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ORIGINAL ARTICLE

Effect of morphine on lower urinary tract discomfort after transurethral resection of prostate under general anesthesia: a randomised clinical study

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Abstract
Background Lower urinary tract (LUT) discomfort is a common complaint after transurethral resection of the prostate (TURP), and it may lead to agitation and restlessnes. We have evaluated the efficacy of morphine for preventing TURP-related LUT discomfort symptoms.
Methods This was a prospective randomised study including 60 patients (American Society of Anesthesiologists class I and II) who were scheduled to undergo TURP. The patients were divided into two equally sized groups (group M: morphine, group C: control). A standartized anesthesia method was used. Group M patients received morphine 0.04 mg/kg intravenous (iv) in 100 ml of normal saline followed by an infusion of morphine for 24 h (0.01 mg/kg/h); group C patients received 100 ml normal saline 20 min before the expected extubation time, followed by a normal saline infusion which looked identical to that of the morphine infusion. The incidences and severity of LUT discomfort, postoperative pain, sedation level, postoperative nausea and vomiting (PONV) and respiratory depression were recorded at 0, 1, 2, 6, 12 and 24 h postoperatively.
Results The incidence of LUT discomfort was lower in group M patients at all time points during the study ($p < 0.05$) except for 2 h postoperatively, and the severity of LUT discomfort was also lower this group at 0, 12 and 24 h postoperatively ($p = 0.001$, $p = 0.04$ and $p = 0.02$, respectively). Pain (numeric rating scale) scores were lower in group M patients at 0 ($p = 0.003$) and 6 h ($p < 0.001$). The need for rescue analgesic was lower in group M patients (19 patients in group C, 10 patients in group M; $p = 0.04$). The incidence of PONV was higher in group M patients ($p = 0.03$). The incidence of pruritus, respiratory depression and over-sedation were similar among the groups.
Conclusion Based on these results, we conclude that morphine effectively reduces LUT discomfort after TURP at a cost of postoperative nausea and vomiting.

Keywords Transurethral resection of the prostate · Lower urinary tract discomfort · Morphine

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Introduction

It is not uncommon for anesthesiologists to encounter patients suffering from lower urinary tract (LUT) discomfort (urge to void, burning sensation and distress about the indwelling catheter) after transurethral resection of the prostate (TURP). These symptoms may be a reason for

postoperative agitation and restlessness. LUT discomfort may be due to an indwelling urinary catheter, residual overactive bladder (OAB) symptoms which remain after TURP, and urethral irritation caused by transurethral maneuvers in patients who have undergone TURP [1–4].

OAB symptoms have been found to be highly prevalent in patients with benign prostatic hyperplasia [5], and they do not resolve after TURP in 20–40 % of patients [2, 3]. Since symptoms of OAB and catheter-related bladder discomfort result from bladder contractions [6], we hypothesised that intravenous morphine, which was shown to inhibit bladder contractions in rats [7], may be superior to placebo in alleviating LUT discomfort in patients after TURP. To the best of our knowledge, no study has been published in English which examines the effects of the postoperative systemic administration of morphine on LUT discomfort after TURP.

Methods

After receiving approval from the ethics committee of Yeditepe University Hospital (25 May 2011/No. 101) and written informed consent from the patients, we enrolled 60 patients (age 40–65 years; American Society of Anesthesiologists I and II) undergoing TURP in this prospective, balanced randomized (1:1), double-blinded, phase IV study conducted between January 2011 and November 2011. Exclusion criteria were patients with chronic analgesic use, drug addiction, chronic pain, sensitivity to study drugs, neurogenic bladder and cardiovascular, hepatic, renal or psychiatric disease.

