의학석사 학위논문

Intrathecal Morphine Injection for Acute Postoperative Pain Control in Patients Undergoing Robot-Assisted Laparoscopic Prostatectomy

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Abstract

Background

Robot-assisted laparoscopic prostatectomy (RALP) is minimally invasive surgery, but also causes moderate to severe pain during immediate postoperative period. We evaluated the efficacy and safety of Intrathecal morphine (ITM) for postoperative pain control in patients undergoing robot-assisted laparoscopic prostatectomy (RALP).

Methods

Thirty patients scheduled for RALP were randomly assigned into one of two groups. In the ITM group (n = 15), postoperative pain was managed using 300 μg intrathecal morphine with intravenous patient-controlled analgesia (IV-PCA). In the IV-PCA group (n = 15), only intravenous patient-controlled analgesia was used. The numerical pain score (NPS; 0 = no pain, 100 = worst pain imaginable), postoperative IV-PCA requirements and opioid-related complications including nausea, vomiting, dizziness, headache and pruritus were compared between the two groups.

Results

NPSs on coughing were 20 (IQR 10-50) in the ITM group and 60 (IQR 40-80) in the IV-PCA group at postoperative 24 h (P = 0.001). NPSs were significantly lower in the ITM group up to postoperative 24 h. The ITM group showed less morphine consumption at postoperative 24 h in the ITM group than in the IV-PCA group (5 [IQR 3–15] mg vs. 17 [IQR 11–24] mg, P = 0.001). Complications associated with morphine were comparable between the two groups and respiratory depression was not reported in both groups.

Conclusions

Intrathecal morphine provided more satisfactory analgesia without serious complications during early postoperative period in patients undergoing RALP. (clinicaltrials.gov, NCT01991275)

Keywords: Injections, Spinal; Morphine; Prostatectomy; Pain, Postoperative

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Introduction

Robot-assisted laparoscopic prostatectomy (RALP) has become popular because of its advantages including three-dimensional visualisation of surgical field and a shorter learning curve.[1] Moreover, the incisional length of RALP is rather short and the postoperative pain is thought to be minimal. However, RALP is reported to cause comparable postoperative pain at immediate postoperative period, compared to the open prostatectomy.[2, 3] The appropriate analgesic modality is required after RALP to manage acute postoperative pain and to minimize complications according to narcotics use.

The intrathecal morphine (ITM) has definite advantages for perioperative pain control including improved quality of analgesia and decreased systemic opioid use.[4-7] It has been widely used for the postoperative pain due to prostatectomy, [8-10] transurethral resection of the prostate, [11, 12] and hepatectomy. [13] Since the effects of the ITM last 18-24 hour, [4] the ITM may provide the optimal analgesia during immediate postoperative period. Although ITM has been studied for many kinds of surgery, the efficacy of ITM needs to be determined following minimally invasive surgery like RALP.

We hypothesised that ITM would improve perioperative pain control and decrease systemic opioid requirements after RALP. The aim of this prospective, randomised study was to compare a single ITM injection combined with intravenous-patient controlled analgesia (IV-PCA) and IV-PCA alone for perioperative pain control and systemic opioid requirements.

Methods

Patients and study design

The Institutional Review Board of Seoul National University Hospital approved this study (Ref:H1308-056-512). After written informed consent, patients scheduled for RALP from November 2013 to June 2014 were enrolled in this study. Patients with ASA physical status I, II or III and aged between 18 and 80 years were included. Exclusion criteria were patients with renal disorder, coagulopathy, neurologic disorder, recent systemic infection, inability to use a PCA device, drug addiction history, or chronic pain. Patients were randomised into the ITM group and the IV-PCA group using a computer-generated randomisation program. The assignments were stored in concealed envelopes and were managed by the anaesthetists who did not part in patient care. The group assignment was noticed to the attending anaesthesiologist in the morning of surgery.

Patients arrived in the operating room without premedication and were monitored using a non-invasive arterial blood pressure, pulse oximetry and three-lead electrocardiogram. Intravenous access was established using an 18 gauge catheter. Patients in the ITM group received a spinal injection of 300 μg morphine before induction of anaesthesia. Spinal injection was performed using a 27 gauge 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.

General anaesthesia was induced using a bolus injection of 2 mg kg^{-1} propofol and target controlled continuous infusion of 4 ng ml^{-1} remifentanil (Orchestra® Base Primea, Fresenius Kabi, Brezins, France). Rocuronium of 0.8 mg kg^{-1} was administered to facilitate tracheal intubation. Anaesthesia was maintained with desflurane in an oxygen-air mixture and continuous infusion of remifentanil. The concentration of desflurane and remifentanil was adjusted to maintain a bispectral index of 40-60 by attending anaesthesiologist.

