Intra-operative Oxycodone Reduced Postoperative Catheter-Related Bladder Discomfort Undergoing Transurethral Resection Prostate: A Prospective, Double Blind Randomized Study

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Purpose: To observe the efficacy of intravenously injected oxycodone intraoperative on postoperative urinary catheter-related bladder discomfort (CRBD).

Materials and Methods: Patients with ASA I-III who received trans-urethral resection of prostate under general anesthesia were observed. Patients who were randomized to the control group(C) (n = 45) received placebo and the group oxycodone(Q) received oxycodone (n =46) 0.03mg/kg of oxycodone before the end of operative 10min. The incidence and severity (mild, moderate, severe) of CRBD were assessed at 0, 1/2 h, 2 h and 6 h postoperatively. VAS scores were used to assess pain intensity during the same period. Postoperative PCA analgesic sufentanil dose and the incidences of nausea, vomiting, dizziness, over sedation were recorded in these patients.

Result: Compared with the control group, the incidence of CRBD was significantly lower in the oxycodone group at 0 [22 (49 %) vs. 10 (22%); *P* = .007], 1/2h [18 (40%) vs. 9 (20%); *P* = .033], 2h [11 (24%) vs. 4 (9%); *P* = .001]. The severity of CRBD at 0 [mild, 9 (38%) ; moderate 9 (20%), severe 4 (9%)] was lower in the group Q than the controlled group [mild, 4 (38%) *P* = .023; moderate 5 (11%), *P* = .034, severe 1 (2%), *P* = .012]. 1/2 h [mild, 11 (24%) Vs 5(11%), P = .020]. Compared with the group C, VAS scores were lower in group Q at 0, 1/2h (*P* = .001) and significantly decreased sufentanil dosage within 6h (*P* = .001). There were no significant differences in the incidence of postoperative adverse effects between two groups.

Conclusion: Oxycodone can effectively prevent patients with CRBD after TURP without incurring serious adverse effects.

Keywords: oxycodone; catheter-related bladder discomfort; postoperative, complication; trans-urethral resection prostate; visual analgesic score

INTRODUCTION

Patients with urinary bladder catheterization frequently complain of catheter-related bladder discomfort (CRBD) postoperatively.[1] CRBD is a common and distressing complication that often occurs in post-anesthesia care unit(PACU). CRBD causes irritability and delirium, aggravates pain, and reduces the quality of recovery.[2] Many risk factors for CRBD have been indentified in previous studies such as male sex, diameter of the Foley catheter, and types of operations.[3,4] In our previous study, we have observed a high occurrences of CRBD in female patients underwent laparoscopic hysterectomy.[5]

Unlike postoperative pain, CRBD may be resistant to conventional analgesic therapy such as opioids, because a different underlying mechanism is involved. Many agents, including the muscarinic receptor blockers such as Oxybutynin, tolterodine, tramadol and butylscopolamine[6-9] and central nerves system inhibitors such as ketamine and gabapentin[10,11], have been investigated as approaches in the prevention or treatment of CRBD. But various side-effects of these agents limited their use. Oxybutynin, tolterodine, are oral agents with various anticholinergic side-effects.[6,7] Tramadol and ketamine were effective for the prevention and treatment of CRBD, but these agents can cause sedation after operation.[8,10,11]

Oxycodone is a semi-synthetic opioids prepared from opium alkaloidthebaine plant derivative.[12] Its μ and κ dual-receptor agonism has a unique effect in the treatment of visceral pain.[13-15] We have reported that oxycodone was effective for the treatment of CRBD after laparoscopic hysterectomy in our previous study.[5] But the effects for CRBD during TURP has no investigated. We conducted a prospective, double-blind randomized, single-center study to investigate whether oxycodone has preventive effects on early postoperative CRBD after TURP.

