on coughing 24 h postoperatively. Secondary outcome measures were the NPS at 3, 6, 12, 48 and 72 h postoperatively, incidence of side effects including nausea, vomiting, dizziness, headache, pruritus, sedation and respiratory depression, cumulative morphine usage and the use of any additional interventions to manage side effects. Student's t-test or Mann-Whitney U-test was applied for continuous variables after the normality test (Kolmogorov-Smirnov test). The incidence of complications was compared between groups using the χ^2-square test or Fisher's exact test. A P-value < 0.05 was considered to indicate a significant difference. Data are presented as means $\pm$ SD, median (interquartile range (IQR)) or number (percentage).

Sample size was calculated based on a study by Nicholson et al.[3] that reported a NPS 24 h postoperatively of 56 (SD 30). For the current study, it was postulated that a 50% reduction in postoperative pain would be clinically relevant. With $\alpha = 0.05$ and power of 0.8, a sample size of 20 in each group was necessary. All statistical analyses were performed using the Statistical Package for the Social Sciences software, v19.0 (SPSS Inc., Chicago, IL, USA). The sample size calculation was performed with the G*power 3 software (Institut für Experimentelle Psychologie, Dusseldorf, Germany).[20]

Results

A total of 46 patients scheduled for open nephrectomy were enroled into the study. One patient was excluded because of withdrawal of participation. Of the 45 patients included, 22 were randomised to the ITM group and 23 to the IV-PCA group (Figure 1). Preoperative patient characteristics were similar between the two groups (Table 1). No differences in surgical or anaesthetic data were observed, including the total amount of remifentanil used during surgery and the time from the end of the surgery to extubation. Postdural puncture headache was not reported in any case.

As shown in Figure 2, the NPS up to 24 h postoperatively was significantly lower in the ITM group compared with the IV-PCA group. At 12 h postoperatively, the median NPS at rest was 20 (IQR, 10–33) in the ITM group and 40 (IQR, 30–60) in the IV-PCA group ($P < 0.001$); values upon coughing were 45 (IQR, 20–60) in the ITM group and 60 (IQR, 60–80) in the IV-PCA group ($P < 0.001$). In the ITM group at 24 h postoperatively, median NPS at rest was 30 (IQR, 8–30) and 40 (IQR, 20–40) in patients receiving ITM or IV-PCA, respectively ($P = 0.01$); values upon coughing were 50 (IQR, 30–60) in the ITM group and 60 (IQR, 45–70) in the IV-PCA group ($P = 0.03$). No differences were observed in the NPS at rest or on coughing between the two groups beyond the first postoperative 24 h.