After induction of anaesthesia, patients were placed in a lithotomy and steep trendelenburg position for RALP. The surgeon performed the conventional six-port approach[14] and 6 sites of the incision were at the level of umbilicus (Fig. 1). The length of the incision varied from 10-15 mm.

All patients received IV-PCA for pain management. The IV-PCA device (AutoMed 3200, Acemedical, Seoul, Korea) was connected to the patient after the robotic devices were

docked out and the surgeon began to close the port insertion sites. The IV-PCA solution contained 100-mg morphine in normal saline and a total volume of 100 ml (1 mg ml^{-1}). The IV-PCA program consisted of a 1 ml bolus injection of the IV-PCA solution with a lockout time of 5 min without continuous infusion. A bolus of IV-PCA solution (morphine 1 mg) was administered to reduce postoperative pain when the PCA device was connected. 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 assessed at 3, 6, 12, 24, 48 and 72 h after surgery. The NPS was evaluated at rest and on coughing with patients sitting. The cumulative morphine consumption by IV-PCA was assessed at 3, 6, 12, 24, 48 and 72 h postoperatively. Patients received 25 mg demerol as a rescue pain treatment when the NPS was >50 at the discretion of the physician blinded to the group assignments. The frequency and dose of rescue therapy were recorded.

Postoperative opioid-related side effects including nausea, vomiting, dizziness, headache and pruritus were assessed using a 4-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 patients. Sedation was assessed on a 5-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. Treatments for side effects were performed by physicians who were blind to the group assignments and were recorded. The postoperative variables including NPS, rescue therapy and opioid related complications were recorded by the investigator who was blinded to the group assignments.

