Original Article

Efficacy and safety of Parecoxib for prevention of catheter-related bladder discomfort in patients undergoing transurethral resection of bladder tumor: Prospective randomised trial

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ABSTRACT

Background and Aims: Catheter-related bladder discomfort (CRBD) is the urge to void or discomfort in the suprapubic region secondary to an indwelling urinary catheter. We aimed to evaluate the safety and efficacy of single-dose of intravenous parecoxib in reducing the incidence and severity of CRBD in patients undergoing transurethral resection of bladder tumor (TURBT). **Methods:** Sixty-one adult patients, American Society of Anesthesiologists physical status I or II, undergoing elective TURBT under spinal anaesthesia, were randomly allocated to receive 40 mg of IV parecoxib (group P; $n = 29$) or an equal volume of normal saline (control group C; $n = 32$). CRBD was graded as none, mild, moderate, and severe. Between-group comparisons were made for the incidence and severity of CRBD, postoperative Visual analog scales (VAS), rescue analgesia equirements, and occurrence of adverse events. Statistical analysis done with the Mann–Whitney U-test and Fisher's Exact Test. A P value of ≤ 0.05 was considered statistically significant. **Results:** Parecoxib significantly reduced the incidence and severity of CRBD at 2, 4, 6, and 12 hours postoperatively compared to placebo ($P < 0.05$). Median pain VAS scores were lower in the P group at all times except the first hour. Rescue analgesia was given to more patients in group C (16/32, 50%) than in group P (1/29) ($P < 0.001$). None of the patients who received parecoxib experienced an adverse event. **Conclusion:** A single intravenous injection of parecoxib is safe and effective in decreasing the incidence and severity of CRBD in patients undergoing TURBT. **Trial Registration Identifier:** NCT02729935(www.clinicaltrials.gov).

Key words: Analgesia, catheter-related bladder discomfort, intravenous parecoxib, transurethral resection of bladder tumor

INTRODUCTION

Catheter-related bladder discomfort (CRBD) is defined as an urge to void or discomfort in the suprapubic region reported postoperatively in patients who have had urinary catheterization intraoperatively.[1] It is characterized by a sensation of frequent and urgent urination, which is similar to overactive bladder syndrome. In the post-anaesthesia care unit (PACU), CRBD is one of the risk factors for the occurrence of emergence agitation.[2]

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Various muscarinic receptor antagonists including ketamine, tolterodine, tramadol, and butylscopolamine have been evaluated for their ability to prevent the CRBD. However, they induce side effects such as dry mouth, sedation, nausea, and vomiting.[3-5]

Parecoxib sodium is an injectable cyclooxygenase-2 (COX-2) selective inhibitor often administered for the management of postoperative pain in adults and is generally well tolerated.[6,7]

Clinically, the effects of parecoxib on CRBD prevention have not been studied. We hypothesised that parecoxib could reduce the incidence of postoperative CRBD.

In the present study, we evaluated parecoxib for preventing CRBD in patients undergoing catheterization after transurethral resection of bladder tumor (TURBT).

METHODS

After approval of the Institutional Ethics Committee and written informed consent, 61 patients undergoing elective TURBT were included in this prospective, randomised, double-blind study. The trial was registered at ClinicalTrials.gov (NCT 02729935).

Inclusion criteria were age ≥18 years and the American Society of Anesthesiologists (ASA) physical status I or II. Patients with cardiac, pulmonary, hepatic, or renal disease and those with a history of alcohol or other substance abuse were excluded.

The day before the surgery patients were instructed to the use of the visual analog scale (VAS; ranging from 0 cm = no pain to 10 cm = worst possible pain). We also educated patients concerning the symptoms of CRBD. No patient received premedication.

On arrival to the operating room, monitoring was performed using 5-lead electrocardiography, noninvasive blood pressure measurement, and pulse oximetry. Intravenous access was secured on the dorsum of the hand with an18-gauge cannula and patients were preloaded with 500 ml of 0.9% normal saline.

