



Sugammadex use can decrease the incidence of post-operative urinary retention by avoiding anticholinergics: a retrospective study

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Received August 7, 2017

Revised 1st, September 4, 2017

2nd, September 6, 2017

Accepted September 27, 2017

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Background: Postoperative urinary retention (POUR) is a common complication after total knee arthroplasty (TKA) and associated with the use of anticholinergics. The introduction of sugammadex has decreased perioperative use of anticholinergics. Since anticholinergics may influence the detrusor muscle, the purpose of this study was to compare incidence of POUR between sugammadex and anticholinergic use for reversal of muscle relaxant.

Methods: This study was a retrospective cohort study in a university-affiliated hospital. A total of 571 patients who underwent TKA between 2015 and 2016 with an American Society of Anesthesiologists class ≤ 3 were included in this study. Patients who received sugammadex (group S, n = 208) were compared to those who received glycopyrrolate with pyridostigmine (group C, n = 363) for reversal of neuromuscular blockade. The primary outcome was the incidence of POUR. Secondary outcomes were hospital length of stay (HOS) and daily residual urine drained from intermittent catheterization. Demographic, intraoperative, and laboratory data were collected.

Results: The incidence of POUR was significantly lower in group S compared to group C (36.1 vs. 48.8%, P = 0.003). On post-operative day (POD) 0, there was no significant difference in the residual urine volume between the two groups. However, from POD 1 to POD 4, the residual urine volume was significantly lower in group S compared to group C. There was no significant difference in HOS between the two groups.

Conclusions: The use of sugammadex was associated with a lower incidence of POUR by avoiding glycopyrrolate in patients underwent TKA.

Key Words: Arthroplasty, replacement, knee, Cholinergic antagonists, Urinary retention.

INTRODUCTION

It is reported that the incidence of post-operative urinary retention (POUR) is about 3.8% in general surgery patients but it is 20 times higher in patients undergoing lower extremity surgery such as total knee arthroplasty (TKA) [1,2]. POUR

may lead to bladder tissue damage and urinary tract infection, which can cause joint infection following arthroplasty [3-5]. Previous studies reported that patient age, diabetes, pre-operative voiding dysfunction, operation time, amounts of intraoperative fluid, perioperative use of opioids and anticholinergics may affect the development of POUR [6-11].

During general anesthesia, anticholinergics are used to decrease oral secretion, to treat bradycardia, or to antagonize the side effects of anticholinesterase used to reverse neuromuscular block at the end of the surgery. However, anticholinergics have an inhibitory effect on bladder contraction in the presence of outlet obstruction, an effect achieved primarily by antagonizing postjunctional excitatory muscarinic receptors in the detrusor muscle, thereby increasing the frequency of POUR [1,9,12]. Recently, a selective relaxant binding agent, sugammadex, has been introduced into clinical practice. Sugammadex restores muscle relaxation through rapid and strong one-to-one bonding with rocuronium or vecuronium in the plasma, which has no effect on acetylcholinesterase [13,14]. Since sugammadex decreases the use of perioperative anticholinergics, it also may affect the incidence of POUR.

The purpose of this study was to compare the incidence of POUR between patients who received sugammadex and those who received anticholinesterases with anticholinergics for reversal of neuromuscular blockade.

MATERIALS AND METHODS

This study was approved by the Hospital Ethics Committee (No. 2017-07-046). A retrospective cohort study was performed on 812 patients who underwent TKA from January 2015 to December 2016. Twelve patients with benign prostatic hyperplasia, 7 patients with chronic kidney disease stages 3–5, 220 patients who underwent bilateral TKA, and two patients with spinal anesthesia were excluded from this study. A total of 571 patients were included in this study. Patients' clinical information was collected via electronic medical records. The primary outcome was the incidence of POUR, and the secondary outcomes were hospital length of stay (HOS) and daily urine volume drained from intermittent urinary catheterization. Collected data were the American Society of Anesthesiologists physical status classification, operation/anesthesia time, amounts of administered fluid during surgery, anticholinergic use (pre-treatment with glycopyrrolate 0.2 mg before induction of anesthesia), number of opioids used during and after surgery, pre- and post-operative blood urea nitrogen/creatinine (Cr), and daily urine volume drained from intermittent urinary catheterization.