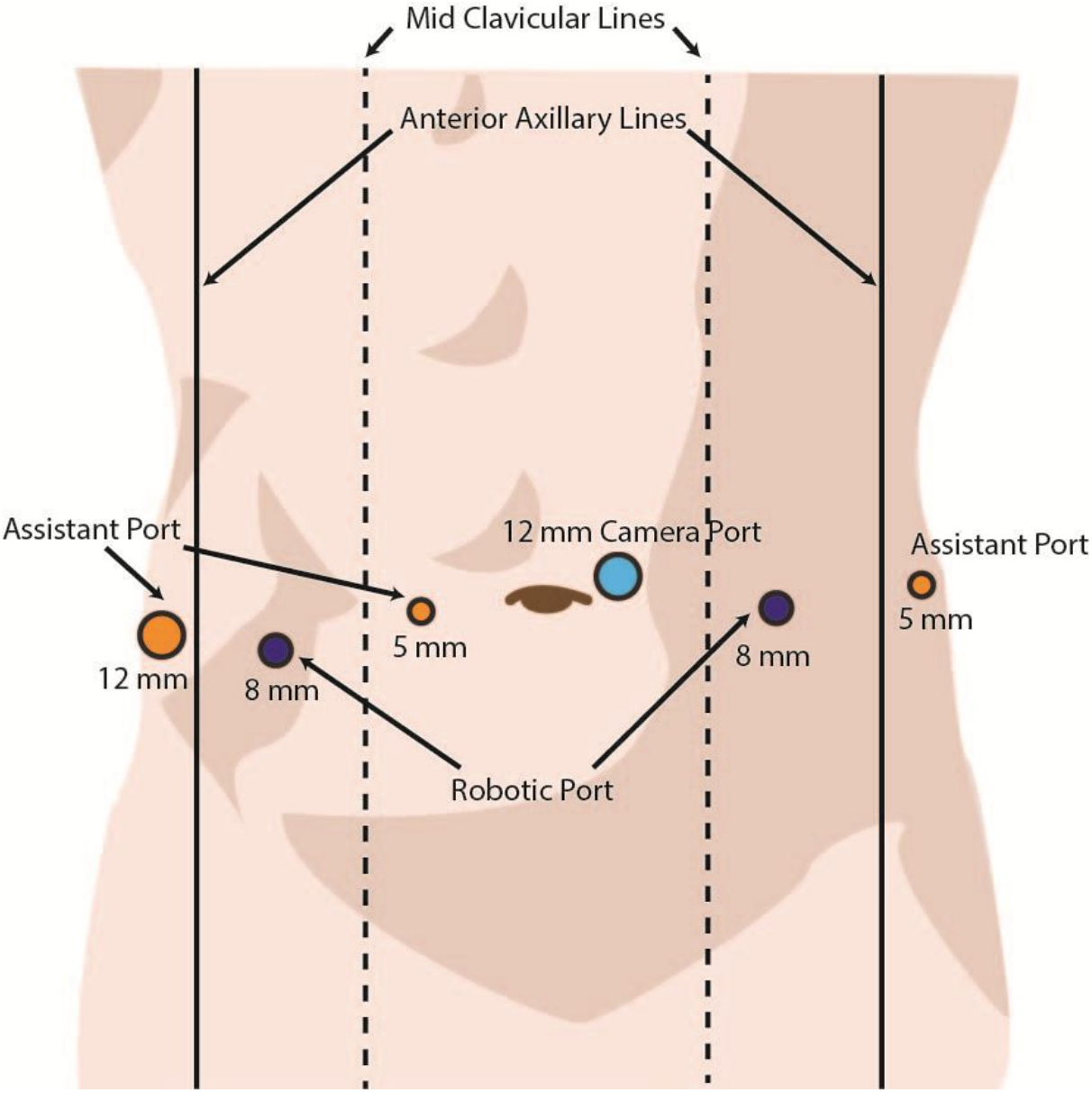
Statistical analysis

The primary endpoint of this study was the NPS at coughing at postoperative 24 h. The secondary endpoints were the NPS at 3, 6, 12, 48 and 72 h postoperatively, incidence of side effects including nausea, vomiting, dizziness, headache, pruritus, sedation, respiratory depression, cumulative morphine usage and the use of any interventions. Mann-Whitney *U*-test was applied for continuous variables after the normality test. The incidence of

complications was compared between the two groups using Fisher's exact test. The alpha value was adjusted with Bonferroni's correction to compare the NPS and cumulative morphine consumption between the two groups at each time point. The *P* values were compared with these adjusted alpha values. Otherwise, a *P* value < 0.05 was taken to indicate a significant difference. Data are presented as median (interquartile range) or number (percentage).

Sample size was calculated based on the previous report by Yoo and colleagues[3] in which the NPS at postoperative 24 h was 33.5 ± 14.5. We assumed that a 50% reduction in postoperative pain would be clinically relevant. With α = 0.05 and power of 0.8, a minimum sample size of 15 in each group was necessary. The statistical analysis was performed using the Statistical Package for the Social Sciences software, ver. 19.0 (SPSS Inc., Chicago, IL, USA). The sample size calculation was performed with the G*power 3 software.[15]

Figure 1. Port placement.



Results

Thirty patients scheduled for RALP were enrolled. Fifteen patients were randomised to the ITM group and 15 to the IV-PCA group (Fig. 2). Preoperative characteristics of patient 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 to extubation. Post-dural puncture headache was not reported in any case.

NPSs until postoperative 24 h were significantly lower in the ITM group than those in the IV-PCA group (Fig. 3). At postoperative 12 h, NPSs at rest were 10 (IQR 0-15) in the ITM group and 50 (IQR 30-50) in the IV-PCA group ($P < 0.001$). At coughing, NPSs at postoperative 12 h were 20 (IQR 10-50) in the ITM group and 60 (IQR 50-70) in the IV-PCA group ($P < 0.001$). At postoperative 24 h, NPSs at rest were 10 (IQR 0-10) in the ITM group and 40 (IQR 30-40) in the IV-PCA group ($P < 0.001$). At coughing, NPSs at postoperative 24 h were 20 (IQR 10-50) in the ITM group and 60 (IQR 40-80) in the IV-PCA group ($P = 0.001$). No differences were observed in the NPS at rest or coughing between the two groups after the first postoperative 24 h.

Postoperative morphine consumption was significantly lower in the ITM group at 12 and 24 hr postoperatively (Fig. 4). Cumulative morphine consumption over 24 h was 5 (IQR 3-15) mg in the ITM group and 17 (IQR 11-24) mg in the IV-PCA group ($P = 0.001$). No patient in the ITM group and 5 patients in the IV-PCA group required rescue analgesic agents during the first postoperative 72 h ($P = 0.042$).

The overall frequencies of opioid-related complications including nausea, vomiting, dizziness, headache, pruritus and sedation were not different between the two groups (Table 2). The overall frequencies of nausea, vomiting, dizziness, headache, pruritus and sedation were 6 (40%) *vs.*6 (40%), 3 (20%) *vs.* 1 (6%), 9 (60%) *vs.* 6 (40%), 3 (20%) *vs.* 2 (14%), 5 (34%) *vs.* 2 (14%) and 2 (14%) *vs.* 6 (40%) in the ITM and IV-PCA groups, respectively. The frequencies of opioid-related complications assessed using 4-point-scale and 5-point-scale (for sedation) between the two groups did not have any significance statistically. Severe nausea, vomiting, dizziness, headache, pruritus and sedation were not reported in any group. No patient experienced respiratory depression. Naloxone was not required for any case. Two patients in the IV-PCA groups required 10-mg metoclopramide for nausea. Otherwise, there

