Low-Dose Spinal Morphine for Pain Control after Transurethral Resection of Prostate: A Prospective Randomized Control Study

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Objective: *To compare postoperative pain in patients undergoing TURP between patient receiving spinal anesthesia with 0.05 mg morphine and 0.5% bupivacaine or spinal bupivacaine alone.*

Material and Method: *This prospective, randomized, double-blinded study included 80 patients which were randomized into 2 groups. Patients in control group (Group C) received only 0.5% hyperbaric bupivacaine. The other group (Group M) received 0.5% hyperbaric bupivacaine with 0.05 mg morphine. Numerical rating scale (NRS) score was recorded at interval during the first 24 hours postoperative. Time to first analgesics requirement, number of patients who required meperidine, and the total 24-hour meperidine requirement were also recorded. The side effects including respiratory depression, pruritus, nausea and vomiting were also evaluated.*

Results: *Median maximum NRS score were 3 and 1 in Group C and Group M, respectively which showed no statistically significantly different (p = 0.08). The number of patients who required meperidine, time to first request analgesic requirement and the total 24-hour meperidine requirement were similar between the two groups. Patients in Group M had higher incidence of pruritus, nausea and vomiting. However, only the incidence of pruritus that was statistically significantly different (5.7% vs. 20%, p = 0.04).*

Conclusion: *This study could not demonstrate the benefit of adding morphine 0.05 mg to spinal anesthesia with 0.5% hyperbaric bupivacaine in patients undergoing TURP.*

Keywords: *Transurethral resection of prostate, TURP, Spinal morphine, Low dose, Postoperative pain*

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Moderate to severe pain has been reported from patients undergoing transurethral resection of prostate (TURP), which mostly explained by detrusor muscle spasm associated with the use of a transurethral balloon to prevent bleeding from the prostatic bed or capsule[1-3]. Several medications and interventions have been demostrated to mitigate these discomforts such as preemptive flurbiprofenaxetil and tramadol[4], preincision ketamine[5], preemptive intravenous oxycodone[6], dexmedetomidine[2], spinal magnesium[7], spinal dexmedetomidine[8], periprostatic nerve blockade[9] and prilocaine irrigation[10]. However, prescribing pain medications in these patients are also very challenging. Most patients are elderly and usually accompanied with many underlying diseases which may be contraindicated with some medication.

The addition of morphine to spinal anesthesia has been effectively used for postoperative analgesia after many operations[11-13]. Spinal morphine is often accompanied by adverse effects such as pruritus, nausea, vomiting and respiratory depression. All these adverse effects are greater when using larger dose of spinal morphine. Nowadays, anaesthesiologists have a tendency to add smaller dose to reduce the incidence of adverse effect especially respiratory depression[14-16].

This study has been carried out to investigate the efficacy of adding 0.05 mg morphine in patients undergoing TURP with spinal anesthesia.

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Material and Method

After the Institutional Review Board (Si 019/

2558) approval and written informed consent was obtained. Patients with ASA classification I-III scheduled for TURP were included. Patients with history of allergy to the study drugs, bleeding disorder, infection of the back, refusing spinal anesthesia, cerebrovascular disease were excluded.

The study was performed as a prospective, randomized and double-blinded study (1: 1). All patients were randomized into 2 groups by block of four. Randomization assignments were placed in envelopes and sealed, anesthesiologists taking care of patients, surgeons and research nurses who evaluated patients postoperatively were blinded to the group assignment. All patients were instructed in the use of the Numeric Rating Scale (NRS) Score (0 = no pain to 10 = worst imaginable pain) for pain assessment during the pre-operative visit. Patients received no premedication. Before spinal block, electrocardiography, non-invasive blood pressure (NIBP) and pulse oximetry were applied. Spinal anesthesia was conducted using 0.5% hyperbaric bupivacaine 2 mL (Group C) and 0.5% hyperbaric bupivacaine 2 mL with 0.05 mg morphine (Group M). After T10 dermatome level was achieved, patients were placed in lithotomy position. Oxygen cannula 2 L/min was given to patient requesting sedation which was midazolam 1-2 mg. The number of patients who requested sedation, duration of surgery were recorded. All patients received oral paracetamol 1 gm every 6 hours.