All patients were premedicated with midazolam of 0.03 mg/kg intravenous (iv) before being brought to the operation room. The participants were randomised and allocated into groups using computerised numbers (Excel; Microsoft, Redmond, WA) by an anesthesiologist not participating in the trial. After monitoring of the electrocardiogram, pulse oximeter and non-invasive blood pressure, anesthesia was induced with propofol 2 mg/kg and fentanyl 1.5 μg/kg, and a laryngeal mask airway was inserted. In all patients anesthesia was maintained with sevoflurane (end tidal 1.3–1.5 %) and remifentanyl infusion (0.1 μg/kg/min). Twenty minutes before the expected extubation time, patients in group M (morphine group) received morphine 0.04 mg/kg iv diluted in 100 ml normal saline, and those in group C (control group) received 100 ml normal saline. These medications were administered by an anesthesia nurse blinded to group allocation. At the end of the surgery urinary catheterisation was performed in all patients using a 16 Fr Foley's catheter, and the balloon was inflated with 10 ml distiled water. Following urinary catheterisation remifentanyl infusion and sevoflurane anesthesia were discontiniued, and all patients were transferred to the post-anesthesia care unit (PACU) after removal of the laryngeal mask airway. Patients in group M received a morphine infusion of 0.01 mg/kg/h during the 24-h post-operative follow-up, whereas patients in group C received normal saline in a solution which looked identical to that of the morphine infusion. An anesthesia nurse blinded to the group allocation observed the incidence and severity of LUT discomfort. Pain was assessed with a numerical rating scale (NRS) score ranging from 0 to 10, and sedation level was assessed with the Ramsay sedation scale (1 = anxious, agitated or restless; 2 = co-operative, oriented and tranquil; 3 = responds to command; asleep; 4 = brisk response to light glabellar tap or loud noise; 5 = a sluggish response to light glabellar tap or loud noise; 6 = no response), postoperative nausea and vomiting (PONV) and respiratory depression immediately after laryngeal mask airway removal and as soon as the patient became cooperative, at 0, 1, 2, 6, 12 and 24 h after the operation.

The primary outcome measures of the study were the incidence and severity of LUT discomfort. Postoperative pain scores, incidence of PONV, pruritus, respiratory depression and requirement of rescue analgesic were the secondary outcome measures.

The severity of LUT discomfort was recorded as follows: none (0)—no LUT discomfort; mild (1)—reported by the patient only by questioning; moderate (2)—reported by the patient without questioning and not accompanied by any behavioral responses; severe (3)—reported by the patient and accompanied by behavioral responses (flailing limbs, strong vocal responses and attempts to remove the catheter). Patients with a sedation scale of $\geq$4 were considered to be oversedated.

In the postoperative period patients in both groups with a NRS of >3 received paracetamol 1 g iv as a rescue analgesic. The incidence and severity of LUT discomfort, pain scores, incidence of PONV, pruritus and respiratory depression (respiratory rate <8 breaths/min) and requirement of rescue analgesic were recorded.

Values are reported as the mean ± standard deviation and median where appropiate. Assuming that morphine would reduce the incidence of LUT discomfort by 30 %, power analysis with $\alpha = 0.05$ and $\beta = 0.8$ showed that the study needed at least 24 patients in each group. Six patients were added to each group to compensate for the possible losses. Fisher's exact test was used to analyse the incidence and severity of LUT discomfort between the two groups. NRS scores were compared using the Mann–Whitney *U* test. The incidence of PONV, pruritus, respiratory depression and patients receiving rescue analgesic were analysed by the Fisher's exact test. Student's *t* test was used to compare the demographic data of the groups.

Results

The flow chart of the study is shown in Fig. 1. None of the patients were excluded from the study after randomisation. There was no significant difference between the groups with respect to patients characteristics (Table 1). The study was stopped after reaching the target sample size.

Table 2 shows the incidence and severity of LUT discomfort in both groups. The incidence of LUT discomfort was lower in group M at all measurement times ($p < 0.05$) except for 2 h postoperatively. The severity of LUT discomfort was lower in group M at 0, 12 and 24 h postoperatively ($p = 0.001$; $p = 0.04$; $p = 0.02$, respectively).

Postoperative NRS scores are shown in Table 3. NRS scores were lower in group M than in group C patients at 0 ($p = 0.003$) and 6 h ($p < 0.001$) postoperatively. The need for rescue analgesic was also lower in group M patients (19 patients in group C and 10 patients in group M; $p = 0.04$). Table 4 shows the incidence of opioid-related side effects. PONV incidence was higher in group M patients versus group C patients ($p = 0.03$). The incidences of pruritus, respiratory depression and over-sedation (Ramsay sedation score ≥ 4) were similar among the groups.

