Dexmedetomidine for prevention of early postoperative catheter-related bladder discomfort in voluntary kidney donors: Prospective, randomized, double-blind, placebo-controlled trial

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Abstract

Background and Aims: Catheter-related bladder discomfort (CRBD) has started to gain recognition as a problem in early postoperative care. Dexmedetomidine reduces bladder contractility via M3 muscarinic receptor antagonism and α-2 receptor agonism, apart from its concomitant therapeutic benefits, such as sedation and sympatholysis, in a postoperative period. We, therefore, evaluated the efficacy of dexmedetomidine in reducing incidence and severity of CRBD.

Material and Methods: This prospective, randomized, double-blind, placebo-controlled trial done on 110 voluntary kidney donors for live related kidney transplantsations were planned for laparoscopic donor nephrectomy. The donors were of ages 18–60 years, American Society of Anesthesiologists physical status I and II of either sex. The control group received 20 ml normal saline (NS) intravenous (IV) infusion over 15 min, whereas the dexmedetomidine group received dexmedetomidine 1 µg/kg made in 20 ml NS as IV infusion over 15 min. The incidence and severity of CRBD were recorded as primary endpoints up to 12 h in early postoperative period. The incidence of bladder discomfort was analysed by Fisher's exact test and severity of bladder discomfort by Mann Whitney U test.

Results: The incidence of CRBD on arrival at postoperative care unit was 18% in dexmedetomidine group compared to 42% in control group (P < 0.05). The incidence and severity of CRBD reduced in dexmedetomidine group at 0, 2, and 4 h compared with control group (P < 0.05).

Conclusions: Dexmedetomidine 1 µg/kg administered IV to patients 30 min before extubation reduces the incidence and severity of CRBD in early postoperative settings with no adverse effects.

Keywords: Bladder, catheter-related bladder discomfort, dexmedetomidine, discomfort, postoperative care

Introduction

In patients undergoing surgery, where urinary bladder of the patient is catheterized and catheter is left in situ for postoperative bladder drainage, patients often complain of catheter-related bladder discomfort (CRBD). CRBD presents as an urge to void or discomfort in the suprapubic region in the postoperative period because of catheter-related bladder irritation. These symptoms are similar to symptoms of overactive bladder (OAB) (urinary frequency and urgency, with or without urge incontinence), which are caused by involuntary contractions of the bladder mediated mainly by muscarinic receptors situated in bladder mucosa and urothelium.

CRBD, nowadays, had started to gain recognition as a problem in postoperative care unit (PACU), which delays...
PACU discharge and causes significant distress to the patient.\cite{3,4} The incidence of CRBD is about 60% from various earlier studies.\cite{1,4} Because the symptoms of CRBD are identical to those of OAB, hence antimuscarinic agents such as tolterodine, oxybutinin, solifenacin, etc., have been tried and found effective in the prevention and treatment of CRBD.\cite{4,5} However, side effects such as dry mouth, dysuria and dyspepsia, and lack of parental formulations prevented them from becoming routine management for CRBD in PACU settings. Dexmedetomidine, an α-2 receptor agonist, has better sedation, analgesia, and anxiolyis over clonidine. Dexmedetomidine has also shown antimuscarinic activity (M3 receptor) in animal studies.\cite{6} Hence the potential of dexmedetomidine to reduce bladder contractility via M3 muscarinic receptor antagonism and α-2 receptor agonism, apart from its concomitant therapeutic benefits, such as sedation and sympatholysis, in a postoperative setup, where CRBD is common, compelled us to further explore its therapeutic potential in CRBD. We, therefore, evaluated the efficacy of dexmedetomidine in reducing incidence and severity of CRBD in early postoperative period.