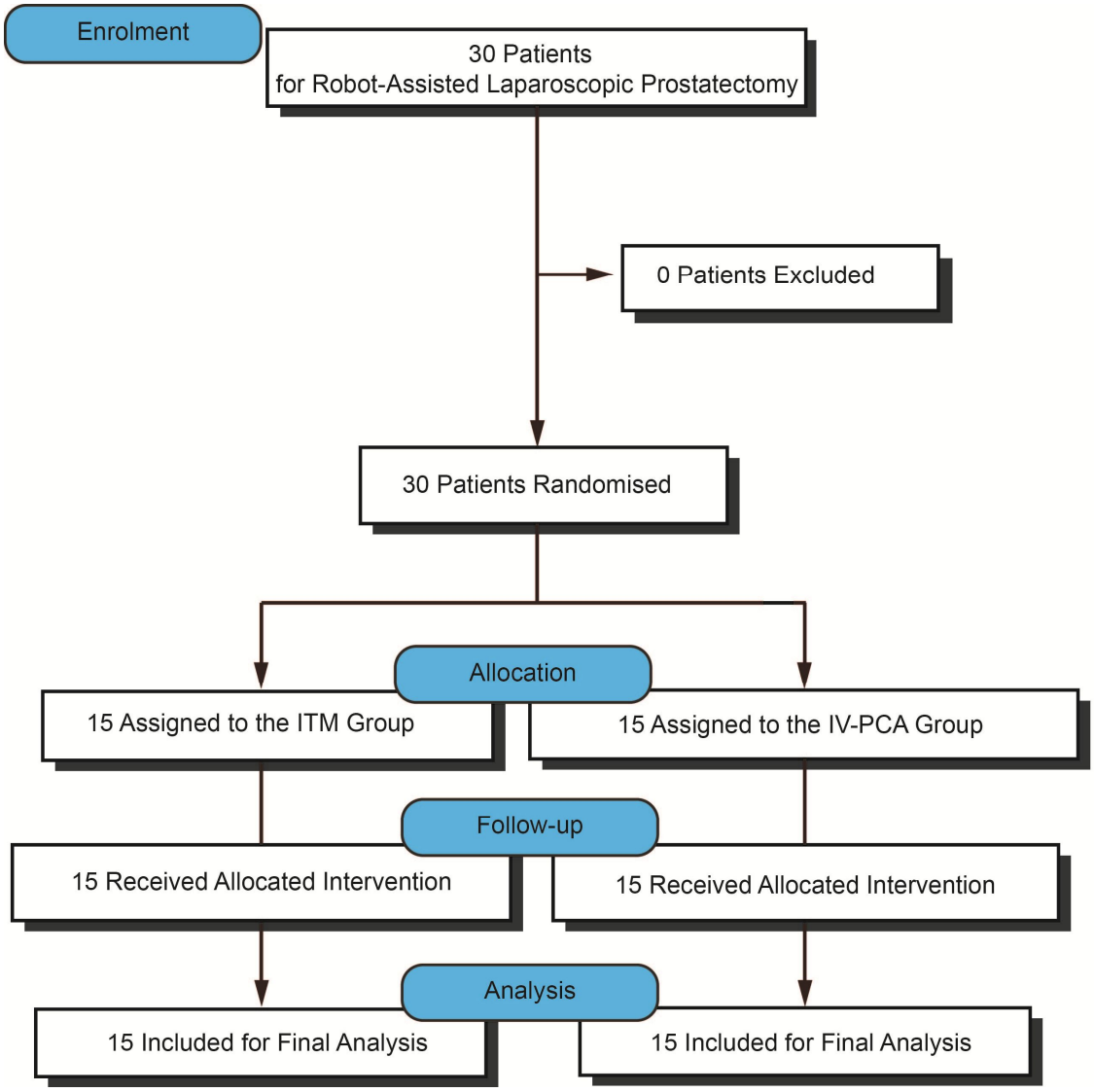
was no case requiring any intervention for opioid-related side effects.

