Comparison of efficacy of prophylactic ketamine and dexmedetomidine on postoperative bladder catheter-related discomfort

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ABSTRACT

الأهداف: لمقارنة التأثيرات الوقائية للكيتامين والديكسميدوتيميدين على الانزعاج والألم المتعلق بقثطار المثانة للمرضى الخاضعين لتنظير المثانة.

الطريقة: أجريت هذه الدراسة المستقبلية في مستشفى جامعة حاجّبة، أنقرة، تركيا. وذلك خلال الفترة ما بين نوفمبر 2011م –يونيو 2012م. شملت الدراسة 75 مريضاً تراوحت أعمارهم 75–18 عاماً طبقاً للجمعية الأمريكية لأخصائي التخدير (ASA I–II) والذين خضعوا لإجراء التنظير المثاني. تم تقسيم المرضى عشوائياً إلى واحدة من ثلاث مجاميع لتلقي 1مكغ/كلغ ديكسميديتوميدين، 250 مكغ/كلغ كيتامين وريديأ أو المحلول الملحي العادي. بعد الانتهاء من العملية الجراحية تم توجيه أسئلة لكل المرضى متعلقة بعدم الارتياح من القثطار، رضا المريض والألم وذلك في الدقائق 0(t4)، 360 (t3)، 120 (t2)، 60 (t1)، 15 (t0) من بعد العملية الجراحة. لقد تم تقييم كل مريض في العناية المركزة (PACU)، غرف العمليات المتنقلة أو طريق المكالمات الهاتفية.

النتائج: أشارت النتائج أن نسبة وقوع الألم في مجموعة الديكسميديتوميدين ومجموعة الكيتامين كانت أقل وبشكل ملحوظ عن مجموعة التحكم (p=0.044، p=0.042). إن مقياس المهدئ المسجل عند الوقت t0 في مجاميع ديكسميدوتيميدين و كيتامين كانت أعلى وبشكل ملحوظ عن مجموعة التحكم ((p=0.17، p=0.004) من ناحية معدل الهلوسة فأن المجاميع كانت متشابهة عند الوقت (t1) ولم تحدث حالات هلوسة لأي مريض في الأوقات (t2، t3، t4) وتمت ملاحظة مجموعة الكيتامين بأن معدل الهلوسة عند (t0) هي أكثر من مجموعة ديكسميديتوميدين (p=0.034) ومجموعة التحكم (p=0.005)

الخاتمة: إن عقاري ديكسميديتوميدين و كيتامين لهما تأثيرات تسكينية مشابهة في وقاية الألم المتعلق بالقثطار غيران ديكسميديتوميدين له تأثيرات جانبية مقبولة. من أجل تحديد الجرعة المثلى لعقاري ديكسميديتوميدين وكيتامين فهناك الحاجة إلى إجراء دراسات واسعة النطاق في هذا المجال

Objectives: To compare the effects of prophylactic ketamine and dexmedetomidine on postoperative bladder catheter-related discomfort/pain in patients undergoing cystoscopy.

Methods: This prospective study was conducted on 75 American Society of Anesthesiologists (ASA) I-II patients between 18-75 years of age and undergoing cystoscopy between November 2011 and June 2012 at Hacettepe University Hospital, Ankara, Turkey. Patients were randomly assigned to one of the 3 groups to receive 1 μ/kg dexmedetomidine, 250 μ/kg intravenous ketamine, or normal saline. All patients were questioned regarding probe-related discomfort, patient satisfaction, and pain at the end of the operation 0 (t_0) and 15 (t_1), 60 (t_2), 120 (t_3), and 360 (t_4) minutes postoperatively. Evaluations were performed in person at the post-anesthesia care unit, or in ambulatory surgery rooms, or by phone calls.

Results: Pain incidence in the dexmedetomidine and ketamine groups (p=0.042) was significantly lower than that in the control group (p=0.044). The sedation scores recorded at t_0 in the dexmedetomidine and ketamine groups (p=0.004) were significantly higher than that of the control group (p=0.017). Patient groups were similar regarding the rate of hallucinations experienced at t_1, no patients experienced hallucinations at t_2, t_3, or t_4. Significantly more patients experienced hallucinations at t_0 in the ketamine group than in the dexmedetomidine group (p=0.034) and the control group (p=0.005).

Conclusion: Dexmedetomidine and ketamine had similar analgesic effects in preventing catheter-related pain; however, dexmedetomidine had a more acceptable side effect profile. To identify the optimal doses of dexmedetomidine and ketamine, more large-scale interventional studies are needed.