**Material and Methods**

The study was conducted after approval from the Institute’s Ethics Committee and registration with clinical trial registry of India between October 2013 and October 2015. It was conducted in compliance with the guidelines for good clinical practice. The written informed consent was taken from the patients before recruitment in the study. The donors who were in 18–60 years age group, American Society of Anesthesiologist (ASA) I and II, with no history of dysuria and urological disorder for live related kidney transplantation after workup as per institute protocol were included in the study. Patients with the history of outflow obstruction/OAB, transurethral resection of prostate for benign prostatic hyperplasia, history of bladder catheterization within last 6 months, morbid obesity, disturbance of the central nervous system, chemical substance abuse, chronic pain, and cardiovascular, hepatic, renal, or any psychiatric disease were excluded from the study because the sign and symptoms might have interfered with the outcome of disease. All the patients who were included in the study were counselled preoperatively regarding the CRBD and the possibility of its occurrence in postoperative period. Patients were educated regarding questionnaire used to detect CRBD incidence and severity.

All patients were premedicated with oral lorazepam 0.04 mg/kg and ranitidine 150 mg the night before and 2 h before surgery. On arrival to operation room, intravenous (IV) assess was achieved with 18G venous cannula under local anesthesia with 2% lignocaine. Monitoring consisted of five lead electrocardiography, pulse oximeter, noninvasive blood pressure, temperature, and end-tidal CO₂.

Following preoxygenation with 100% oxygen, patients were induced with fentanyl 2 μg/kg and propofol 2 mg/kg. Tracheal intubation was facilitated by vecuronium bromide 0.1 mg/kg. Depending on the results of simple or unrestricted randomization process done by computer, 50 patients in each group received medications half an hour before the expected time of extubation. Control group received 20 ml normal saline (NS) IV infusion over 15 min; Dexmedetomidine group received dexmedetomidine 1 μg/kg (Dexem, Themis Medicare India Ltd) made in 20 ml NS as IV infusion over 15 min. Dexmedetomidine and NS infusions were prepared according to the weight of patient in identical 50 ml syringes, labeled with respective patient’s name by the anesthesia technician who had the list of enrolled patients with their allocated groups. The method of allocation concealment was pharmacy controlled. In this identical 50 cc syringes, similar 20 ml volume were prepared with study drug or saline. These medications were administered by an anesthesia registrar. Both technician and anesthesia registrar were not involved in the study. Urinary catheterization was done with a 16 Fr Foley’s catheter and its balloon was inflated with 10 ml distilled water after induction of anesthesia. KY jelly (a water base lubricating gel) was used to lubricate the catheter, which was later fixed in the suprapubic area with an adhesive tape without any traction and was always left to free drainage.

Anesthesia was maintained by using sevofurane along with air and oxygen and a propofol infusion at 50–150 μg/kg/min and intermittent bolus of fentanyl and vecuronium whenever required. At the end of surgery, the neuromuscular blocking agent was antagonized with a combination of neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg, and the patients were transferred to the PACU. Bladder discomfort (urge to pass urine or discomfort in the suprapubic region) was assessed by an anesthesia registrar in PACU, who was unaware of the type of medication received by the patient, on arrival at the PACU (0 h) and again at 2, 4, and 12 h later. Severity of bladder discomfort was recorded as mild (reported by the patient only on questioning), moderate (reported by the patient without questioning; not accompanied by any behavioral responses), or severe (reported by the patient and accompanied by behavioral responses). Behavioral responses observed were flailing limbs, strong vocal response, and attempts to remove the catheter. This severity score had been used previously in other studies on CRBD.\cite{1,5}
All patients reporting CRBD of moderate to severe degree of CRBD received rescue medication in the form of tab tolterodine 2 mg (Tolter 2 mg, Zydus Cadilla Healthcare India Ltd) orally via Ryles tube to alleviate their symptoms.

The same anesthesia resident also observed the patients postoperatively for level of sedation, pain, nausea and vomiting, respiratory rate, pulse rate, and mean blood pressure on arrival at PACU (0 h) and again at 2, 4, and 12 h later. Sedation was assessed using Ramsay sedation scale. Postoperative pain was assessed at 0, 2, 4, and 12 h using a visual analog scale (VAS) score of 0–10, where 0 represented no pain and 10 represented worst imaginable pain. Postoperative nausea vomiting (PONV) was measured as: Zero = no PONV, one = only nausea, no vomiting, two = vomiting once, three = vomiting twice or more.