Table 1. Patients baseline characteristics

	ITM group (*n* = 15)	IV-PCA group (*n* = 15)
Age (years)	64 (55-76)	66 (54-77)
Male gender	13 (59%)	18 (78%)
Weight (kg)	68 (49-94)	69 (50-82)
Duration of surgery (min)	164 (105-271)	171 (119-280)
Intraoperative use of remifentanil (μg kg^{-1} h^{-1})	2.8 (1.3-5.8)	2.2 (1.0-4.6)
Time to extubation (min)	8.7 (4.0-20.0)	9.0 (3.0-20.0)

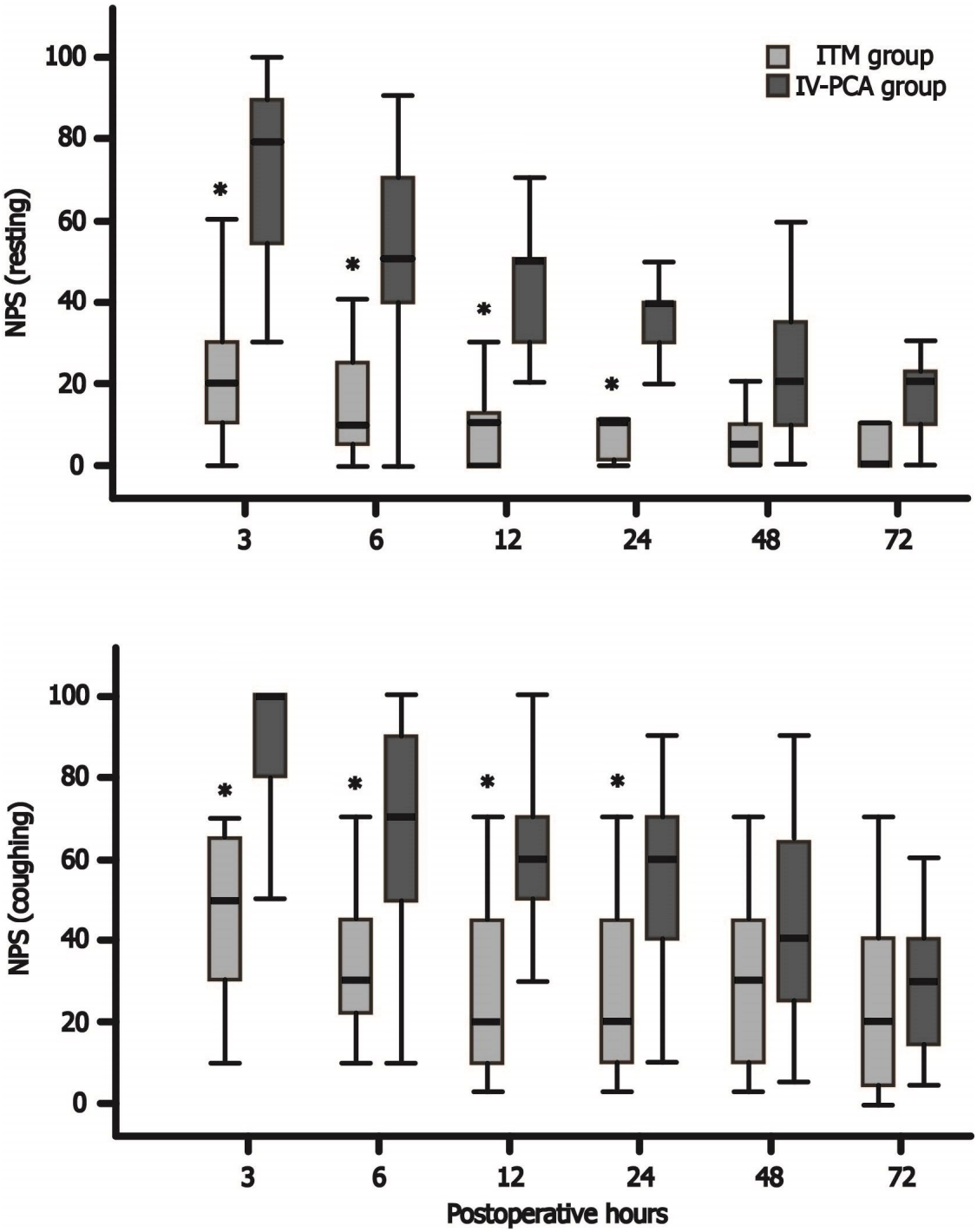
Data are presented as mean (range) or number (proportion). ITM, intrathecal morphine; IV-PCA, intravenous patient-controlled analgesia

Figure 2. CONSORT diagram showing the flow of participants through the phases of the trial