Postoperative morphine consumption was significantly lower in the ITM group at 6, 12, 24, 48 and 72 h postoperatively (Figure 3). Median cumulative morphine consumption over 24 h was 9 (IQR, 7–20) mg in the ITM group and 22 (IQR, 10–31) mg in the IV-PCA group ($P = 0.01$). The corresponding values at 72 h were 20 (IQR, 9–33) mg and 31 (IQR, 21–49) mg in the ITM and IV-PCA groups, respectively ($P = 0.03$). Median time to first rescue analgesic was 3.0 (IQR, 1.6–24.3) h in the ITM group and 1.0 (IQR, 0.5–2.0) h in the IV-PCA group ($P = 0.01$). Ten patients in the ITM group and 18 patients in the IV-PCA group required rescue analgesia during the first postoperative 24 h ($P = 0.03$).
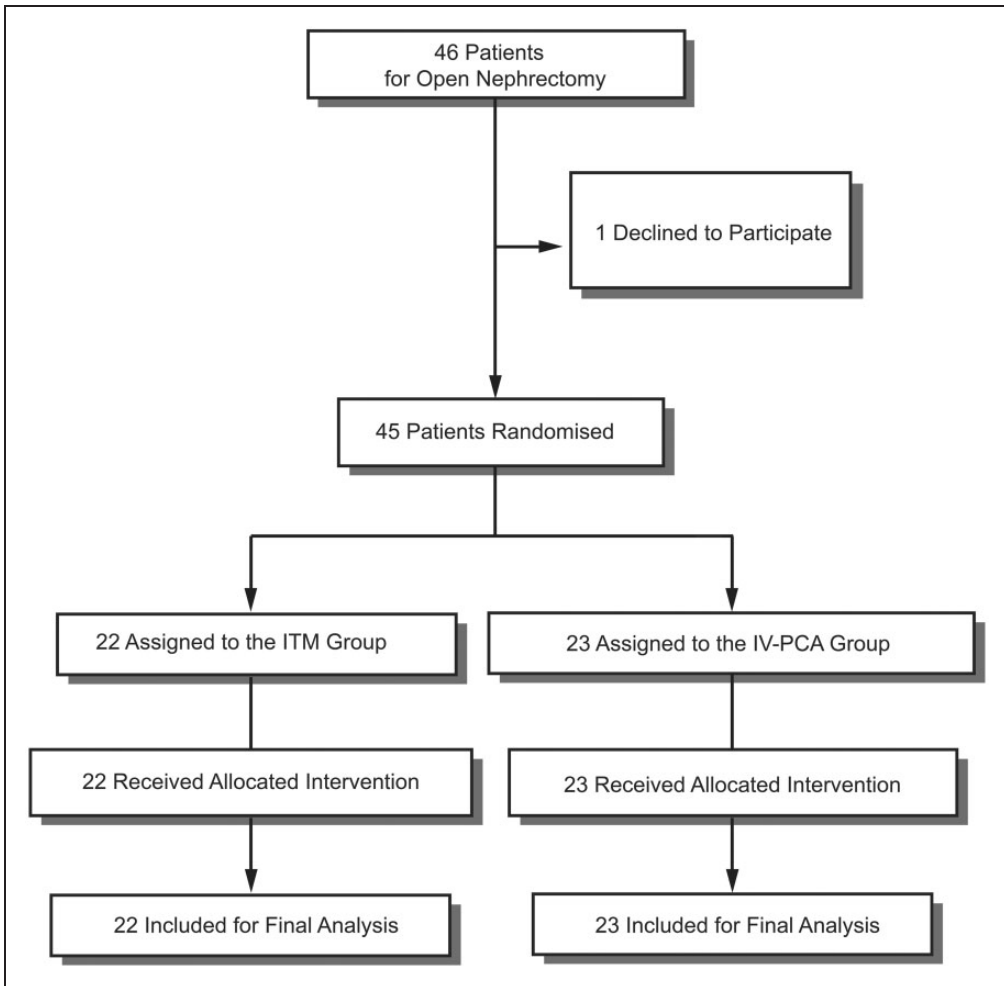
Figure 1. CONSORT diagram showing the flow of participants through the phases of the trial
ITM: intrathecal morphine; IV-PCA: intravenous patient-controlled analgesia.

Postoperative meperidine consumption (up to 72 h after surgery) was 25 (IQR, 0–25) mg in the ITM group and 50 (IQR, 25–50) mg in the IV-PCA ($P = 0.21$).

The overall frequencies of opioid-related complications including nausea, vomiting, dizziness, sedation and headache were not significantly different between the two treatment groups (Table 2). Severe nausea, vomiting, dizziness, headache and pruritus were not reported in any group and no

patients experienced respiratory depression. Naloxone was not required in any patient. There was no significant difference between the number of patients in the ITM group and IV-PCA groups who required metoclopramide for nausea (two and four patients, respectively, received 10 mg metoclopramide). A significantly higher incidence of pruritus was observed among patients in the ITM group compared with the IV-PCA group (17 [77%] patients vs. six [26%]

Table 1. Demographic and clinical characteristics of patients with renal cell carcinoma undergoing open nephrectomy who received intrathecal morphine (ITM) with or without intravenous patient-controlled analgesia (IV-PCA) for postoperative pain.

	ITM group ($n = 22$)	IV-PCA group ($n = 23$)
Age, years	59 ± 13	58 ± 12
Geriatrics (age > 65 y)	8 (36)	7 (30)
Gender, male	13 (59)	18 (78)
Weight, kg	68 ± 9	68 ± 11
Creatinine clearance (ml/min)	108 ± 17	114 ± 16
Duration of surgery, min	161 ± 48	171 ± 58
Intraoperative use of remifentanil, µg/kg/h	2.8 ± 1.8	2.9 ± 1.2
Time to extubation, min	7.0 ± 3.0	6.7 ± 2.4

Data are presented as means $\pm$ SD or *n* (%) patients.
No statistically significant between-group differences were observed ($P > 0.05$) (Student's *t*-test or Mann-Whitney *U*-test).

patients, $P = 0.01$). No cases, however, required intervention for pruritus.

Discussion

The present study demonstrated that patients with renal cell carcinoma who underwent open nephrectomy and received ITM plus IV-PCA for postoperative pain had lower NPS (at rest and upon coughing) and a lower opioid requirement for up to 24 h postoperatively compared with patients who received IV-PCA alone, and did not experience serious opioid-related complications including respiratory depression.