POUR was defined as a case of urinary retention of more

than 400 ml due to self-voiding difficulties until post-operative discharge [15]. In our hospital, the residual urine volume of patients undergoing TKA and who have self-voiding difficulties or complain of a sense of residual urine is routinely assessed with a nelaton catheter until residual urine is less than 100 ml. All patients received 2 mg/kg of propofol and 0.8 mg/kg of rocuronium for induction, and maintenance remifentanyl (0.05–0.2 µg/kg/min) was administered. Patient-controlled analgesia (PCA) for postoperative pain control consisted of fentanyl 0.5 µg/kg/h for all patients.

Patients were divided into a sugammadex group (group S, n = 208) or control group (group C, n = 363) according to the reversal agent used to reverse neuromuscular blockade. Patients in group S received sugammadex 2 mg/kg and patients in group C received the combination of glycopyrrolate 0.4 mg (an anticholinergic agent) and pyridostigmine 15 mg (an anticholinesterase agent). The choice of reversal agents was decided by the anesthesiologist depending on preference. In the postanesthesia care unit (PACU), patients with voiding difficulties were treated with intermittent urinary catheterization.

Values were expressed as mean ± standard deviation and number of patients (percent). Comparisons between groups were analyzed with the *t*-test for continuous variables and χ^2 test for categorical data. The relationship between each variable and POUR was analyzed through univariable logistic regression, and multivariable logistic regression was conducted with variables with a P value of 0.05 or less. Statistical analysis was conducted using SPSS 21.0 for Windows (IBM Corp., USA). P values less than 0.05 were considered statistically significant.

RESULTS

Patient characteristics are presented in Table 1. The mean age of patients was statistically higher in group S compared to group C. There was no significant difference in hypertension, diabetes, cerebrovascular disease, hyperlipidemia, and chronic kidney disease between the groups. Compared to group S, the number of patients with cardiovascular disease was significantly lower in group C.

Perioperative data are listed in Table 2. Mean duration of surgery was significantly longer in group C than that in group S ($P = 0.013$) (Table 2). The amount of administered crystal-

loid fluid was significantly higher but colloid was lower in group C compared to group S (both $P < 0.001$). The mean Cr levels before and after surgery were within normal limits. There was no difference in the use of anticholinergics for premedication and duration of anesthetic between the groups. There was no difference between the groups in the amount of fentanyl in PCA (Table 2). The amount of oxycodone administered in the PACU was significantly higher in group C com-

pared to group S; however, the amount of fentanyl administered in the PACU was significantly higher in group S than in group C.

The urinary outcomes are presented in Table 3. The incidence of POUR was significantly lower in group S compared to group C ($P = 0.003$). There was no difference in the incidence of urinary catheterization between the groups at postoperative day (POD) 0, but this was significantly higher in group C compared to group S from POD 1 to POD 4. Total

Table 1. Patients' Characteristics

Variable	Group C (n = 363)	Group S (n = 208)	P value
Age (yr)	69.4 ± 7.0	70.7 ± 6.7	0.033
Sex (male)	29 (8.0)	23 (11.0)	0.220
Height (cm)	154.2 ± 6.4	154.6 ± 7.0	0.507
Weight (kg)	62.1 ± 9.4	62.3 ± 9.1	0.800
Medical history			
Diabetes mellitus	97 (26.7)	64 (30.8)	0.301
Hypertension	250 (68.9)	138 (66.3)	0.534
Hyperlipidemia	34 (9.4)	30 (14.4)	0.065
Cerebrovascular disease	33 (9.1)	23 (11.1)	0.450
CKD stage 1	1 (0.3)	2 (1.0)	0.301
CKD stage 2	0 (0)	1 (0.5)	0.364
Coronary artery disease	15 (4.1)	21 (10.1)	0.005

Data are expressed as mean ± SD or number (%). Group C: control group used glycopyrrolate with pyridostigmine, Group S: the group used sugammadex, CKD: chronic kidney disease.

Table 3. Comparison of Outcomes

Variable	Group C (n = 363)	Group S (n = 208)	P value
Incidence of POUR	177 (48.8)	75 (36.1)	0.003
Hospital length of stay (d)	10.9 ± 2.0	10.7 ± 1.7	0.240
Incidence of urinary catheterization			
POD 0	211 (58.1)	135 (64.9)	0.111
POD 1	194 (53.4)	82 (39.4)	0.001
POD 2	116 (32.0)	40 (19.2)	0.001
POD 3	56 (15.4)	14 (6.7)	0.002
POD 4	20 (5.5)	4 (1.9)	0.040
POD 5	11 (3.0)	3 (1.4)	0.238
POD 6	6 (1.7)	3 (1.4)	1.000
POD 7	2 (0.6)	2 (1.0)	0.625
POD 8	1 (0.3)	1 (0.5)	1.000

Data are expressed as number (%) or mean ± SD. Group C: control group used glycopyrrolate with pyridostigmine, Group S: the group used sugammadex, POUR: postoperative urinary retention, POD: postoperative day.