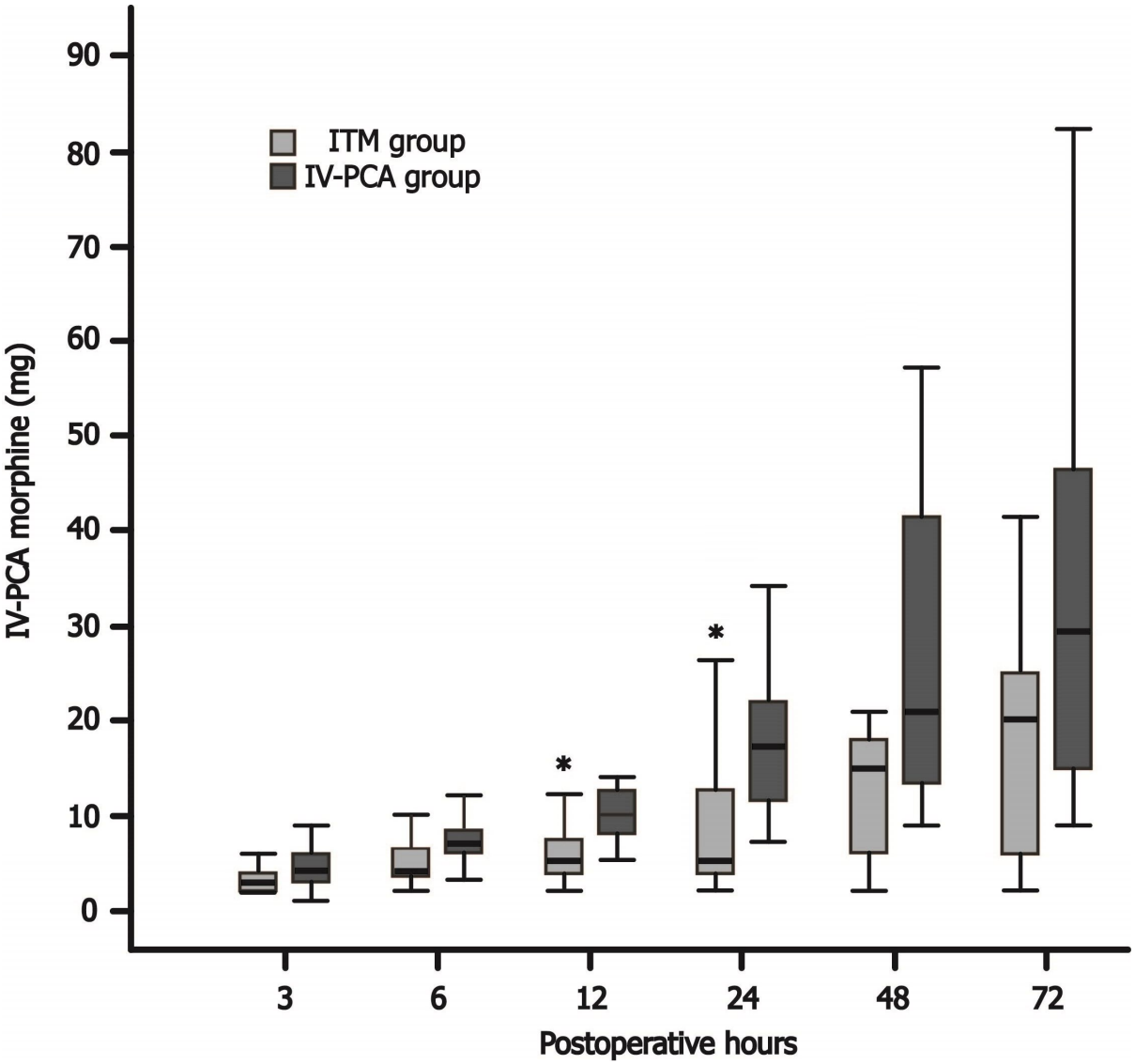
ITM, intrathecal morphine; IV-PCA, intravenous patient-controlled analgesia

Figure 3. Numerical pain score (0 = no pain, 100 = worst imaginable) at rest and on coughing.



NPS up to postoperative 24 h were significantly lower in the ITM group than in the IV-PCA group. NPS, numerical pain score; ITM, intrathecal morphine; IV-PCA, intravenous patient-controlled analgesia. The box represents the interquartile range and a line across the box means the median. * $P < 0.05$ *vs.* the IV-PCA group.

Figure 4. Cumulative morphine consumption by IV-PCA.



Postoperative morphine consumption was significantly lower in the ITM group at 12 and 24 h postoperatively. ITM, intrathecal morphine; IV-PCA, intravenous patient-controlled analgesia. The box represents the interquartile range and a line across the box means the median. * $P < 0.05$ *vs.* the IV-PCA group.