Patients were randomised using the sealed envelope method in a rater-blind manner to receive either parecoxib or placebo. For randomization, we referred to a random number table, with sequentially numbered, opaque, sealed envelopes used to conceal the allocation sequence. On the morning of surgery and before induction of anaesthesia, a "blinded" nurse prepared the study solutions. None of the other investigators involved in patient management or data collection were aware of the group assignment. Patients in group P were administered parecoxib sodium (Dynastat®, Pfizer Pharmaceutical) 40 mg (2 ml) intravenously (IV) 30min before spinal anaesthesia. Patients in group C were considered as placebo group and received an equal volume (2 ml) of normal saline 0.9%.

Lumbar subarachnoid block was administered with 2 ml 0.5% hyperbaric bupivacaine and 2.5 μg sufentanil. The need of additional intraoperative sedation (an IV bolus of Midazolam 1 mg) was recorded. At the end of the surgery, urinary catheterization was performed with a 16-Fr Foley's catheter, and the balloon was inflated with 10 ml of 0.9% NaCl. The catheter was fixed with an adhesive tape without any traction on the urethra. The bladder was continuously irrigated through the urinary catheter with normal saline. The Foley catheter was removed 24 h postoperatively.

The primary endpoint was the incidence of postoperative CRBD. Predefined secondary end points included the severity of CRBD, postoperative VAS pain scores, rescue analgesia requirements, and occurrence of adverse events.

CRBD was evaluated with a 4-point scale (1: no discomfort, 2: mild, revealed on questioning only, 3: moderate, stated by the patient without questioning, 4: severe, urinary urgency executed by behavioral responses, such as attempts to remove urinary catheter, restless extremity movements, verbal responses) 30 minutes and 1, 2, 4, 6, and 12 hours postoperatively.

In the PACU, additional postoperative analgesia was provided in the two groups by the combination of 1 g paracetamol IV (Perfalgan®, Bristol-Myers Squibb, Rueil-Malmaison, France) and 20 mg nefopam IV (Acupan®, Biocodex, Gentilly, France) in cases of severe and intolerant CRBD or VAS pain score >3. Good pain relief was defined as VAS score ≤3. Both rescue analgesics were administered on demand and recorded.

Adverse events were assessed using yes/no questions (Postoperative nausea and vomiting PONV, constipation, dizziness), vital signs (blood pressure, heart rate, oxygen saturation) were measured, and blood samples (haemoglobin, platelet count,

and serum creatinine measured at baseline and 24 h postoperatively) were collected. Blood loss was evaluated in terms of reduction in the serum haemoglobin level: delta haemoglobin defined as the difference between the preoperative haemoglobin level (Hb H0) and the haemoglobin level on first postoperative day 1 (Hb H24).

A previous study reported that approximately 60% of patients complained of CRBD due to an indwelling urinary catheter. Assuming that this incidence would decrease to 20% after treatment, we calculated that a sample size of 50 patients (25 per group) would be needed to achieve 80% power with a two-sided type 1 error rate of 5%.[8] We added 10 patients because we expected that 20% of all participants will be lost to follow-up or will drop out of the study.

Continuous variables were compared between the two groups using Mann–Whitney test. Incidence and severity of CRBD were compared by Fisher's exact test. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using STATA version 11.0 software (Stata Corp., College Station, TX, USA).

RESULTS

Sixty-one patients were selected and all patients completed the present study for the final analysis. Therefore, a total of 61 patients (control group = 32, parecoxib group = 29) were assessed in this study [Figure 1]. The two groups were comparable with respect to demographic data, ASA physical status, duration of surgery, and the duration of motor block [Table 1]. No additional intraoperative sedation and no systemic anaesthetic agents were required.

The incidence of CRBD was significantly lower in the parecoxib group than in the control group at 2, 4, 6, and 12 hours postoperatively [Table 2]. The number of patients who experienced moderate discomfort was significantly lower in group P compared with group C at 2, 4, 6, and 12 hours ($P < 0.05$). None of the patients in parecoxib group had severe discomfort [Table 2].

