Dexmedetomidine reduces Catheter-Related Bladder Discomfort: A Prospective, Randomized, Placebo-Controlled, Double-Blind Study

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Objective: To evaluate the efficacy of dexmedetomidine in preventing catheter-related bladder discomfort (CRBD) in a postanesthesia care unit (PACU).

Methods: A total of 138 consecutive adult male patients, classified by the American Society of Anesthesiologists (ASA) as ASA class I and ASA class II, were scheduled for elective open upper-middle abdominal surgery. They were randomized into 2 groups, C and D, comprising 69 patients each. Group C was given a saline solution as placebo, and group D received dexmedetomidine. Either placebo or drug was administered intravenously at 0.5 μg/kg as each patient's abdomen was being closed. After induction of anesthesia, each patient was catheterized with a 16F Foley catheter and the balloon inflated with 10 mL of distilled water. In the PACU, the incidence and severity (mild, moderate, or severe) of CRBD were assessed 0, 1, 2, and 6 hours after extubation. Postoperative pain (numeric rating scale) and sedation level (Ramsay score) were also assessed at the same time points. The incidence of adverse clinical events after the injection of dexmedetomidine or placebo was monitored.

Results: Measured at 0, 1, 2, and 6 hours after extubation, the incidence and severity of CRBD in postoperative group D were significantly reduced compared with those of group C ($p<0.01$). Dexmedetomidine also helped to relieve postoperative pain and induce deeper sedation 0 and 1 hour after extubation ($p<0.05$). No significant differences in adverse events other than bradycardia and hypotension were observed in group D ($p<0.05$).

Conclusion: Dexmedetomidine (0.5 μg/kg IV) administration during surgery reduced the incidence and severity of CRBD in the PACU without causing significant side effects. [*P R Health Sci J 2016;35:191-196*]

Key words: Dexmedetomidine, Catheter-related bladder discomfort, General anesthesia, Procedure, Urinary catheterization

Catheter-related bladder discomfort (CRBD) secondary to the use of an indwelling urinary catheter is one of the most distressing symptoms patients experience during recovery from anesthesia in the immediate postoperative period. Such patients characterize it as an urge to void or discomfort in the suprapubic region. The symptoms of CRBD, which are due to catheter-related bladder irritation, mimic those of an overactive bladder (OAB): urinary frequency and urgency with or without urge incontinence(1,2). It has been reported that 27% to 55% of the patients in the postanesthesia care unit (PACU) who have undergone intraoperative bladder catheterization suffer from moderate or severe CRBD(3,4), whereas mild CRBD is experienced by more than 80% of such patients. Because this condition is as a major cause of postoperative agitation(5), recent studies have evaluated various drugs in the prevention and treatment of CRBD, including ketamine(6), gabapentin(7), butylscopolamine(8), tramadol(9), oxybutynin, and tolterodine(4). However, these work involves 2 major concerns and limitations. First, bladder irritation and discomfort experienced by patients after urinary surgery, as in the studies mentioned, can be due to the surgical procedure directly. In other words, the effects of those drugs in nonurinary surgeries are not clear. Second, none of the studied drugs have been shown enhance the effects of general anesthesia, whereas dexmedetomidine, as an ancillary drug for general anesthesia, can maximize the efficacy of the anesthetic, thereby reducing the need for additional sedatives and/or analgesics. In clinical practice we noticed that patients given dexmedetomidine were

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less agitated after surgery. However, the mechanism underlying this observation is not clear, although it has been reported that dexmedetomidine has a sedative effect. Our hypothesis is that by blocking the sensory input from the lower urinary tract and suppressing the sympathetic nervous system, dexmedetomidine reduces bladder tone and thus relieves CRBD. In the present study we sought to evaluate the efficacy of dexmedetomidine in preventing or reducing the incidence and severity of CRBD in the PACU.