Table 2. Opioid-related complications in intrathecal morphine (ITM) group and intravenous patient-controlled analgesia (IV-PCA) group

	ITM group (*n* = 15)	IV-PCA group (*n* = 15)	*P* -value
Nausea incidence	6 (40)	6 (40)	1.000
Severity			
None/Mild/moderate/severe	9 / 4 / 2 / 0	9 / 4 / 2 / 0	1.000
Vomiting incidence	3 (20)	1 (6)	0.598
Severity			
None/Mild/moderate/severe	12 / 2 / 1 / 0	14 / 1 / 0 / 0	0.475
Dizziness incidence	9 (60)	6 (40)	0.273
Severity			
None/Mild/moderate/severe	6 / 7 / 2 / 0	9 / 5 / 1 / 0	0.531
Headache incidence	3 (20)	2 (14)	1.000
Severity			
None/Mild/moderate/severe	12 / 3 / 0 / 0	13 / 2 / 0 / 0	1.000
Pruritus incidence	5 (34)	2 (14)	0.390
Severity			
None/Mild/moderate/severe	10 / 4 / 1 / 0	13 / 2 / 0 / 0	0.357
Sedation incidence	2 (14)	6 (40)	0.215
Severity			
None/Drowsy/dozing/mostly sleeping/not responding	13 / 2 / 0 / 0 / 0	9 / 6 / 0 / 0 / 0	0.215
Respiratory depression	0 (0)	0 (0)	1.000

Data are presented as frequency (percentage). ITM, intrathecal morphine; IV-PCA, intravenous patient-controlled analgesia

Discussion

We found that the ITM group had lower pain scores and less of an opioid requirement up to postoperative 24 h without serious complications. The NPSs up to postoperative 24 h were significantly lower in the ITM group than those in the IV-PCA group both at rest and coughing. The ITM group used significantly less morphine than the IV-PCA group throughout the study period. There were no opioid-related side effects requiring medical treatment in the ITM group.

Minimally invasive surgery has been known to cause less postoperative pain comparing with open surgery. At immediate postoperative period, however, patients experienced moderate to severe pain after laparoscopic surgery.[3, 16, 17] Though the size of the incision is small, visceral irritation and prolonged pneumoperitoneum with high pressure may increase the postoperative pain after the laparoscopic surgery. In our study, the NPSs in the IV-PCA group were 40 (IQR 30-40) and this result is consistent with other study related to RALP.[3] Patients with such a high pain scores need to be appropriately managed to increase the quality of life and to minimize perioperative morbidities. A single shot of ITM reduced postoperative pain scores for 24 h after RALP in the present investigation. Patients after minimally invasive procedure experience the moderate to severe pain for 24 hr postoperatively and pain decrease to minimal degree after 24 hr postoperatively.[2, 3] The duration of ITM is reported as 24 h because of the hydrophilic nature of morphine.[4] In that regards, the duration of ITM may be optimal for pain management of laparoscopic surgery. As a multimodal approach, a single injection of ITM may be a good modality for postoperative pain management to provide an optimal analgesia after minimally invasive surgery like RALP.

Our study showed that ITM with IV-PCA showed better analgesia with less opioid requirements. Two patients in the IV-PCA group required medical therapy for nausea until 24 hr postoperatively while there was no patient who require medical therapy for opioid-related side effects in the ITM group. Opioid requirements after laparoscopic approach are relatively high at immediate postoperative period which may cause the side effects.[3, 16, 18] The ITM reduced the narcotic usage and the side effects which neccessitated treatments successfully until 24 hr postoperatively. The ITM can be an ideal choice to reduce systemic opioid

requirements and subsequent opioid-related side effects.

An ITM injection is related to complications such as pruritus, nausea, vomiting and delayed respiratory depression.[4, 5, 19-23] In our investigation, however, similar incidences of complications between the two groups were reported. There was none of the patients who developed respiratory depression after surgery and none required intravenous naloxone for the reversal of opioid-related adverse effects. Although high dose of morphine (>1.0 mg) administered intrathecally cause delayed respiratory depression,[19-23] relatively low dose of morphine (<1.0 mg) provided adequate analgesia effectively without respiratory depression.[24-29] Pruritus after ITM injection is common and the incidence is reported as 30% to 100%.[30, 31] Pruritus requires medical therapy such as naloxone, diphenhydramine and 5-HT_3-receptor antagonists if it is severe after an intrathecal injection of morphine.[7, 30, 32] In this study, the incidence of pruritus, however, was not different between the IV-PCA group and the ITM group. We believe that the relatively high dose of morphine consumption in the IV-PCA group is the reason for the similar incidence of pruritus.