**Sample size calculation**

Based on the results of the previous studies, the incidence of CRBD is about 60%, and assuming that it can be reduced to 30% (with $\alpha = 0.05$, $\beta = 0.8$) following the administration of dexmedetomidine, we needed to study 42 patients in each group. To make provision for dropouts if any, we had enrolled 50 patients in each group. Patients who could not be extubated at the end of the surgery or were re-explored within the study period were considered as dropouts.

The incidence of bladder discomfort between groups was analyzed by Fisher’s exact test or Chi-square test to compare the population between two groups, i.e., univariate analysis, whereas the severity of discomfort (mild, moderate, and severe) was analyzed by Mann–Whitney U test. Ramsay sedation score, VAS score, and PONV score were analyzed using Mann–Whitney U test. The pulse rate, respiratory rate, and mean blood pressure were analyzed using independent $t$ test. The number of patients requiring rescue medication was analyzed using Chi-square test. Additionally, Yates’ correction was done in Chi-square test to adjust the significance level. Statistical Package for the Social Sciences, version 21.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. $P < 0.05$ was considered as significant.

**Results**

One hundred and sixty-three voluntary kidney donors were evaluated, out of which 110 patients were planned for laparoscopic donor nephrectomy. Ten donors were converted intraoperatively into open donor nephrectomy and thus were considered as dropouts; eventually only 100 patients were included in the study and randomized into two groups [Figure 1]. There were no dropouts as none of the patients were ventilated or re-explored during the postoperative course. The patient characteristics were similar and comparable in both the studied groups [Table 1].

The incidence of CRBD on arrival at PACU was 18% in dexmedetomidine group compared to 42% in control group ($P = 0.02$). The incidence of CRBD in dexmedetomidine group at 2, and 4 hours was also less than that in control group. ($P < 0.05$) [Table 2]. Six patients required rescue medication in dexmedetomidine group compared to 20 in control ($P = 0.001$).

Level of sedation was higher in the dexmedetomidine group as compared to control at 0 and 2 h ($P < 0.05$). Significant reduction in pain was observed in the dexmedetomidine group at 0 hour only ($P < 0.05$). There was no difference in incidence of PONV in the two groups. Respiratory rate had significantly reduced in dexmedetomidine group at 0 hour only ($P < 0.05$). The pulse rate and mean blood pressure were significantly lower in dexmedetomidine group at 0 and 2 hours ($P < 0.05$).

**Discussion**

In the present study, the dexmedetomidine group had lower incidence of CRBD, less need for rescue medication, and better pain relief on arrival of patients in the PACU ($P < 0.05$).

Various treatment modalities have been suggested for prevention and cure of CRBD.\(^{12}\) Other agents such as butylscopolamine,\(^{8,9}\) ketamin,\(^{10,11}\) tramadol,\(^{12}\) gabapentin,\(^{13,14}\) and even paracetamol\(^{15}\) had been found to reduce the incidences of
CRBD in early postoperative period with variable efficacy.[12–15]

Searches for an ideal agent to prevent early postoperative CRBD are still ongoing.

Dexmedetomidine is a highly selective alpha-2 agonist. Following IV administration, dexmedetomidine has a distribution half-life (t ½ α) of 6 min and a terminal elimination half-life (t ½ β) of 2 hours. Dexmedetomidine exhibits linear kinetics when infused in the dose range of 0.2–0.7 µg/kg/h for no more than 24 h. Dexmedetomidine is metabolized in liver and excreted by kidney. Dose reduction is required in hepatic disease.[16]

The urinary bladder is supplied by thoracolumbar sympathetic nerves, sacral parasympathetic nerves, and sacral somatic nerves (mainly by pudendal nerve). The parasympathetic nervous system is responsible for maintaining normal intestinal and bladder function, contracting the smooth muscle by releasing the neurotransmitters acetylcholine (ACh) and ATP and relaxing sphincters by releasing nitric oxide. ACh is the main transmitter released and smooth muscle contraction is mediated via a mixed M2/M3 (Muscarinic) receptor population; M3 receptors act via phospholipase-C and M2 receptors act via inhibition of adenylate cyclase.[17] The M2:M3 ratio is 3:1 in most species including man.[15]