During postoperative period, NRS score was recorded every one hour for 12 hours then every 2 hours until complete 24 hours. If NRS $\geq$4 and the patient request for analgesia, intravenous meperidine 15 mg would be given every 2 hours. The number of patients who required meperidine and time to first rescue analgesia were recorded. Pruritus was measured on 4-point categorical scale in which 0 = no symptom, 1 = mild symptom need no treatment, 2 = moderate symptom with regular treatment required and 3 = severe symptom with naloxone required for treatment. Nausea vomiting score was defined as 0 = no symptom, 1 = mild nausea, 2 = severe nausea, 3 = vomiting. Nausea and vomiting were treated with 8 mg of ondansetron intravenously, repeated every 6 hours as needed. If the symptom persisted, metoclopramide was given.

Statistical analysis

Based on the Sakai et al study[17], the mean $\pm$ SD of maximum NRS score within 24 hours was 42 $\pm$ 30. A sample size of 34 subjects per group would allow to detect a 50% reduction in pain with 80% power using an nQuery program at the *p*-value 0.05. Assuming an estimated 15% drop rate, 40 subjects per group were enrolled.

Continuous data were reported as mean $\pm$ SD or median (minimum-maximum) as appropriated. Categorical data were reported as number (%). Comparisons between the groups were performed with independent Student t-test, Mann-Whitney U test, Chi-square test or Fisher's exact test as appropriate. A *p*-value 0.05 was considered statistically significant. Statistical analysis was performed using PASW Statistics for Windows, 18.0 Chicago: SPSS Inc.

Results

During April 2015 to February 2016, 84 patients originally enrolled. But only 70 patients completed the analysis (Fig. 1). Four patients were initially excluded before starting the study due to change into prostate laser surgery (3) and newly detected huge abdominal aorta aneurysm (1). One patient in the Group C had to convert to general anesthesia because of unexpected long operative time. Nine patients were excluded from the study due to protocol violations, incorrect dose of spinal bupivacaine (3), incorrect dose of spinal morphine group received morphine 0.5 mg at ward, (Fig. 1).

There was no significant difference in demographic and operative data between groups except

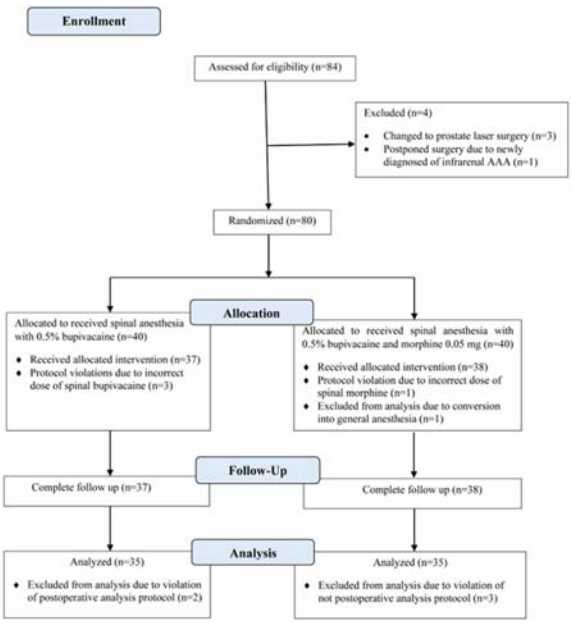

Fig. 1 Consort flow.

age which were 73.0±7.4 and 69.4±7.4 years in Group C and Group M, respectively (p = 0.04) (Table 1). The median maximum NRS score within 24 hours was 3 (0 to 10) and 1 (0 to 9) in Group C and Group M, respectively which was not significantly different (p = 0.08). The incidence of moderate to severe pain in the Group C seemed to be higher than Group M (42.9% and 25.7%, p = 0.07) (Fig. 2). Moreover, there were 4 patients (2 patients in each group) in moderate to severe pain group having blood clot. Time to first analgesic requirement was 21.2±1.4 hours in Group C and 21.3±1.4 hours in Group M (p = 0.78). In addition, the amount of meperidine required within 24 hours in Group C and M were 22.5±12.6 mg and 30.0±13.4 mg, respectively which showed no statistically significant (p = 0.34) (Table 2). No patients experienced delayed respiratory depression. There was no significant difference in the incidence of nausea (p = 0.15). The number of patients who experienced pruritus was significantly higher in spinal morphine group (5.7% vs. 20%, p = 0.04) and four patients (11.4%) required medication for treatment.