Table 1 Patient characteristics

Patient characteristics	Group[a]	
	C (control)	M (morphine)
Age (years)	67 ± 5	66 ± 5
Weight (kg)	79 ± 7	80 ± 9
Duration of the operation (min)	46 ± 5	47 ± 6

Data are presented as the mean ± standard deviation (SD)

[a] Group M (morphine group) patients received morphine 0.04 mg/kg intravenously diluted in 100 ml normal saline; group C (control group) received 100 ml normal saline—both 20 min before the expected extubation time

Discussion

The results of our study show that perioperative morphine effectively reduced the incidence and severity of LUT discomfort and reduced the need for postoperative rescue analgesics during the first 24 h after TURP operations. It also produced better analgesia compared to paracetamol along with a reduction in the number of patients requiring rescue analgesic.

There are three underlying factors that account for the symptoms of LUT discomfort after TURP, namely,

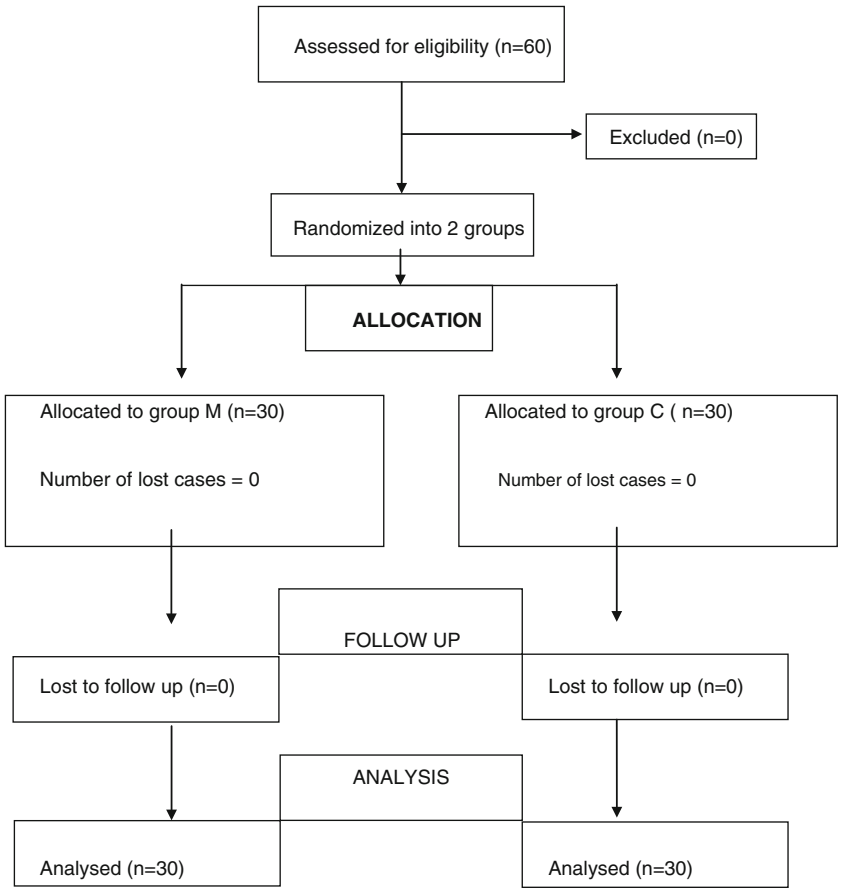

Fig. 1 Flow chart of the study

Table 2 The incidence and severity of lower urinary tract discomfort

Time point[a]:	T0		T1		T2		T6		T12		T24	
Group:	C	M	C	M	C	M	C	M	C	M	C	M
Incidence of LUT discomfort	24 (80)	11 (37)*	25 (83)	17 (57)*	21 (70)	16 (53)	20 (83)	9 (30)*	17 (57)	3 (10)*	6 (20)	0 (0)*
Severity of LUT discomfort												
Mild	7 (29)	6 (55)	6 (24)	7 (41)	2 (9)	3 (19)	11 (55)	4 (44)	9 (53)	2 (67)*	6 (100)	0 (0)*
Moderate	8 (33)	3 (27)	9 (36)	7 (41)	10 (48)	10 (63)	6 (30)	5 (56)	6 (35)	1 (33)	0 (0)	0 (0)
Severe	9 (38)	2 (18)*	10 (40)	3 (18)	9 (43)	3 (18)	3 (15)	0 (0)	2 (12)	0 (0)	0 (0)	0 (0)

Data are presented as number of the patients, with the percentage given in parenthesis

LUT Lower urinary tract

[a] T0, immediately following extubation; T1, T2, T6, T12, T24, 1, 2, 6, 12, 24 h, respectively after the operation