Compared with pain control after laparoscopic surgery, acute pain control following open nephrectomy is a challenging issue.[3] The large incision necessary in an open nephrectomy generally causes severe pain, which is an important factor for early recovery after surgery and may restrict ambulation and movement.[21] Poor pain management may increase morbidities including thromboembolism, myocardial ischaemia, pneumonia, wound dehiscence and chronic pain. Therefore, appropriate analgesic support is essential during the early postoperative period. In the present study, a single dose of ITM significantly

reduced postoperative pain for 24 h after surgery. This result is consistent with those of other investigations showing an improvement in analgesia with ITM during the immediate postoperative period compared to IV-PCA alone or intrathecal local anaesthetics without morphine.[10–12,15,16] Because morphine is a hydrophilic opioid, its analgesic effect develops slowly and lasts for up to 24 h.[9] As such, a single injection of ITM may represent a promising multimodal approach for postoperative pain control following open nephrectomy.

In the present study, an ITM dose of 300 µg was chosen based on previous investigations. Doses of >500 µg may provide a greater analgesic effect, but may result in side effects such as nausea, vomiting, sedation and late respiratory depression.[11,22] The optimal dose of ITM depends on the type of surgery, with doses <100 µg used in caesarean delivery and up to 500 µg used in extensive abdominal surgery.[23,24] In previous studies, 300–400 µg ITM was shown to be effective following liver resection and radical prostatectomy, and was without serious complications.[13,16] For the purposes of the current study, it was hypothesised that 300 µg ITM would provide effective analgesia without opioid-related complications
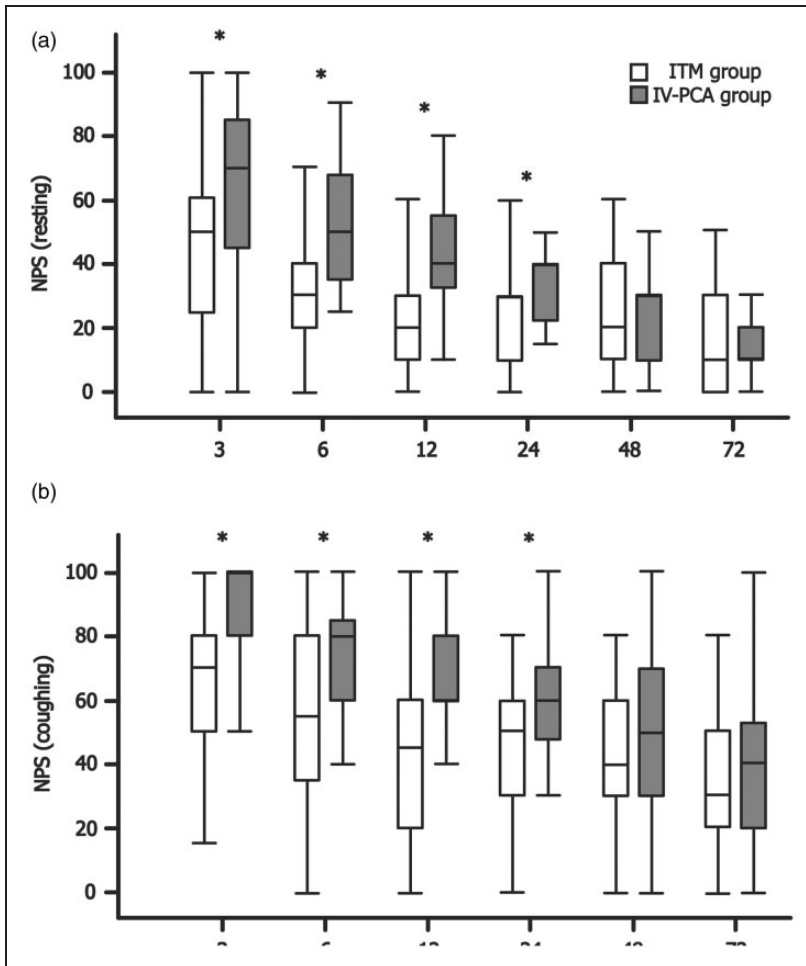
Figure 2. Numeric pain scores (0 = no pain, 100 = worst imaginable pain) at (a) rest and (b) on coughing in patients with renal cell carcinoma who underwent open nephrectomy and received intrathecal morphine (ITM) in combination with intravenous patient-controlled analgesia (IV-PCA) or IV-PCA alone for postoperative pain. NPS was significantly lower in the ITM group compared with the IV-PCA group up to 24 h postoperatively. Boxes represent the interquartile range with the bold line across each box indicating the median NPS. *$P < 0.05$ versus IV-PCA group (Student's *t*-test or Mann-Whitney *U*-test).

in open nephrectomy. Since elderly patients are at increased risk of respiratory depression,[25] patients aged >80 years were excluded from participation in the present study and careful monitoring was undertaken to prevent any adverse events due to respiratory depression.