Materials and Methods

This was a randomized controlled trial conducted at the Second Xiangya Hospital of Central South University, a tertiary university-affiliated hospital that had 3500 beds with more than 40 clinical departments in Changsha, Hunan Province, PRC. For this prospective randomized double-blind placebo-controlled study, approval was obtained from the Medical Ethics Committee of the hospital as well as written informed consent from the patients. A total of 138 ASA class I and II male patients were recruited, all of whom were scheduled for elective open upper-middle abdominal surgery requiring catheterization of the urinary bladder.

Exclusion criteria included age >60 years, chronic opioid use, bladder outflow obstruction, OAB (frequency >3 times in the night or >8 times in 24 hours), neurogenic bladder, diabetes mellitus, Parkinson's disease, or end-stage renal disease (urine output <400 mL in 24 hours), and abnormal liver function (Child-Pugh score ≥7).

All the patients received phenobarbital (100 mg IM) and atropine (0.5 mg IM) 30 minutes before the induction of anesthesia. With the help of a computer-generated table of random numbers, they were randomized into 2 groups, C and D, of 69 patients each. Group D received dexmedetomidine (0.5 μg/kg IV) (Jiang Su Heng Rui Medicine Co., Ltd., China) at the rate of 5 μg/kg per hour as the abdominal cavity was being closed; group C (control) received saline solution administered in the same way. Anesthesia was induced with midazolam (0.04 μg/kg), sufentanil (0.3 μg/kg), and propofol (1.5 mg/kg). Orotracheal intubation was facilitated with cis-atracurium (0.2 mg/kg). Urinary bladder catheterization was implemented with a 16F Foley catheter lubricated with paraffin oil and its balloon was inflated with 10 mL of distilled water. Thereafter, to prevent traction, the catheter was fixed with adhesive tape in the suprapubic region. Anesthesia was maintained with propofol infused at the rate of 50 to 200 μg/kg per minute as well as intermittent sufentanil and cis-atracurium as required, with standard ASA monitoring. At the conclusion of surgery, postoperative nausea and vomiting were prevented with tropisetron (5 mg), while neuromuscular blockade was reversed with neostigmine (0.04 mg/kg) and atropine (0.02 mg/kg). After satisfactory recovery, the patients were extubated and offered intravenous sufentanil via a patient-controlled analgesia system set to deliver a bolus dose of 1 μg (1 mL) with a 10-min lockout interval and background infusion of 1.5 μg/h. Patient bladder discomfort was evaluated at the time of extubation and again at 1, 2, and 6 hours postoperatively by an anesthesiologist who was unaware of the type of medication received by the patient. The severity of CRBD was graded according to the method described by Agarwal(5),with the degree of bladder discomfort set as severe (subjective complaint with behavioral abnormalities such as flailing limbs, pulling out of catheter, or loud vocalization) or moderate (complaint without questioning and no behavioral abnormalities).When interviewed in the PACU, in order to exclude pain caused by previous procedures, patients reporting discomfort were required to point to the affected region. Confirmed complaints of bladder discomfort (urge to urinate or discomfort in the suprapubic area) were classified as mild bladder discomfort.

Postoperative pain was assessed at 0, 1, 2, and 6 hours after extubation using a verbal numeric rating scale (NRS-11). Patients were asked to rate their pain on a scale from 0 to 10, where 0 represents "no pain" and 10 represents "the worst pain possible," using whole numbers (11 integers including 0). The same registrar observed patients postoperatively for sedation using the Ramsay score (from 1 to 6)(10).

To assess possible adverse reactions caused by dexmedetomidine, multiple clinical indexes were quantified and compared between the 2 groups, including the incidence of nausea, vomiting, hypotension (systolic blood pressure <90 mmHg, or 30% lower than preinfusion values, or diastolic blood pressure <50 mmHg), hypertension (systolic blood pressure >180 mmHg, or 30% higher than preinfusion values, or diastolic blood pressure >100 mmHg), bradycardia (heart rate <60 beats per minute, or 30% lower than preinfusion values), respiratory depression after extubation (respiratory rate <8 breaths per minute, or SpO2 <90), and excessive sedation (Ramsay score of 5 or more).