Discussion

The result from this study could not show the benefit of adding spinal morphine to spinal anesthesia with 0.5% hyperbaric bupivacaine 2 mL. Both groups had maximum pain score within 24 hours as mild pain and the number of patients required meperidine postoperatively were not significantly different between groups. Contrary to Sakai et al conclusion, spinal morphine at a dose of 0.05 could demonstrate a better analgesic effect compared with control group[17]. Average visual analogue scale (VAS) in control group, spinal anesthesia with tetracaine 10 mg, was moderate pain and 92% required additional analgesics. While average VAS in spinal morphine 0.05 mg was mild pain and no patient required additional analgesics. Both tetracaine and bupivacaine have quick onset and short duration. However, using 0.33% hyperbaric tetracaine 3 mL and 0.5% hyperbaric bupivacaine 2 mL might influence the postoperative pain score and could not compare the effect of spinal morphine 0.05 mg. Duman et al reported similar postoperative characteristics between spinal morphine 0.05 mg and 0.025 mg[18]. Their operative time were 45±13 minutes in spinal morphine 0.05 mg and 48±11 minutes in spinal morphine 0.025 mg which were shorter than this study (63.1±32.1 minutes in Group C and 69.6±31.0 minutes in Group M). Their operation might be less extensive than this study and could be covered with spinal morphine 0.025 mg for postoperative analgesia. Moreover, their study lacked control group for comparison. The postoperative pain score might be acceptable even in the control group using only 0.5% bupivacaine 5 mg.

Similarly, adding 0.05 mg morphine to spinal anesthesia with 0.5% hyperbaric bupivacaine could not demonstrate any significant difference in time to first rescue analgesic drug and the amount of meperidine

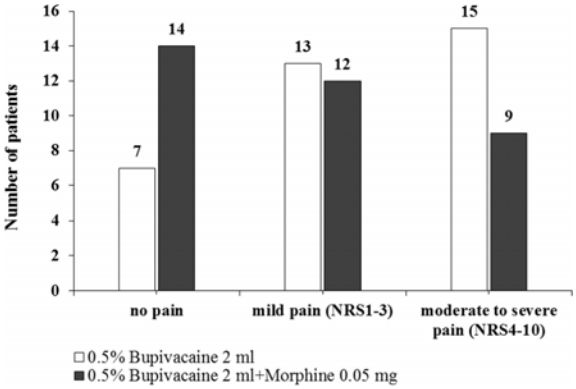

Fig. 2 Number of patients and maximum 24-hour post-operative numeric rating scale (NRS) score.

Table 1. Demographic and operative data

	Group C (n = 35)	Group M (n = 35)	p-value
Age (yr)	73.0±7.4	69.4±7.4	0.04
Weight (kg)	62.9±9.7	65.3±9.6	0.32
Height (cm)	163.7±6.9	165.2±6.4	0.36
BMI (kg/m^2)	23.5±3.5	23.9±3.2	0.58
ASA physical status (II:III)	21:14	24:11	0.45
No. of patients who required sedation	27 (77.1)	28 (80.0)	0.50
Duration of surgery (min)	63.1±32.1	69.6±31.0	0.39

Data presented as mean ± SD and n (%)
BMI = Body mass index; ASA = American Society of Anesthesiologists

Table 2. Postoperative outcomes

	Group C (n = 35)	Group M (n = 35)	*p*-value
Maximum pain score in 24 hours	3 (0-10)	1 (0-9)	0.08
Patients request meperidine	15 (42.9)	9 (25.7)	0.07
Time to first rescue analgesics (h)	21.2±1.4	21.3±1.4	0.78
24-hour meperidine requirement	22.5±12.6	30.0±13.4	0.34
Nausea and vomiting	3 (8.6)	7 (20)	0.15
Pruritus	2 (5.7)	7 (20)	0.04
No. of patients who need treatment for pruritus	0 (0)	4 (11.4)	0.12

Data presented as mean ± SD, median (min-max) or n (%)

required between groups. The total 24-hour meperidine usage in Group M was slightly higher due to repeated dose in patients having blood clot before bladder irrigation.