The analgesic effect of ITM is believed to reduce opioid use throughout the postoperative period. In the present study, patients who received ITM experienced a profound reduction in intravenous morphine use in the immediate postoperative period up to 24 h, during which patients in the IV-PCA group administered more than twice as much morphine. Moreover, the quality of analgesia was significantly better in the ITM group both at rest and on
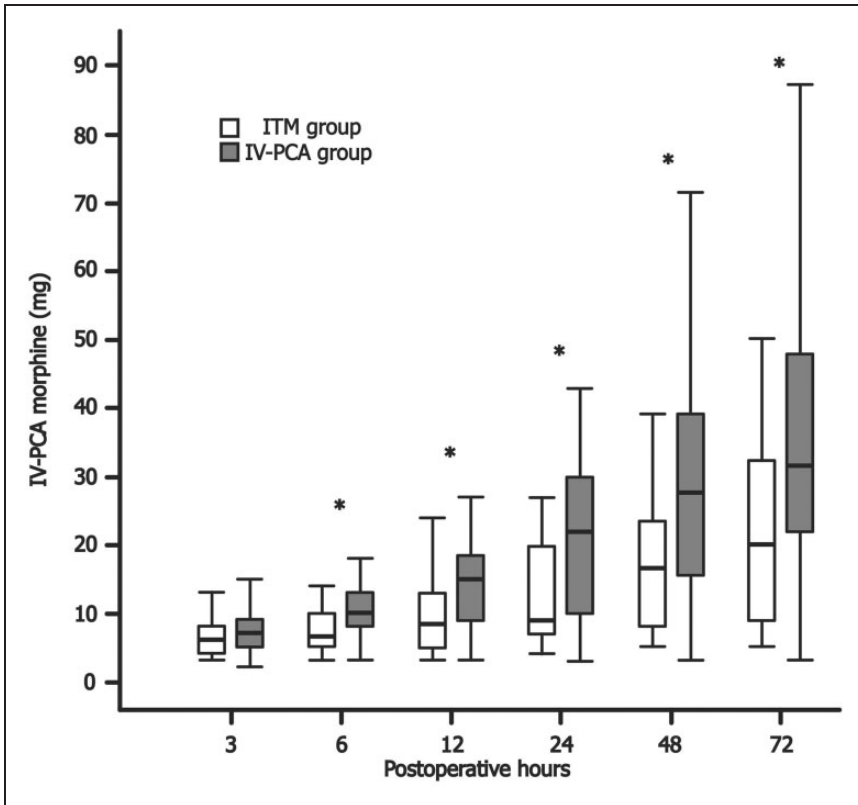
Figure 3. Cumulative morphine consumption by intravenous patient-controlled analgesia (IV-PCA) in patients with renal cell carcinoma who underwent open nephrectomy and received intrathecal morphine (ITM) in combination with IV-PCA or IV-PCA alone for postoperative pain. Postoperative morphine consumption was significantly lower in the ITM group compared with the IV-PCA group at 6, 12, 24, 48 and 72 h postoperatively. Boxes represent the interquartile range with the bold line across each box indicating the median NPS. *P < 0.05 versus IV-PCA group (Student's *t*-test or Mann-Whitney *U*-test).

coughing. Therefore, ITM may provide effective analgesia with lower intravenous morphine usage.

Rescue analgesic requirements during the first 24 h postoperatively were lower in the ITM group compared with the IV-PCA group and time to the first rescue analgesic agent was also delayed. This may be as a consequence of the slow onset of action of ITM (1–2 h) and prolonged duration of analgesia (18–24 h).[9] Meperidine is metabolised into normeperidine, which is eliminated by the kidneys.[19] The analgesic effect of ITM reduced the requirements for

additional meperidine, which may decrease the burden on the kidneys for 24 h postoperatively.

An ITM injection often results in complications such as pruritus, nausea, vomiting and delayed respiratory depression.[9,10] Incidence of complications was, however, similar between the two groups, with the exception of pruritus. No patient in either group developed respiratory depression after surgery and none required any antiopioid treatments such as intravenous naloxone. Although high doses of morphine (2–15 mg) admistered intrathecally may

Table 2. Opioid-related complications in patients with renal cell carcinoma undergoing open nephrectomy who received intrathecal morphine (ITM) with or without intravenous patient-controlled analgesia (IV-PCA) for postoperative pain.