Statistical analysis

The incidence of CRBD (58%) at 1 hour after extubation was ascertained from Agarwal's study (4) and applied in the sample size calculation. At least a 25% difference in incidence rate between groups C and D was considered to be clinically significant. Given $\alpha = 0.05$ (statistically significant level), $\beta = 0.2$ (power of a test), a sample size of 69 subjects in each group was calculated by STATA 12.0 (Stata Corp, College Station, Texas). A flowchart of the study's progress is presented in Figure 1.

Quantitative variables were compared by student's t-test. The incidence of bladder discomfort and related adverse clinical events was analyzed by Fisher's exact test, while the severity of discomfort (mild, moderate, or severe), postoperative pain (NRS-11), and sedation level (Ramsay score) were analyzed with the Mann–Whitney test. SPSS 15.0 (SPSS Inc., Chicago, Illinois) was used for statistical analysis. A p-value of less than 0.05 was considered significant.

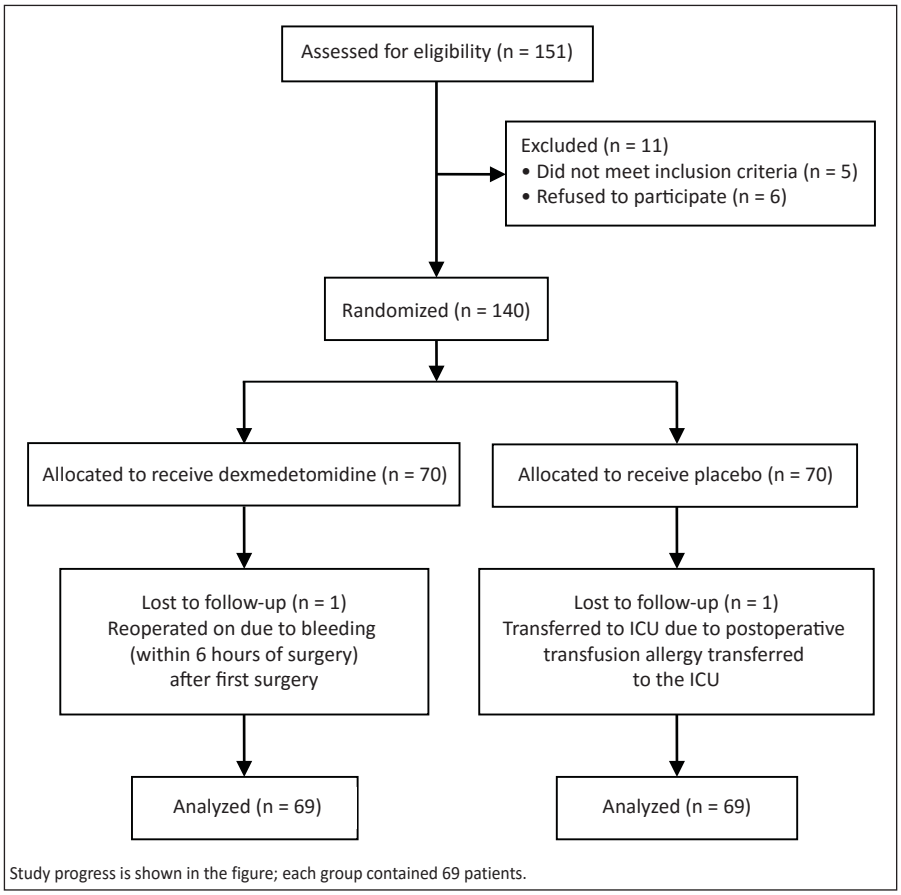

Figure 1. Flowchart of study progress

Results

There were no significant differences between groups C and D in general characteristics as reviewed based on age, weight, duration of surgery, or sufentanil use (p>0.05; Table 1).

At 0 hours after extubation, the incidence of CRBD in group D was reduced to 23%, compared with 74% in group C (p<0.05; Table 2). The absolute risk reduction in group D was 51% at this time point. At 1, 2, 6 hours after extubation, the incidence of CRBD in group D remained at a level significantly lower than that in group C (p<0.05). The severity of CRBD was also reduced in group D at all the time points evaluated in this study (p<0.05).