Using post hoc power analysis, this study had power less than 80%. Thus, the sample size was necessary to be increased for further investigation. Moreover, due to the uneven distribution of population age between groups, this might be influenced with postoperative pain score. Group C were slightly older than Group M which generally older patients can tolerate pain better than younger patients.

The incidence of moderate to severe pain after TURP in this study with spinal anesthesia with 0.5% bupivacaine 2 mL was 42.9%. However, the median postoperative pain score was mild pain. From the literature review, the number of patients undergoing TURP under spinal local anesthetics only, having moderate to severe pain, and requesting analgesic drugs varied from 17 to 40.7%[8,19]. Patient discomfort from TURP mostly explained by detrusor muscle spasm associated with the use of a transurethral balloon to prevent bleeding from the prostatic bed or capsule[1-3]. Other possible mechanism of pain was tissue damage resulting from surgical procedures can induce sensitization of the peripheral and central nervous systems and then lead to hyperalgesia and increased postoperative pain[4]. There was one case reporting severe pain although receiving spinal morphine dose 1 mg because of tearing prostatic capsule[19]. Thus, it is unclear whether operative technique, extensive of operation, operative time, strapping technique or other surgical factors may affect pain score in TURP patients. In this study, there were 4 patients having blood clot and all of them demonstrated moderate to severe pain. They requested meperidine for rescue pain but all of them were better after bladder irrigation.

About the side effects of spinal morphine, this study found the number of patients experiencing pruritus was significantly higher in spinal morphine group. Although the low dose of spinal morphine (0.05 mg) was selected to reduce the adverse effects, approximately 10% of patients with pruritus episodes still needed medication to relieve their symptoms. Duman et al also showed the side effects of spinal morphine at both dose 0.05 and 0.025 mg[18]. Spinal morphine 0.05 mg exhibited 15% of patients with pruritus, 15% of patients with emesis and 26% of patients required treatment for emesis. Moreover, with even lower dose spinal morphine 0.025 mg still exhibited 14% of patients with emesis and 28% of patients required treatment for emesis. Although these side effects (nausea and vomiting and pruritus) were not life-threatening conditions, they could disturb patients' comfort. In addition, the unusual dose of routine practice can cause medication error. In this study, there was one patient receiving 0.5 mg of spinal morphine because of confusing of diluted technique. Fortunately, he had no serious complications. Cunningham et al found only 50% of patients having acute uncompensated respiratory acidosis by using larger dose spinal morphine 1 mg[19].

The limitations of this study were the sample size, the uneven distribution of population age between groups and the neglect of possible surgical factors that may influence the postoperative pain. Selected patients may be more appropriately received pain medication. With easing of adding spinal morphine for postoperative pain control, the authors suggest that balancing between benefits and disadvantages need to be considered.

Conclusion

There was no benefit of adding spinal morphine to spinal anesthesia with 0.5% hyperbaric bupivacaine 2 mL in patients undergoing TURP. Even

though the incidence of moderate to severe pain in patients using only spinal anesthesia was almost 50 percent, the (median) maximum pain score in 24 hours was mild pain. It may be better to identify the factors associated with moderate to severe pain in patients undergoing TURP such as tearing capsule or having blood clot. Pain prescribing medications will be more appropriate, given to selected patients. Moreover, suspected postoperative complications should be more concerned in patients with unexplained severe postoperative pain.

What is already known on this topic?

Moderate to severe pain has been reported from patients undergoing TURP. Low dose spinal morphine with spinal bupivacaine has never been compared with spinal bupivacaine alone for postoperative analgesia after transurethral resection of prostate (TURP) operation.

What this study adds?

This study could not demonstrate the benefit of adding spinal 0.05 mg of morphine to spinal anesthesia with 0.5% hyperbaric bupivacaine 2 mL in patients undergoing TURP. However, this study had power less than 80% by using post hoc power analysis. In addition, the incidence of moderate to severe pain in patients undergoing TURP with 0.5% hyperbaric bupivacaine 2 mL was 42.9%.

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Trial registration

ClinicalTrials.gov as NCT02458742.

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Potential conflicts of interest

None.