Table 2. Perioperative Data

Variable	Group C (n = 363)	Group S (n = 208)	P value
Anesthetic agent used			0.004
Sevoflurane	204 (56.2)	144 (69.2)	
Desflurane	157 (43.3)	64 (30.8)	
TIVA	2 (0.6)	0 (0)	
Anticholinergics premedication	355 (97.8)	204 (98.1)	1.000
Duration of anesthesia (min)	165.1 ± 20.9	162.0 ± 22.0	0.095
Duration of surgery (min)	115.2 ± 18.6	110.5 ± 23.4	0.013
Intraoperative colloid (ml)	20.5 ± 92.9	121.4 ± 276.7	< 0.001
Intraoperative crystalloid (ml)	682.6 ± 215.5	476.0 ± 304.2	< 0.001
Preoperative BUN (mg/dl)	19.0 ± 7.1	23.6 ± 8.6	< 0.001
Postoperative BUN (mg/dl)	29.8 ± 9.5	28.9 ± 8.4	0.263
Preoperative Cr (mg/dl)	0.7 ± 0.2	0.6 ± 0.2	0.001
Postoperative Cr (mg/dl)	0.6 ± 0.2	0.6 ± 0.1	0.008
PCA fentanyl (μg)	808.9 ± 306.3	784.6 ± 208.2	0.261
PACU fentanyl (μg)	24.7 ± 25.6	32.1 ± 29.0	0.002
PACU oxycodone (mg)	0.4 ± 1.1	0.1 ± 0.7	< 0.001
PACU demerol (mg)	0.9 ± 4.7	0.5 ± 3.4	0.225

Data are expressed as number (%) or mean ± SD. Group C: control group used glycopyrrolate with pyridostigmine, Group S: the group used sugammadex, Anticholinergics premedication: glycopyrrolate 0.2 mg before induction, TIVA: total intravenous anesthesia, BUN: blood urea nitrogen, Cr: creatinine, PCA: patient-controlled analgesia, PACU: postanesthesia care unit.

Table 4. Daily Residual Urine Volume Drained from Urinary Catheterization after Surgery

Variable	Group C (n = 363)	Group S (n = 208)	P value
Residual urine volume (ml)			
POD 0	261.8 ± 280.0	276.1 ± 361.1	0.717
POD 1	527.0 ± 876.3	330.0 ± 544.0	0.001
POD 2	277.3 ± 541.0	137.0 ± 541.0	< 0.001
POD 3	96.9 ± 290.1	35.4 ± 157.6	0.001
POD 4	34.7 ± 176.0	20.0 ± 187.4	0.041
POD 5	20.5 ± 145.3	12.7 ± 115.3	0.244
POD 6	14.1 ± 131.5	9.9 ± 97.9	0.846
POD 7	4.1 ± 55.7	7.2 ± 75.9	0.572
POD 8	1.9 ± 36.7	1.2 ± 17.3	0.692
Total residual urine volume (ml)	1,238.3 ± 1,733.6	829.3 ± 1,204.1	0.001

Data are expressed as mean ± SD. Group C: control group used glycopyrrolate with pyridostigmine, Group S: the group used sugammadex, POD: post-operative day, Total residual urine volume: total mean residual urine volume drained from urinary catheterization from postoperative day 0 to 8.