Table 1. Demographic data, Duration of surgery, and Sufentanil requirement

Groups	Control	Dexmedetomidine
Number of patients	69	69
Age (years)	42.1 ± 10.5	39.8 ± 9.7
Weight (kg)	60.7 ± 10.8	62.5 ± 11.0
Duration of surgery (min)	160 ± 28	167 ± 31
Intraoperative sufentanil Requirement (μg/kg)	0.72 ± 0.06	0.68 ± 0.05

Data are presented as number of patients or mean ± standard deviation.

Postoperative pain was assessed with NRS-11 (Table 3); the postoperative sedation level was quantified with the Ramsay score in the same cohorts of patients (Table 4). Compared with patients in group C, patients in group D showed better pain control and deeper sedation.

We also assessed the incidence of potential adverse reactions to dexmedetomidine, as shown in Table 5. Bradycardia, hypotension, hypertension, nausea/vomiting, respiratory depression, and oversedation were reviewed; among these indexes, only bradycardia and hypotension were significantly different in group D as compared with group C (p<0.05).

Discussion

On the basis of percentages given in Agarwal's study, in our study patients in group C experienced a higher incidence of CRBD (68% at 1 hour after extubation) compared with the expected incidence (58% at 1 hour after extubation)(4). A plausible explanation could be that all of the patients in the present study were male, since Binhas(3) has pointed out that male gender is an independent risk factor for CRBD. Our study demonstrated that the administration of dexmedetomidine (0.5 μg/kg IV) at the conclusion of the surgery could reduce the incidence and severity of CRBD in the PACU without causing severe drug-related adverse events. Dexmedetomidine hydrochloride is an alpha2 adrenergic receptor agonist with high efficacy and selectivity(11). Alpha2 adrenergic receptors are distributed widely throughout the central and peripheral nervous systems, including autonomic ganglia; therefore dexmedetomidine can enhance sedation, analgesia, and inhibition of sympathetic nerve activity by activating alpha2 adrenergic receptors.

Based on these facts we hypothesized that dexmedetomidine would reduce the incidence and severity of CRBD through its suppressing effect on the central and peripheral nervous systems.

Bladder sensation is generated by cerebral cortex as it perceives afferent nervous signals originating from the lower urinary tract. The mechanisms underlying the pathogenesis of micturition and its related disorders are still unclear. Micturition is fundamentally a spino-bulbo-spinal reflex facilitated and inhibited by more advanced brain centers, such

Table 2. Incidence and Severity of CRBD

Time (h)	0		1		2		6	
Groups	Control	DEX	Control	DEX	Control	DEX	Control	DEX
Number of patients	69	69	69	69	69	69	69	69
No discomfort	18 (26)	53 (77)*	22 (32)	55 (80)*	28 (41)	55 (80)*	36 (52)	54 (78)*
Discomfort	51 (74)	16 (23)*	47 (68)	14 (20)*	41 (59)	14 (20)*	33 (48)	15 (22)*
Grading of discomfort								
Mild	19 (28)	10 (14)*	21 (30)	11 (16)*	22 (32)	11 (16)*	21 (30)	13 (19)*
Moderate	25 (36)	6 (9)*	20 (29)	3 (4)*	15 (22)	3 (4)*	11 (16)	2 (3)*
Severe	7 (10)	0 (0) *	6 (9)	0 (0)*	4 (6)	0 (0) *	1 (2)	0 (0)

Data are presented as number of patients (percentage), DEX denotes Dexmedetomidine, *p<0.05 in intergroup comparison.