Median pain VAS scores were lower in the parecoxib group than in the control group at all times except the first hour [Table 2].

In group P, only one patient required rescue analgesia, whereas in group C, 16 patients needed additional doses of paracetamol and nefopam [Table 2].

None of the patients who received parecoxib experienced an adverse event. The heart rate and blood pressure were comparable among groups during the postoperative period. There were no significant differences between the two groups in terms of serum creatinine levels and perioperative blood loss estimated by the delta haemoglobin (preoperative haemoglobin H0 –haemoglobin on postoperative day 1) [Table 3].

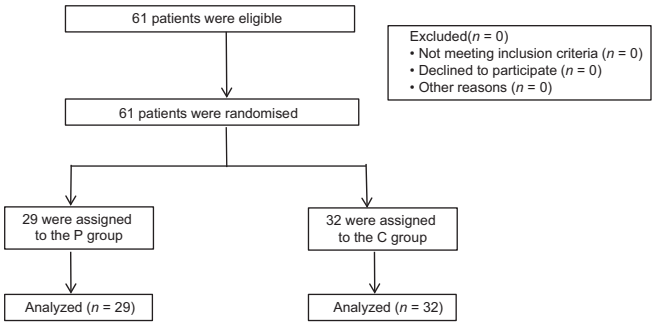

Figure 1: Study flow chart

DISCUSSION

We observed a significant reduction in the incidence and severity of CRBD in patients treated with parecoxib ($P < 0.05$). Our study also indicated that 50% of patients who were given saline required rescue analgesia after TURBT in the PACU.

TURBT is associated with a higher risk of CRBD compared with percutaneous nephrolithotomy and non-urologic surgery.[9] In our study, the incidence of CRBD was 60% in the control group. Several factors could explain this high incidence in our series –the predominance of male patients who have a longer urethra than female patients, the cumulative effects of large-sized Foley catheter, resection of the bladder wall, and postoperative continuous bladder irrigation.

Table 1:Baseline characteristics of study population

	Control (*n*=32)	Parecoxib (*n*=29)	*P*
Age (y)	66.4±11.2	64.2±9.8	0.492
Sex (M/F), *n*	30/2	28/1	1.000
Weight (kg)	74.9±6.4	75.4±11.3	0.490
ASA physical status (I/II), *n*	26/6	19/10	0.088
Duration of surgery (min)	64.4±34,4	62.9±26.1	0.839
Duration of motor block (min)	173.3±11.1	174.8±11.4	0.631

Values are expressed as mean±SD or *n* (%)

Table 2: Bladder discomfort, severity of pain and rescue analgesia requirements

	Group C (*n*=32)			Group P (*n*=29)			*P*	*P*†	*P*‡
	CRBD Yes/No	Grading of CRBD† 1/2/3/4	VAS‡ (0-10)	CRBD Yes/No	Grading of CRBD† 1/2/3/4	VAS‡ (0-10)	CRBD Yes/No	Grading of CRBD	VAS
H1	5/27	27/2/3/0	1 (0-4)	1/28	28/1/0/0	1(0-2)	0.198	0.421	0.064
H2	13/19	19/9/4/0	2 (0-4)	3/26	26/2/1/0	1(0-4)	0.009	0.028	0.008
H4	19/13	13/13/6/0	3(1-5)	4/25	25/3/1/0	1(0-3)	0.000	0.001	0.000
H6	18/14	14/13/4/1	2 (0-6)	4/25	25/3/1/0	1(0-5)	0.001	0.003	0.001
H12	15/17	17/12/2/1	2 (0-8)	3/26	26/2/1/0	1(0-8)	0.002	0.004	0.001
H24	7/25	25/5/2/0	1 (0-6)	1/28	28/0/1/0	1(0-2)	0.055	0.051	0.018
	Group C			Group *P*			*P*		
RA, *n* (%)	16/32 (50%)			1/29 (3.5%)			0.000		