MATERIALS AND METHODS

Study Population

This prospective, randomized, double-blind and placebo controlled study was performed after approval from

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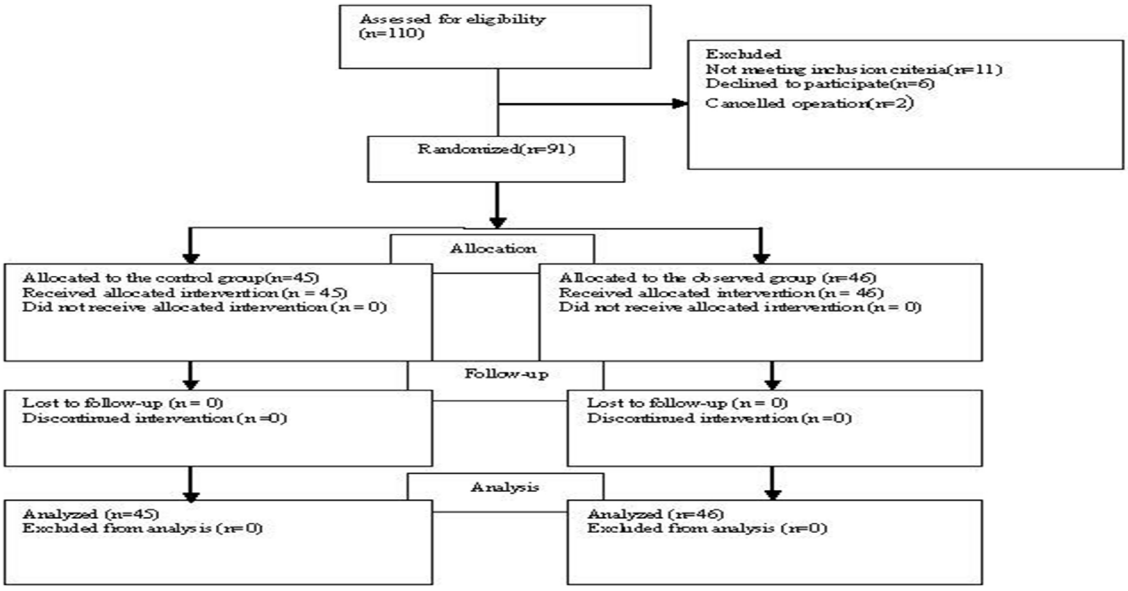

Figure1. Patient flow diagram

ethic committee of Wenzhou people's hospital, number: 2016003. The protocol for this clinical trial was registered at CHICTR.ORG.CN (ChiCTR-IPR-16008814). During preoperative visit, all patients provided informed consents and were educated about the symptoms of CRBD (characterized as a burning sensation with an urge to void or as discomfort in the suprapubic area).

Inclusion and exclusion criteria

Patients with an ASA physical status I to III, who were scheduled to transurethral resection prostate, were included. Patients were excluded if they had a history of severity heart disease, lung disease, psychiatric disease, chronic pain or long-term administration of analgesics.

Procedures

Patients were randomly assigned to one of two groups (control(C) or oxycodone(Q)) with the help of a computer generated random number table. The assignments were concealed in opaque envelopes and opened immediately before induction by a nurse who was blinded to this study and was responsible for preparing the study drugs. All medications were administered in identical 2 mL syringes.

All patients had no premedication, standard monitoring consisted of ECG, non-invasive arterial pressure (NIBP), and pulse oximetry (SpO2). Anesthesia was induced with 0.05 mgkg midazolam, 4μg/kg fentanyl, 1.5 mg/kg propofol and 0.6mgkg-1rocuronium. Intraoperative maintenance anesthesia relied on intravenous anesthesia; remifentanil infusion were maintained 0.2 μg/kg/min; intraoperative propofol infusion rate was adjusted to maintain BIS value within 40-60; rocuronium was intermittently injected. 10min before the end of operative, the group controlled received same volume normal saline, whereas the oxycodone group received intravenous inject oxycodone 0.03mgkg-1(product batch number: AW259, Mundipharma, Britain). 22/24 Foley urinary catheter was inserted and 5 mL sterile normal saline was injected into the balloon at the end of operation. After the surgery, 0.5 mg atropine and 1 mg neostigmine were administered to antagonize residual muscle relaxation. These patients were transferred to PACU after the endotracheal catheter was removed. PCIA analgesia was postoperatively applied. The analgesic was 100 μg sufentanil added to 100ml normal saline, the background infusion was 1 mL per hour, the predetermined time was 8 min and the volume of each press was 2 mL.