Despite the predominance of M2-receptors, direct contraction of intestinal and detrusor smooth muscle is mediated via the M3-receptor subtype and only this subtype is involved in contraction in vitro. Thus, the main muscarinic receptor mediating contraction in normal smooth muscle is the M3 receptor, but M2 receptors are also present and possibly may have an enhanced role in disease.[18]

Apart from muscarinic receptors, few animal studies have revealed possible role of adrenoceptors in regulating bladder contractility. Radioligand studies have demonstrated presence of α2-adrenoceptors in bladder neck and detrusor muscle, in concentrations far greater than α1-adrenoceptors though less than those of β-adrenoceptors.[19] α2-adrenoceptors inhibit neurotransmitter release from both postganglionic sympathetic and parasympathetic nerve terminals.[20] Streng et al. have reported that dexmedetomidine reduces maximum bladder pressure, urinary flow rate, and amplitude of rhabdosphincter electromyography.[21] Hence we presumed the ability of dexmedetomidine to reduce bladder contractility results via α-2 receptor agonism and probably by M3 antagonism.

The effect of dexmedetomidine was significantly better for prevention of CRBD as compared to placebo in early postoperative period up to 4 h. As evidenced by data in control group, CRBD troubles more in initial few hours in early postoperative period, which dexmedetomidine may help in overcoming. Then the patients may be allowed to take oral medications with sip of waters in PACU for CRBD or the catheter can be removed or changed to condom catheter as per the need.

Limitations of the present study are that we have evaluated the response of a single dose of dexmedetomidine on CRBD patients undergoing laparoscopic donor nephrectomy for live related kidney transplantation. We did not evaluate the dose response titration. Because our patients are voluntary kidney donors, who did not have prior lower urinary tract symptoms, we cannot predict the effect of dexmedetomidine on patients having preexisting overactive bladder symptoms. We have not evaluated its role in patients undergoing other types of surgical procedures. Moreover, the potent sedative nature of dexmedetomidine, unfamiliarity of physicians with the drug, precludes its use in patients who are catheterized for other medical procedures, as its use is allowed in settings where hemodynamic monitoring is possible. Efficacy of dexmedetomidine is also unknown in patients who require urinary catheterization for longer periods. Because dexmedetomidine has shown promise to reduce incidence of CRBD in our chosen sample in early postoperative period, along with its synergism with anesthesia and mild analgesic in postoperative care settings, we strongly feel there is scope for further research in the above-mentioned areas.

| Table 1: Demographic data presented either as number of patients or mean±SD |
| Groups | Control (n=50) | Dexmedetomidine (n=50) |
| Age of patients (years) | 43.4±9.0 | 42.3±9.8 |
| Sex | | |
| Male | 22 | 21 |
| Female | 28 | 29 |
| Weight of patients (kg) | 51.4±8.7 | 53.6±7.9 |

| Table 2: Incidence and severity of CRBD in both the groups |
| Time (hours) | 0 | 2 | 4 | 12 |
| Groups | C | D | C | D | C | D | C | D |
| Number of cases | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| CRBD present | 21 | 09* | 21 | 08* | 20 | 05* | 05 | 0 |
| Severity of CRBD | | | | | | | | |
| Mild | 04 | 03 | 05 | 02 | 20 | 04 | 05 | 0 |
| Moderate | 11 | 05 | 14 | 05 | 0 | 01 | 0 | 0 |
| Severe | 06 | 01 | 02 | 01 | 0 | 0 | 0 | 0 |

*Denotes P<0.0; * denotes Yates' correction P; intergroup comparison between groups.
CRBD = Catheter-related bladder discomfort, C = control, D = Dexmedetomidine
Conclusion

Intravenous Dexmedetomidine 1 µg/kg administered 30 min before extubation in patients undergoing laparoscopic donor nephrectomy reduces the incidence and severity of postoperative CRBD.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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