Table 5. Univariable Logistic Regression of POUR

Variable	POUR		P value	Odds ratio (95% CI)	P value
	Yes (n = 252)	No (n = 319)			
Age (yr)	70.8 ± 6.3	69.1 ± 7.2	0.016		
Sex (male)	32 (12.7)	20 (6.3)	0.008	2.18 (1.21–3.90)	0.009
ASA					
1	2 (0.8)	7 (2.2)	0.023	Reference	
2	226 (89.7)	298 (93.4)		2.65 (0.55–12.90)	0.226
3	24 (9.5)	14 (4.4)		6.00 (1.09–32.98)	0.039
Hypertension	178 (70.6)	210 (65.8)	0.222	1.25 (0.87–1.78)	0.222
Diabetes mellitus	83 (32.9)	78 (24.5)	0.025	1.52 (1.05–2.19)	0.026
Hyperlipidemia	35 (13.9)	29 (9.1)	0.071	1.61 (0.96–2.72)	0.073
Cerebral vascular disease	35 (13.9)	21 (6.6)	0.004	2.29 (1.30–4.04)	0.004
CKD					
Stage 1	2 (0.8)	1 (0.3)	0.586	2.54 (0.23–28.22)	0.447
Stage 2	0 (0)	1 (0.3)	1.000	< 0.001 (< 0.001, > 999.99)	0.986
Coronary artery disease	12 (4.8)	24 (7.5)	0.178	0.62 (0.30–1.26)	0.181
Intraoperative colloids (ml)	59.7 ± 206.7	55.3 ± 173.8	0.994	1.00 (1.00)	0.782
Intraoperative crystalloids (ml)	633.5 ± 272.7	586.7 ± 266.6	0.007	1.00 (1.00)	0.041
Sugammadex	75 (29.8)	133 (41.7)	0.003	0.59 (0.42–0.84)	0.003
Anesthesia					
Sevoflurane	178 (70.6)	170 (53.3)	0.001	Reference	
Desflurane	73 (29.0)	148 (46.4)		0.47 (0.33–0.67)	< 0.001
TIVA	1 (0.4)	1 (0.3)		0.96 (0.06–15.39)	0.974

Data are expressed as mean ± SD or number (%). POUR: postoperative urinary retention, ASA: American Society of Anesthesiologists physical status classification, CKD: chronic kidney disease, TIVA: total intravenous anesthesia.

volume of residual urine was significantly higher in group C compared to group S ($P = 0.001$) (Table 4). Daily residual urine volume drained from urinary catheterization after surgery revealed no difference between the groups at POD 0, but this was significantly higher in group C than group S from POD 1 to POD 4.

Univariable logistic regression analysis revealed that the

incidence of POUR in group S was 0.59 times lower than that in group C (odds ratio, 0.59; 95% CI, 0.42–0.84; $P = 0.003$) (Table 5). Univariable logistic regression analysis revealed that increased age, male sex, diabetes mellitus, cerebrovascular disease, American Society of Anesthesiologists physical status classification 3, and the amount of intra-operative crystalloid increased the risk of POUR. On the other hand, desflurane

Table 6. Multivariable Logistic Regression of POUR

Variable	Odds ratio (95% confidence interval)	P value
Sugammadex	0.50 (0.34–0.75)	0.001
Age (yr)	1.04 (1.01–1.06)	0.009
Sex (male)	2.09 (1.13–3.87)	0.018
DM	1.40 (0.95–2.07)	0.089
CVA	1.86 (1.01–3.42)	0.045
ASA 3	1.78 (0.91–3.49)	0.093
Crystalloids	1.00 (1.00)	0.297
Desflurane	0.48 (0.34–0.70)	< 0.001

POUR: postoperative urinary retention, DM: diabetes mellitus, CVA: cerebrovascular accident, ASA: American Society of Anesthesiologists physical status classification, Crystalloids: amounts of crystalloid administered during surgery.

anesthesia and the use of sugammadex reduced the incidence of POUR (Table 5). In multivariate logistic regression analysis, all variables except diabetes and American Society of Anesthesiologists physical status classification were consistently significant (Table 6).

DISCUSSION

Compared to conventional reversal agents combined with glycopyrrolate, the incidence of POUR was lower when sugammadex was used for reversal of neuromuscular blockade in patients undergoing TKA. From POD 1 to POD 4, the incidence of urinary catheterization was also lower in patients received with sugammadex compared to those that received conventional reversal agents.

As mentioned above, it is reported that the incidence of POUR is 20 times higher in patients undergoing lower extremity surgery such as TKA compared to general surgery patients (3.8%) [1,2]. In this study, the total incidence of POUR after TKA was 44%. The definition of POUR varies according to researchers. Pavlin et al. [15] reported that urinary retention is an inability to void despite a bladder volume of more than 400 ml. Balderi and Carli [16] defined POUR as a bladder volume of more than 600 ml after self-voiding as measured by ultrasound. Lee et al. [6] defined POUR as the inability to urinate or a residual urine volume of more than 100 ml after self-voiding for two days after surgery. It has been reported that a normal bladder volume is 400–600 ml in healthy adults and that individuals begin to feel the sense of voiding at a bladder volume of 150 ml [17]. When bladder volume reaches 300 ml,

patients feel a sense of urinary urgency. If patients do not feel a voiding sense despite bladder volume of more than 300 ml, there is a voiding problem. In this study, the POUR was defined according to the study by Pavlin et al. [15].