	ITM group ($n = 22$)	IV-PCA group ($n = 23$)	Statistical significance
Nausea	12 (55)	8 (35)	NS
Mild/moderate/severe	7 (32)/5 (23)/0 (0)	5 (22)/3 (13)/0 (0)	NS
Vomiting	6 (27)	2 (9)	NS
Mild/moderate/severe	2 (9)/4 (18)/0 (0)	1 (4)/1 (4)/0 (0)	NS
Dizziness	10 (46)	8 (35)	NS
Mild/moderate/severe	6 (27)/4 (18)/0 (0)	6 (26)/2 (9)/0 (0)	NS
Headache	4 (18)	4 (17)	NS
Mild/moderate/severe	3 (14)/1 (5)/0 (0)	3 (13)/1 (4)/0 (0)	NS
Pruritus	17 (77)	6 (26)	$P = 0.01$
Mild/moderate/severe	16 (73)/1 (5)/0 (0)	5 (22)/1 (4)/0 (0)	$P = 0.01$
Sedation	3 (14)	7 (30)	NS
Drowsy/dozing/mostly sleeping/not responding	3 (14)/0 (0)/0 (0)/0 (0)	6 (26)/1 (4)/0 (0)/0 (0)	NS
Respiratory depression	0 (0)	0 (0)	NS
Yes/no	0 (0)/0 (0)	0 (0)/0 (0)	NS

Data presented as *n* (%) patients.

NS, no statistically significant between-group difference ($P > 0.05$) (χ^2-square test or Fisher's exact test).

cause delayed respiratory depression,[22,26] low-dose morphine (<1.0 mg) can effectively manage postoperative pain without this complication.[27,28] It is likely that the similar incidence of complications between treatment groups was due to the relatively low dose of intravenous morphine used in the ITM group. Pruritus is a common adverse event following ITM injection and has an incidence of 30–100%.[29,30] In severe cases, it requires medical therapy such as naloxone, diphenhydramine and 5-hydroxytryptamine-3 receptor antagonists.[12,29,31] No cases of moderate or severe pruritus requiring medical therapy were observed in the present study.

Epidural infusion of local anaesthetics and opioids with an epidural catheter is a well-established technique after various major surgeries.[32,33] This approach provides effective pain control and reduces opioid-related complications.[5] Epidural analgesia is, however, technically difficult, and is associated with postdural puncture headache, infection, spinal haematoma and local anaesthetic toxicity.[34,35] A spinal injection of morphine can be performed more easily than epidural catheterisation. Thoracic epidural catheterisation is required for effective analgesia after major abdominal surgery, but ITM can provide analgesia at the lumbar level. Spinal injection is thought to cause fewer infections and haematomas.[20] In the present study, ITM provided adequate analgesia up to 24 h postoperatively, which could have positive effects on early mobilisation and respiratory care. No patient experienced postdural puncture headache after using the small-gauge Sprotte needle suggesting that ITM may be an effective and well tolerated method for pain management compared with epidural analgesia.

The present study had some limitations. Firstly, patients were not blinded to the group assignments. Spinal injections were

performed before induction of anaesthesia to reduce potential neurologic injury and infection and patients in the IV-PCA group did not receive a sham injection as a control. The investigators who recorded the study variables and attending physicians were, however, blinded to group assignments. Secondly, the sample size was insufficient to evaluate the effects of ITM on post-operative morbidities. The primary outcome measure of this study was the pain score upon coughing at 24 h postoperatively and ITM resulted in effective pain relief with reduced opioid requirements with the sample size included. A larger-scale study may reveal further benefits of ITM with respect to reductions in postoperative mor-bidities. Thirdly, the optimal dose of ITM for open nephrectomy was not determined in the present study. Although 300 µg ITM was a well-tolerated and effective dose in the present study, nearly 50% of the ITM patients needed rescue analgesics within the first 24 h. It cannot be ruled out that a higher dose of ITM may have provided appropriate analgesia with fewer complications and a reduced requirement for additional rescue analgesics. Further exploration is required to evaluate the optimal dose of ITM in open nephrectomy. Finally, success of the spinal injection of morphine was not evaluated although the procedure was performed by an expert anaesthesiologist with experience of more than 1000 neuraxial blocks.

Conclusions

A single spinal injection of morphine com-bined with IV-PCA provided more effective postoperative analgesia than IV-PCA alone and reduced opioid requirements in patients with renal cell carcinoma undergoing open nephrectomy. These results suggest that preoperative ITM may represent an effective and well tolerated treatment modality for immediate postoperative pain management following open nephrectomy.

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