Table 3. Severity of pain, by verbal numeric rating scale (NRS-11) (presented as median With interquartile range)

Time (h)	0		1		2		6	
Groups (n = 69)	Control	DEX	Control	DEX	Control	DEX	Control	DEX
NRS-11 (0-10)	3 (2.0-4.0)	1.5* (1.0-2.0)	2.5 (2.0-4.0)	2* (1.75-3.0)	2.5 (2.0-3.0)	2.5 (2.0-3.0)	2 (1.0-2.0)	2 (1.0-2.0)

DEX denotes Dexmedetomidine, *p<0.05 during intergroup comparison

Table 4. Sedation level, quantified by Ramsay score (presented as median with interquartile range)

Time (h)	0		1		2		6	
Groups (n = 69)	Control	DEX	Control	DEX	Control	DEX	Control	DEX
Ramsay score (1-6)	3 (1.75-3.0)	3* (2.0-4.0)	2.0 (2.0-3.0)	2.0* (2.0-3.0)	2.0 (2.0-2.0)	2.0 (2.0-2.0)	2.0 (2.0-2.0)	2.0 (2.0-2.0)

DEX denotes Dexmedetomidine, *p<0.05 during intergroup comparison

as the pontine micturition center(12). The completion of the physiological reflex pathway is dependent on both brain function and the firing rate of sensory fibers from the bladder and urethra(12). The neural signals generated by the bladder and urethra are transmitted to midbrain periaqueductal gray substance through the spinal cord, then projected to the pontine micturition center and the cerebrum(13). When the activity of this pathway passes a threshold, the urge to void becomes difficult to ignore. Meanwhile the flow of urine through the urethra plays an overall excitatory role itself, promoting voiding in a positive feedback loop until the bladder has been emptied(14). An indwelling urinary catheter may stimulate the mucous membrane of the urethra and thus initiate the micturition reflex, leading to an urgent need to urinate; this may be one of the key mechanisms in the pathogenesis of CRBD. Dexmedetomidine appears to have a sedative effect on the locus ceruleus, lateral parabrachial nucleus, pontine nuclei, pontine tegmental reticular nucleus, and lateral septal nucleus(15). At the same time it lowers the level of consciousness and reduces the cerebral cortex's sensitivity to signals from lower urinary tract, thereby ameliorating the symptoms of CRBD.

Dexmedetomidine inhibits the activity of the sympathetic nervous system and decreases bladder tension, thereby reducing the transmission of afferent impulses. In 1992, Harada proved that dexmedetomidine inhibits the micturition reflex activated by high bladder volume in rats(16). In 1993, Harada further demonstrated that dexmedetomidine reduces detrusor muscle tone and pressure in the bladder(17). Inhibition of the sympathetic nervous system by dexmedetomidine decreases sympathetic tone, mainly by selectively activating the postsynaptic α2 adrenergic receptors in the central nucleus tractus solitarius, thereby preventing sympathetic neurons in the anterior lateral horn of the spinal cord from transmitting impulses(17). The bladder's detrusor muscle is controlled by sacral parasympathetic preganglionic neurons and lumbar sympathetic preganglionic neurons(18). During the storage phase, these afferent neurons fire at low frequencies because the bladder wall is insufficiently stretched. High-frequency afferent signals generated by a stretched urinary bladder wall initiate contraction of the bladder by simultaneously exciting sacral parasympathetic preganglionic neurons and inhibiting lumbar sympathetic preganglionic neurons. Afferent inputs induce contraction of the sphincter by the excitation of Onuf's nucleus; contraction of the bladder neck and urethra is initiated by the excitation of sympathetic preganglionic neurons. Dexmedetomidine may reduce the generation of excitatory signals from the bladder, thereby preventing pontine micturition center and cerebrum from initiating the impulse to urinate.