Table1. Characteristics of patients, anesthesia and surgery.

A	Con group	Oxy group	*P* value
Age (yr)	71 ± 8	74 ± 9	.577
BMI (kg/m^2)	24 ± 6	26 ± 5	.087
ASA class (I~II/III)	32/14	34/11	.522
Urinary catheter size (F22/F24)	26/20	28/17	.580
Duration of anesthesia (min)	118 ± 25	123 ± 32	.409
Duration of surgery (min)	101 ± 24	105 ± 18	.372
Time to extubation (min)	7.1 ± 1.6	7.7 ± 2.2	.140
Intraoperative remifentanil resumption (mg)	1.84 ± 0.25	1.79 ± 0.32	.409
Intraoperative propofol resumption (mg)	697 ± 185	731 ± 223	.431

[a] Data are presented as mean ± SD or number (percent)

Abbreviations: BMI, Body Mass Index□ASA, American society of anesthetists

Table 2. Incidence and severity of postoperative CRBD, VAS scores and sufentanil consumptions 6 h after operation

A	Group Group Oxycodone				Group control			
Time (h)	0	1/2	2	6	0	1/2	2	6
CRBD	10	9	9	5	22	18	16	12
CRBD severity								
Mild	4	5	3	2	9	11	7	4
Moderate	5	3	1	1	9	5	3	1
Severe	1	1	0	0	4	2	1	0
Postoperative VAS value	3.05 ± 0.14	2.61 ± 0.66	1.79 ± 0.67	1.75 ± 0.17	6.72 ± 0.21	4.89 ± 0.14	3.52 ± 0.33	3.06 ± 0.41
Sufentanil consumption(ug)	8.2 ± 0.85				12.1 ± 1.16			

[a] Data are presented as mean ± SD or number (percent)

Abbreviation: CRBD, catheter related bladder discomfort

Evaluations

The primary outcome was defined as the reduction in the severity of CRBD.[7] Occurrences and severity of bladder discomfort was recorded as: none, when patients did not complain of any CRBD on questioning; mild discomfort, patients were reported CRBD on questioning only; moderate, urge to pass urine reported by the patient without questioning; severe discomfort, urge to pass urine accompanied by behavioral responses, such as flailing limbs, strong vocal responses or attempts to pull the catheter out.

Secondary outcomes were time to extubation, sufentanil consumption, heart rates (HRs), mean arterial pressure (MAP) in PACU, and adverse effects included PONV, over sedation, dry mouth and facial flushing. All these outcomes were assessed at 0, 1/2 h, 2, and 6 h after administration of the study drug by blinded assessors.

VAS scores were used to assess pain in these patients: 0 point, no pain; 10 points, unbearable pain. The Ramsay Sedation Scale was measured postoperatively at 0, 1/2 h, 2, 6 hand recorded as follows: 1 (anxious, agitated or restless); 2 (cooperative, oriented and tranquil); 3 (responds to commands, asleep); 4 (brisk response to light glabellar tap or loud noise); 5 (sluggish response to light glabellar taps or loud noise); or 6 (no response). Patients with a sedation scale score of at least 4 were considered over sedation.

The patients with severe vomiting received intravenous injection of 4 mg ondansetron. Analgesic doses received by the two groups of patients within 6 hours after the operation were recorded.