The ITM dose of 300 μg was chosen based on previous studies regarding ITM and laparoscopic surgery. High does (> 500 μg) of the ITM can provide a better analgesic effect, but may cause adverse effects including nausea, vomiting, sedation and late respiratory depression.[6, 19-23] For laparoscopic surgeries, relatively low dose of the ITM was administered to obtain analgesia and prevent side effects. The dose of 100-400 μg was administered intrathecally with local anaesthetics in investigations of minimally invasive surgeries.[16, 18, 33] Those studies did not found differences in the incidence of side effects between groups and report any serious side effects such as respiratory depression. We thought that the ITM dose of 300 μg is sufficient to provide analgesia for RALP without side effects. To prevent respiratory depression, patients older than 80 years were excluded and all of patients were monitored meticulously. In our report, 300-μg ITM combined with IV-PCA reduced postoperative pain and opioid requirements during the first postoperative 24 h without serious complications such as respiratory depression.

Multimodal analgesia for RALP has been investigated.[34-36] Epidural analgesia showed better diaphragmatic function after RALP.[34] Preemptive analgesia with pregabalin and celecoxib decreases opioid requirements perioperatively.[35] Those studies, however, did not find the significant difference in pain scores. In contrast, our study shows that ITM lowers pain scores and postoperative opioid use. The ITM is relatively easy and more successful

compared to the epidural injection. The high success rate may contribute the adequate pain control by the ITM. For patients with moderate pain for 24 hr, the ITM can be effective for the pain management as a multimodal analgesia.

Our study had some limitations. First, it was impossible to blind patients and the attending anaesthesiologist to the group assignments. The ITM were performed before induction of anaesthesia to prevent potential neurologic injury and infection and the IV-PCA group did not receive a sham injection as the control. However, the investigators who measured the study variables and the attending physicians were blinded to the group assignments. Second, sample size was insufficient to evaluate the effects of ITM on postoperative complications. The primary endpoint of this study was the postoperative numerical pain score. A study with large population may show the advantages of ITM use to reduce postoperative morbidities. Lastly, we could not evaluate the dose-response relationship to decide the optimal dose of ITM for RALP. A further exploration is needed to evaluate the optimal dose of ITM in RALP.

Conclusions

A single spinal injection of morphine combined with IV-PCA provided effective postoperative analgesia and reduced opioid requirements in patients following RALP. This result suggests that preoperative single-shot ITM may be an effective and safe modality for immediate postoperative pain management for RALP.

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국문 초록

배경 및 목적

로봇 보조 복강경 전립선절제술은 최소 침습적 수술인 장점이 있어 많이 시행되고 있지만, 수술 직 후 중등도 이상의 심한 통증을 유발한다. 본 연구는 로봇 보조 복강경 전립선절제술을 받는 환자들의 수술 후 통증 조절을 위해서 시행한 경막내 모르핀 투여의 효능과 안정성에 대해서 알아보고자 한다.

연구 방법

로봇 보조 복강경 전립선절제술을 받는 30명의 환자를 대상으로 하였으며, 이들은 무작위로 2개의 그룹으로 나뉘어 졌다. 15명은 ITM(Intrathecal Morphine) 군으로 수술 후 300 μg의 모르핀을 경맥내 투여하였고 정맥 자가 통증 조절기를 이용하여 통증을 조절하였다. 남은 15명은 IV-PCA(Intravenous patient controlled anesthesia) 군으로 수술 후 통증 조절을 위해 정맥 자가 통증 조절기만을 사용하였다. 수술 후 통증숫자점수, 수술 후 자가 통증 조절기 요구량, 아편유사제 관련 합병증에 대하여 조사하여 두 군 간의 차이를 비교 하였다.

연구 결과

ITM 군에서 수술 후 24시간에 조사한 숫자통증점수가 유의하게 낮았다. 기침 시 숫자통증점수는 ITM 군에서는 20 (IQR 10-50)이고, IV-PCA 군에서는 60 (IQR 40-80)으로 유의한 차이를 보였다(P = 0.001). ITM 군에서 통증 조절을 위해 IV-PCA 군에 비하여 더 적은 모르핀 요구량을 보였다. 수술 후 24시간에 모르핀 누적 사용량은 ITM 군에서 4 (IQR 3-15) mg이었으며, IV-PCA 군에서는 17 (IQR 11-24) mg으로 유의한 차이를 보였다(P = 0.001). 모르핀 사용과 관련된 합병증을 비교해 보았으며, 합병증의 빈도는 두 군 사이에 차이를 보이지 않았고, 호흡 억제는 두 군에도 모두 보고 되지 않았다.

결론

로봇 보조 복강경 전립선 절제술 받은 환자에서 경막내 모르핀 투여는 심각한 합병증 없이 효과적인 통증 조절을 제공할 수 있다. (clinicaltrials.gov, NCT01991275)

주요어: 경막내, 모르핀, 수술 후 통증, 전립선 절제술

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