POUR is associated with multiple factors which interact with each other. A previous study described age 50 years or older, more than 750 ml of intraoperative fluid, and bladder volume more than 270 ml on arrival in PACU as predictive factors of POUR [18]. Another study reported that elderly and lengthy operation time were significant risk factors for POUR [6]. The effect of morphine on the lower urinary tract is complex. Morphine tightens the detrusor muscle and urethral sphincter by inhibiting the release of acetylcholine and makes the bladder distension unrecognizable by acting on the central nervous system [19].

Anticholinesterases, which increase the amount of acetylcholine, are used for reversal of neuromuscular blockade at the end of general anesthesia. Increased acetylcholine molecules act not only on the nicotinic receptor but also on the muscarinic receptor, resulting in a parasympathetic dominance effect, which manifests as bradycardia, bronchial contraction, and vomiting. Furthermore, increased acetylcholine released from parasympathetic fibers causes contraction of the detrusor muscle and relaxation of the neck, permitting micturition [20]. Anticholinergics such as atropine and glycopyrrolate used to prevent the muscarinic effect of anticholinesterases can block detrusor contractions and cause bladder hypotonia, resulting in urinary retention [9]. On the other hand, sugammadex reverses neuromuscular blockade by selectively binding with a steroidal non-depolarizing neuromuscular blocking agent [12]. In this study, the incidence of POUR and daily residual urine volume from POD 1 to POD 4 were significantly lower in the sugammadex group. Results are likely due to the avoidance of glycopyrrolate. A potential explanation for the delayed recovery of POUR until POD 4 despite the half-life of glycopyrrolate being 1.7 hours may be age-related progressive neuronal degeneration because relatively elderly patients (mean age of about 70 years) were included in this study [20].

In this study, the amount of intra-operative crystalloid administered was significantly higher in the control group than the sugammadex group ($P < 0.001$). This is consistent with the results of a previous study reporting that the incidence of POUR increases as the amount of intra-operative crystalloid

increases [18]. However, the amount of colloid administered was not associated with the incidence of POUR.

In univariable logistic regression analysis, the probability of POUR was increased to 1.52 in diabetic patients ($P = 0.026$). Decrease in bladder function due to diabetic neuropathy may have affected this result. The incidence of POUR was significantly higher in patients with cerebrovascular disease, with an odds ratio of 2.29 ($P = 0.004$). Although more research is needed, it is thought that urination is coordinated by neurons of the pontine-mesencephalic gray matter and pontine micturition center, and this neuronal pathway may have an effect on POUR if accompanied by cerebrovascular disease [21]. Interestingly, when desflurane was used as an inhalation agent, the incidence of POUR was reduced. However, desflurane activates the sympathetic nervous system during inhalation at a high concentration, which is contradictory to results of this study. Further studies are needed to consider the effect of various anesthetic agents on POUR.

There was no difference in the dose of fentanyl used in the PCA between the groups, but the amount of opioids used in the PACU varied according to the type of opioids. Opioids may affect urinary retention through changes in parasympathetic tone and decreased pain threshold in the bladder [19,22]. Several studies have revealed that opioids are associated with the occurrence of POUR [10,23]. However, the difference in the amount of opioid used in the PACU in this study was due to the analgesic choice of the anesthesiologist.

Limitations of this study are as follows. First, this study was a retrospective study and did not completely exclude the influence of confounding variables. The types of opioids used in PACU and the types of fluid used during the operation were not consistent. Second, the definition of POUR is not fully established. Although the criteria used to define POUR relied on previously published studies, the definition used in this study did not strictly diagnose POUR. Third, since the study was conducted by one institution, the guideline of voiding management of our institute may have affected the outcome of POUR.

Nevertheless, the results of this study demonstrate that the use of sugammadex was associated with a lower incidence of POUR by avoiding glycopyrrolate in patients that underwent TKA.

ACKNOWLEDGMENTS

The authors want to thank our residents who provided help in collecting data.

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