Statistical analysis

According to a previous study, 53% of patients complain of CRBD postoperatively.[7] Assuming that this incidence would decrease to 15% after intervention, we calculated that 36 patients would be needed in each group to achieve statistical significance (α = .05 and β = .20). Considering a 20% dropout rate, 91 patients per group were included.

All data were analyzed with SPSS16.0 software package(SPSS, Inc., Chicago, IL,USA). The severity of CRBD were analyzed by Mann-Whitney *U* test, HR and MAP over time between the groups were analyzed by repeated measures analysis of variance (ANOVA) and then t-test was used to compare values at each time point. Rescue analgesics was analysed by t-test. Analyses of categorical variables (incidence of side effects) were performed by χ^2 or Fisher's exact-tests. Data were analyzed according to the intention-to-treat principle. $P < 0.05$ indicated statistically significant differences.

RESULTS

110 patients from August 2016 to December 2016were screened for inclusion in the study. Nineteen patients were excluded [not meeting inclusion criteria (n = 11), declined to participate (n = 6), cancelled operation (n = 2)]. The remaining 91 patients comprised the study group (**Figure 1**). No differences in the demographic characteristics of the groups were observed (**Table 1**). Compared with the control group, the incidence of CRBD was significantly lower in the group Q at 0 [22(49%) vs. 10 (22%); *P* = .007], 1/2h [18 (40%) vs. 9(20%); *P* = .033], 2 h [11 (24%) vs. 4(9%); *P* = .001], respective.

The severity of CRBD at 0 [mild, 9 (38%) ; moderate 9 (20%), severe 4 (9%)] was lower in the group Q than the controlled group [mild, 4 (38%) *P* = .023; moderate 5 (11%), *P* = .034, severe1 (2%), *P* = .012]. 1/2 h [mild, 11 (24%) Vs 5(11%), *P* = .020]. (**Table 2**)

The difference in VAS scores in 0 and 1/2h in group Q was significance lower compared with group C (*P* = .001). Sufentanil dosage within 6 hours after the operation was lower in observation group than in control group (*P* = .001). There were no statistical significant differences in MAP, HR and SPO2 in any period be-

Table 3. Patients' vital signs of preoperative and postoperative

A	Group	T0	T1	T2	T3	T4
MAP (mmHg)	Group C	88 ± 22	82 ± 19	85 ± 18	74 ± 16	72 ± 22
	Group Q	92 ± 18	75 ± 7	76 ± 12	77 ± 18	74 ± 18
HR (bpm)	Group C	78 ± 12	65 ± 8	71 ± 7	73 ± 8	72 ± 8
	Group Q	82 ± 10	63 ± 9	75 ± 7	68 ± 8	65 ± 8
SpO2 (%)	Group C	97 ± 2	98 ± 1	98 ± 2	96 ± 2	99 ± 1
	Group Q	98 ± 1	96 ± 2	97 ± 2	98 ± 2	98 ± 1

[a] Data are presented as mean±SD

Table 4. The incidence of adverse reactions postoperative

A	Group C	Group Q	*P* value
Over-sedation	1(2%)	3(7%)	.317
Nausea 1(2%)	3(7%)	.317	
Vomiting	1(2%)	2(4%)	.570
Dizziness	3(7%)	5(11%)	.479

[a] Data are presented as number (percent)

tween two groups (**Table 3**).
During this study, 3 cases (7%) in trial group and 1 case (2%) in control group experienced over-sedation (P = .317); There were no significant differences nausea [3(7%) vs. 1 (2%); *P* = .317], and vomiting [2 (4%) vs. 1 (2%); *P* = .570] between group Q and group C. The difference in dizziness between twogroups had no significance [5 (11%) vs. 3 (7%); *P* = .479] (**Table 4**).