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การศึกษาเปรียบเทียบแบบสุ่มการบริหารมอร์ฟีนขนาด 0.05 มิลลิกรัมทางช่องไขสันหลังเพื่อควบคุมอาการปวดหลังการผ่าตัดต่อมลูกหมากโดยใช้วิธีส่องกล้อง

ภาวิณี ปางทิพย์อำไพ, ภมรา ซุ้มโชคชัยกุล, พัชรียา นิวัฒน์ภูมินทร์, ธัชวรรณ จิระติวานนท์, สุกัญญา เดชอาคม

วัตถุประสงค์: เพื่อเปรียบเทียบอาการปวดหลังผ่าตัดในผู้ป่วยที่มาเข้ารับการผ่าตัดต่อมลูกหมากโดยใช้วิธีส่องกล้องระหว่างผู้ป่วยที่ได้รับยามอร์ฟีน 0.05 มก. ร่วมกับ 0.5% บูพิวาเคนทางช่องไขสันหลังและกลุ่มที่ได้รับ 0.5% บูพิวาเคนเท่านั้น

วัสดุและวิธีการ: เป็นการศึกษาวิจัยเชิงทดลองแบบสุ่มที่มีกลุ่มควบคุมในผู้ป่วยทั้งหมด 80 ราย โดยกลุ่มควบคุมใช้ยาชา 0.5% hyperbaric bupivacaine ปริมาณ 2 มล. และกลุ่มทดลองใช้ยาชา 0.5% hyperbaric bupivacaine ปริมาณ 2 มล. ร่วมกับมอร์ฟีนขนาด 0.05 มก. ทางช่องไขสันหลังระยะ 24 ชั่วโมงภายหลังการผ่าตัดทำการเก็บข้อมูล คะแนนความปวดมากที่สุดโดยใช้คะแนนความปวด 0 ถึง 10 จำนวนผู้ป่วยที่ได้รับยาเมพเพอริดีนและปริมาณยาเมพเพอริดีนทั้งหมดที่ได้รับ นอกจากนั้นได้ทำการบันทึกอาการข้างเคียง เช่น กดการหายใจ คลื่นไส้ อาเจียน และคัน

***ผลการศึกษา:** คะแนนความปวดที่มากที่สุดในกลุ่มควบคุมคือ 3 ในขณะที่กลุ่มมอร์ฟีนคือ 1 ซึ่งไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ (p = 0.08) อุบัติการณ์ของอาการปวดปานกลางและปวดรุนแรงในผู้ป่วยที่มาเข้ารับการผ่าตัด ต่อมลูกหมากโดยใช้วิธีส่องกล้องภายใต้การระงับความรู้สึกโดยวิธีการฉีดยาชาเข้าช่องน้ำไขสันหลัง เพียงอย่างเดียว มีปริมาณร้อยละ 42.9 ส่วนจำนวนผู้ป่วยที่ขอยาแก้ปวดเมพเพอริดีนภายหลังการผ่าตัด, ระยะเวลาตั้งแต่หลังผ่าตัด จนกระทั่งขอยาแก้ปวดเมพเพอริดีนครั้งแรก และปริมาณยาเมพเพอริดีนทั้งหมดที่ผู้ป่วยขอภายใน 24 ชั่วโมง ไม่พบว่ามีความแตกต่างอย่างมีนัยสำคัญทางสถิติระหว่าง 2 กลุ่ม การฉีดยามอร์ฟีนเข้าช่องน้ำไขสันหลัง พบมีผลข้างเคียงเรื่องคลื่นไส้อาเจียนและคันมากขึ้น แต่เฉพาะอาการคัน ที่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ ร้อยละ 5.7 และร้อยละ 20 ในกลุ่มควบคุมและกลุ่มทดลองตามลำดับ (p = 0.04)*

***สรุป:** การบริหารยามอร์ฟีนร่วมกับยาชาเข้าช่องน้ำไขสันหลังในผู้ป่วยที่มาเข้ารับการผ่าตัดต่อมลูกหมาก โดยใช้วิธีส่องกล้องไม่มีประโยชน์ในการระงับปวดหลังผ่าตัด แม้ว่าอุบัติการณ์ของอาการปวดปานกลางและปวดรุนแรง ในผู้ป่วยดังกล่าวจะสูงเกือบร้อยละ 50 แต่ค่ามัธยฐานของคะแนนความปวดมากที่สุดภายใน 24 ชั่วโมงโดยเฉลี่ยเท่ากับ 3 ซึ่งจัดเป็นอาการปวดน้อย*