* $p < 0.05$ compared to control group

Table 3 Postoperative numerical rating scale pain scores

Time points:	T0		T1		T2		T6		T12		T24	
Group:	C	M	C	M	C	M	C	M	C	M	C	M
NRS scores[a]	3 (1–4)	1 (0–4)*	3 (1–4)	3 (1–4)	2 (0–3)	1 (0–3)	2 (1–3)	0 (0–3)*	0 (0–3)	1 (0–3)	1 (0–3)	1 (0–2)

[a] Numerical rating scale (NRS) score ranges from 0 to 10 and is presented as the median score with the range given in parenthesis

* $p < 0.01$ compared to control group

Table 4 Incidence of opioid-related side effects

Opioid-related side effects	Group	
	C ($n = 30$)	M ($n = 30$)
PONV (n)	4	12*
Pruritus (n)	0	1
Respiratory depression (n)	0	0
Over-sedation (n)	0	0

PONV Postoperative nausea and vomiting

* $p < 0.05$ compared to control group

indwelling urinary catheterization, OAB-related symptoms and urethral irritation caused by transurethral maneuvers. From the embryological and anatomical standpoint, the urethral plate is a continuation of the trigone of the urinary bladder [8]. According to this, Shorrab et al. [4] suggested that urethral maneuvers may induce bladder irritation through trigonal stimulation.

An indwelling urinary catheter is routinely inserted after TURP operations. Catheter-related bladder discomfort (CRBD) secondary to an indwelling urinary catheter is common and can be very distressing, possibly leading to a reduced quality of life [9]. CRBD is caused by involuntary contractions of the bladder, and these contractions are mediated by muscarinic receptors located in the urothelium and on efferent nerves [6, 10]. OAB symptoms are similar to those of CRBD and the principle behind pharmacologic management of OAB is inhibition of bladder contractions [11].

Morphine, a commonly used opioid for postoperative analgesia has been shown to inhibit bladder contractions in rats [7, 12]. The inhibitory effects of morphine on bladder contraction are mediated by central opioid receptors. It has been demonstrated that the opioid receptors involved are of the mu and possibly delta subtypes [7, 13–16]. Morphine has also a weak direct peripheral depressant effect on detrusor muscle [17]. The alleviation of LUT symptoms after TURP by morphine administration may be due to its inhibitory effect on bladder contractions, thereby decreasing both OAB and CRBD symptoms.

Muscarinic receptor activation causes the contraction of the detrusor muscles of the urinary bladder [18]. Muscarinic receptor antagonists, such as tolterodine, oxybutynin and tramadol (the latter being an opioid analgesic with antimuscarinic properties), inhibit bladder contraction. The efficacy of these substances in inhibiting involuntary bladder contractions related to urinary catheter has been demonstrated [19, 20]. Gabapentin and ketamine have also been successfully used for the prevention of involuntary contractions of the bladder secondary to urinary catheterization [1, 21]. All of the aforementioned drugs might be suitable alternatives to morphine in relieving LUT discomfort symptoms, but further studies are required to evaluate their effect on LUT discomfort after TURP.

Tolretodine has to be administered orally, which is an inconvenient administration route in the postoperative

period, and morphine has the advantage of having a more rapid onset of action compared to tolterodine (1–2 h). Since the elimination half-life of gabapentin is 5–7 h, an i.v. morphine infusion seems to be more advantageous than a single dose of gabapentin for a urinary catheterization time of at least 24 h. Ketamine has been used to alleviate catheter-related bladder discomfort [21]; in this study the authors found that i.v. ketamine 250 μg/kg was associated with an increased sedation incidence postoperatively [21]. In contrast, we did not observe this association in our current study. Although ketamine, tolterodin and gabapentin may be used for inhibiting bladder contractions, an analgesic drug, most commonly an opioid, is still needed to treat postoperative pain which is frequently associated with increased incidence of PONV. Therefore, despite the high incidence of nausea and vomiting among our patient cohort, morphine still has the advantage of concomitantly alleviating postoperative pain and LUT discomfort.

Our study is limited by the fact that the patients were not evaluated urodynamically in terms of pre-existing overactive bladder symptoms during the preoperative period. Since the severity of preoperative OAB symptoms may affect LUT discomfort postoperatively, studies with additional preoperative OAB evaluation may be a subject for further studies.

Based on our results, we conclude that morphine effectively reduces LUT discomfort after TURP at the cost of PONV.

Conflict of interest None.

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