DISCUSSION

We have demonstrated that intraoperative oxycodone reduces the incidence and severity of postoperative CRBD and postoperative opioid requirements in patients undergoing TURP.
CRBD is one of the most important factors causing postoperative irritability. The incidence of CRBD in previous studies was reported with various ranges of 64 to 90% after general anesthesia in varies operations. In this study, 28 (60%) of 46 patients in the control group complained of CRBD at 6 h postoperatively undergoing TURP, which is lower than the incidence of CRBD after urological operations, and according to the previous study. The causes for CRBD include urethral mucosa injury due to urethral catheterization, the central nervous system is in the inhibitory state and the patients psychologically reject catheter-related discomfort. Gynecological endoscopic procedures and retraction the uterus through the vagina may irritate the neck of bladder, constituting one of the causes for occurrence of CRBD. The peripheral nerves of lower urinary tract consist of sacral parasympathetic nerve, thoracolumbar sympathetic nerve and sacral-pudendal nerve.[16] Previous studies had shown that application of muscarinic subtype 3 receptor inhibitors Oxybutynin, tolterodine, can substantially reduce the risk or severity of CRBD. But these drugs have many adverse effects, such as dry mouth, dizziness and facial flushing, that cannot be fully avoided.[6-8,10] CNS acting drugs and opiods receptors agonists ketamine, pentazocine, tramadol, were effective for the prevention and treatment of CRBD, but these agents can cause sedation and PONV after operation.[11]
Oxycodone is μ and κ opioid receptor dual agonist. It can be used intraoperatively and postoperatively to relieve pain, especially with unique analgesic effect on visceral pain.[17,18] The onset of iv. oxycodone is 2-3 min, with a peak effect at 5min, and a elimination halt effects ranged from 4-6 h. In our study, we administered oxycodone 0.03mg/kg, which is used to treatment of acute pain postoperative single injection, reduced the postoperative incidence of CRBD at 0, 1, 2, and 6h respectively. The mechanism of oxycodone action in the treatment of CRBD may include: Firstly, oxycodone activates κ receptor to effectively relieve pain induced by spasms of vesical neck and urethra mucosal injury in patients. Secondly, oxycodone acts on central nervous system to regulate and control the central excitability of vesical afferent reflex and sacral reflex, leading to reduced sensitivity to CRBD in patients. Thirdly, the inhibitory effect of oxycodone on M1 and M3 muscarinic receptors is not yet confirmed, but previous studies showed that tramadol, a drug similar to oxycodone, was able to inhibit M1 and M3 muscarinic receptors to effectively prevent the occurrence of CRBD in addition to its opioid receptor agonism.[8] I.V. oxycodone was clinically effective for the treatment of CRBD as an antimuscarinic agent, but an inhibitory action of oxycodone on the activity of the detrusor muscle has not been reported in animal or human studies. Further experiments in these areas are warranted. This study showed that oxycodone could reduce VAS scores and PCA dosage in all postoperatively periods, suggesting that oxycodone was able to relieve postoperative pain and reduce postoperative analgesic dosage in addition to its efficacy on CRBD. There was no significant difference of extubation time. 3 cases in the observed group and 1 case in the control group had finger pulse oxygen saturation less than 90%, the condition returned to normal after oxygen inhalation through the mask. Compared with the controlled group, the incidence of nausea and vomiting was not higher in the oxycodone group. There were no significant differences in other adverse reactions such as dizziness and sedation between the two groups. Several limitations of the current study should be considered. First, a single dose of 0.03 mg/kg oxycodone was used in this study. We did not evaluate the dose–response effect of oxycodone for the prevention of CRBD. In our previous study, however, it was shown that increase dose of oxycodone could result in adverse effects of vomiting and dizziness.[19] Secondly, various agents are routinely used to decrease CRBD. In this study, however, a direct comparison between the effect of oxycodone and others agents on the incidence of CRBD was not performed.

CONCLUSIONS

Intravenous injection of 0.03mg/kg oxycodone 10 minutes before the end of operation can effectively prevent the occurrence and severity of CRBD, decrease PCA dosage, and reduce VAS scores without causing severe adverse reactions in these patients after the operation.

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CONFLICT OF INTEREST

No other competing interests declared.

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