Table 5. Incidence of adverse clinical events after injecting Dexmedatomidine or Placebo

Groups	Control	DEX
Number of patients	69	69
Bradycardia	0 (0)	32* (46)
Hypotension	0 (0)	4* (6)
Hypertension	0 (0)	2 (3)
Nausea and vomiting	4 (6)	3 (4)
Respiratory depression	0 (0)	0 (0)
Oversedation	0 (0)	0 (0)

Data are presented as number of patients (percentage), DEX denotes Dexmedetomidine, *p<0.05 during intergroup comparison

In this study, extubation was performed at about 40 minutes after the administration of dexmedetomidine. The NRS-11 values at 0 and 1 hour after extubation in group D were lower than those in group C; at the same time points the Ramsay scores were higher in group D, and there was no significant difference between the 2 groups at 2 and 6 hours after extubation. However, the incidence and severity of CRBD were significantly reduced in group D at each time point (0, 1, 2, and 6 hours) compared with group C. We also noticed that the incidence and severity of CRBD decreased in the control group with the passage of time after extubation.

Although Ramsay scores were higher in group D, no instance of oversedation was observed in either group. In the present study, no patients had orientation problems after waking up and all were able to clearly report any discomfort they might be having. Thus our results suggest that dexmedetomidine does not reduce CRBD simply by compromising the patients' ability to perceive discomfort. Besides the sedative effect of dexmedetomidine, other mechanisms may also be involved in reducing the incidence of CRBD, since sedatives such as midazolam or propofol had no significant effect in the prevention of CRBD.

Although the incidence of bradycardia was higher in group D, bradycardia that affects hemodynamic stability (heart rate <45 beats per minute or bradycardia accompanied by hypotension) was not observed. Several patients suffered from episodes of transient hypotension or hypertension and were stabilized quickly by treatment with ephedrine or nitroglycerin. We therefore concluded that the effect of dexmedetomidine on hemodynamic stability was acceptable and easily managed, which supports the practicability of our proposal to use dexmedetomidine in preventing CRBD.

Conclusions

We evaluated the effect of dexmedetomidine in preventing or ameliorating CRBD in patients after open upper-middle abdominal surgeries. However, detailed data demonstrating the dose-effect relationship were not collected in this study. We suggest that a comparative study be conducted between dexmedetomidine and other anticholinergic drugs, such as oxybutynin chloride and tolterodine. In conclusion, the single use of dexmedetomidine (0.5 μg/kg IV) can safely reduce the severity and incidence of CRBD.

Resumen

Objetivo: Evaluar la dexmedetomidina para prevenir molestias en la vejiga relacionada con el catéter (CRBD, por sus siglas en inglés) en una unidad de cuidado post-anestesia (PACU, por sus siglas en inglés). Métodos: Un total de 138 pacientes masculinos adultos consecutivos clasificados por la Sociedad Americana de Anestesiología (ASA, por sus siglas en inglés) como ASA I y II fueron programados para una cirugía abdominal superior abierta electiva. Estos fueron distribuidos aleatoriamente en dos grupos de 69 pacientes en cada uno: grupo C (placebo) y grupo D (dexmedetomidina 0.5 ug/kg). Tanto el placebo como la droga fueron administradas a 0.5 ug/kg vía intravenosa al cerrar la cavidad abdominal. Después de la inducción de la anestesia, los pacientes fueron cateterizados con un catéter de Foley 16F y el globo se infló con 10 ml de solución salina normal. En PACU, la incidencia y la severidad (leve, moderada, severa) de CRBD fueron evaluados a 0, 1, 2, y 6 h luego de la extubación. El dolor post-operatorio y el nivel de sedación fueron también estimados en los mismos horarios. La incidencia de eventos clínicos adversos después de la inyección de dexmedetomidina o placebo fue evaluada. Resultados: La incidencia y severidad de CRBD fue reducida significativamente en el grupo D post-operatorio comparado con el grupo C ($p<0.01$) medidas a 0, 1, 2 y 6 horas después de la extubación. La dexmedetomidina también ayudó a aliviar el dolor post-operatorio e indujo sedación profunda a 0 y 1 hora después de la extubación ($p<0.05$). No diferencias en eventos adversos más allá de bradicardia e hipotensión fueron observadas en el grupo D ($p<0.05$). Conclusión: La dexmedetomidina (0.5 ug/kg) administrada durante cirugía redujo la incidencia y la severidad de CRBD en PACU sin causar efectos adversos significativos.

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