Table 3: Incidence of adverse events during the first postoperative day

Variables	Control (*n*=32)	Parecoxib (*n*=29)	*P*
PONV *n* (%)	0	0	
Oxygen desaturation events (SpO_2<92%) *n* (%)	0	0	
Mean SBP in 24 h observation (mmHg)	124.85±13.02	120.64±11.05	0.216
Mean HR in 24 h observation (bpm)	76.01±8.01	74.74±8.84	0.590
Delta Hb (mg/dl) (H0–H24) median (min–max)	1(−1-4.9)	1(0.3-2.3)	0.890
Postoperative platelet count (10^9/l)	230.6±47.8	197.8±61.6	0.191
Number of patients receiving transfusion *n* (%)	0	0	
Postoperative creatinine concentration (µmol/l)	70.37±13.31	69.25±10.31	0.836

Values are expressed as mean ± SD or *n* (%). PONV: Postoperative nausea and vomiting. SBP: Systolic blood pressure. HR: Heart rate. Delta Hb (H0–H24): delta haemoglobin (preoperative haemoglobin H0- haemoglobin on postoperative day 1)

CRBD is an extremely distressing condition and interferes with the quality of recovery. Muscarinic receptor activation is the major mechanism in CRBD development. As it has already been reported, most anti-muscarinic agents have significant side-effects, especially in the elderly.[3,4,10,11] Other molecules, including analgesics (Paracetamol),[12] antiepileptic agents (Gabapentin),[13] and recently anaesthetics (Sevoflurane)[14] were found to be effective in reducing the incidence and the severity of CRBD compared with placebo.

Recently, another mechanism of CRBD was found to be mediated by increased urinary levels of PGE2. The presence of urinary catheter and the mucosal layer damage could trigger local inflammation with increased activation of cyclooxygenase-2 (COX-2) enzyme and release of prostaglandin E2.[15-18]

Considering this possible mechanism of CRBD, we hypothesised that the use of parecoxib, a highly selective COX-2 inhibitor, would improve the symptoms of CRBD. Parecoxib is a selective COX-2 NSAID, which is widely used for postoperative analgesia. It acts by reducing the surrounding inflammatory response, regulating nociceptors, and attenuating central sensitization.[19] It is an injectable inactive prodrug of valdecoxib. Regarding the pharmacokinetic properties, parecoxib had a rapid onset of action within 10–15 min and reached its maximum concentration around 30 min after administration. Pain is usually well controlled within 2 h after injection and the analgesic effect persisted for about 6–12 hours.[20,21] Parecoxib is recommended for controlling postoperative pain in a variety of surgery types, including gynecologic and orthopedic procedures.[22-24] However, there is a gap in the literature regarding the use of parecoxib sodium in bladder discomfort.

In our study, parecoxib sodium was administered before the resection because it has been shown that NSAIDS can inhibit the activation of nociceptors due to tissue damage.[25]

Regarding adverse events, parecoxib appears to be safe with some minor adverse effects such as haemodynamic changes associated with its administration.[26] However, these adverse effects were not observed in our study. No other serious adverse events, such as renal dysfunction or increased perioperative bleeding, were observed during the trial period.

Parecoxib tolerability can be explained by the fact the parecoxib sodium does not interfere with platelet aggregation compared to other non-selective NSAIDS.[27] Patients at risk of worsening of renal function and with severe renal impairment (creatinine clearance <30 ml/min) were not included in our study. Adverse renal effects increased with greater dose and duration of parecoxib administration, which is not the case with our study protocol.[28]

The limitations of this study include its single center design and the possibility of misperception between CRBD and suprapubic pain despite preoperative education. A standard dose (40 mg) was given to all patients, and we did not evaluate the effects of parecoxib with different doses.

CONCLUSION

In conclusion, we suggest that a single intravenous injection of parecoxib sodium 40 mg is safe and effective in decreasing the incidence and severity of CRBD in patients undergoing TURBT.

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Conflicts of interest
There are no conflicts of interest.

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