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Postoperative pain and discomfort are frequent complaints in patients undergoing surgery requiring bladder catheterization. Catheter-related bladder discomfort (CRBD) is defined as an urge to urinate, and discomfort in the suprapubic region postoperatively in patients who undergo urinary catheterization during surgery.[1,2] Discomfort caused by the probe is frequently a stressful situation resistant to conventional opioid treatment in patients hospitalized in the post-anesthesia care unit (PACU). A number of studies have been conducted to reduce the problems caused by bladder catheterization and identify agents that can be used for prophylactic postoperative treatment.[3] Ketamine is a general anesthetic, which acts rapidly. An anesthetic state that characterized by deep analgesia, normal pharyngeal-laryngeal reflexes, and normal or increased skeletal muscle tone can be provided using ketamine.[4] A series of intervention that ketamine used for postoperative shivering have shown that it also relieves catheter-related discomfort.[5-7] Dexmedetomidine is a D-dimer form of the alpha-2 agonist agent medetomidine and a highly selective, specific, and strong agonist of the alpha-2 adrenoreceptor.[8] Dexmedetomidine has anxiolytic, hypnotic, sedative, and analgesic effects and supporting features to anesthesia without significant depressive effects on the respiratory system.[9] These features make dexmedetomidine a very useful adjuvant for general anesthesia procedures.[10] There is strong evidence that alpha-2 receptor stimulation has an analgesic effect at the spinal cord level, and this "opioid supporting effect" of dexmedetomidine is still under investigation.[2] In this study, our primary outcome was to evaluate the effects of prophylactic ketamine and dexmedetomidine on postoperative CRBD/pain in patients undergoing cystoscopy.

Methods. This randomized, double-blind, single-centered trial was conducted after obtaining approval from the Hacettepe University Medical Research Ethics Committee (HEK 11/96-30). After informed consent was obtained from all patients, 75 American Society of Anesthesiologists (ASA) I-II patients between 18 and 75 years of age and undergoing cystoscopy were included. Our study was carried out between November 2011 and June 2012 at Hacettepe University Hospital, Ankara, Turkey. Exclusion criteria were bladder outlet obstruction, or overactive bladder (frequency of urination >3 times at night, >8 times in 24 hours), multisystemic diseases (central nervous system, cardiovascular system, hepatic, psychiatric, and end-stage renal diseases), chronic pain, morbid obesity, known allergy to medications used in the study, and need for urgent intervention. Electrocardiogram, peripheral oxygen saturation, and non-invasive blood pressure were monitored in all patients. Induction of anesthesia was performed using 2.5 mg/kg of propofol and 2 μg/kg of fentanyl, and an appropriately sized laryngeal mask airways were placed in each patient. Anesthesia was maintained using 2% sevoflurane in a mixture of 50% oxygen (O_2) and 50% nitrous oxide (N_2O). After the procedure, patients were randomly assigned to one of the 3 groups to receive 1 μg/kg dexmedetomidine (Group D, n=25), 250 μg/kg intravenous ketamine (Group K, n=25), or normal saline (Group S, n=25). The patients received the intervention drugs 5 minutes before the end of the surgery. All patients were assessed as per CRBD, patient satisfaction, and pain at the end of the operation (t_0) and 15 (t_1), 60 (t_2), 120 (t_3), and 360 (t_4) minutes postoperatively. The evaluations were performed in person at the PACU, or in ambulatory surgery rooms, or by phone calls. A blinded anesthesiologists performed the postoperative assessments.

The severity of CRBD using a 4-point scale as: 1 - none; 2 - mild (reported when questioned); 3 - moderate (reported without questioning); and 4 - severe (reported without questioning, additionally the patient reflects his/her discomfort with behaviors. Patient satisfaction was evaluated using Likert scale, a 4-point scale: 1 - satisfied with the medical management; 2 - mostly satisfied; 3 - mostly dissatisfied; and 4 - dissatisfied 24 hours postoperatively. Postoperative pain scores were assessed using visual analog score (VAS). This is a scale which zero means no pain and 10 means the worst pain. We used paracetamol (intravenous) (15 mg/kg) when VAS score was higher than 3, as a rescue analgesic. Sedation, nausea, vomiting, respiratory depression, hallucination, bad dreams, and diplopia were recorded at several times. Nausea in the first 6 postoperative hours was considered "early nausea," and nausea between 6 and 24 postoperative hours was considered "late nausea." Nausea severity was graded as: 0=none; 1=mild; 2=moderate; and 3=severe. Vomiting in the first postoperative 6 hours was considered "early vomiting," and vomiting between 6 and 24 hours postoperatively was considered "late vomiting". The Ramsay sedation scale was used to evaluate sedation.

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Statistical analysis. The normality of numerical variables was tested using the Kolmogorov-Smirnov test. Numerical variables with normal distribution are presented as mean ± standard deviation, and median (minimum-maximum) values are given for non-normally distributed variables. Categorical variables were expressed as numbers and percentages. Repeated measures analysis of variance was used to determine within-group changes across time and group-time interactions. In paired-group comparisons, the independent groups t-test was used to analyze variables with normal distribution, and Mann-Whitney U test with Bonferroni correction was used for non-normally distributed variables. Group comparisons for categorical variables were performed using the chi-square test (Pearson's chi-square test, Yates' correction for continuity, and Fisher's exact chi-square test). For discontinuous numerical data, Dunn's test, and Friedman's test were used to evaluate the changes over time. A $p<0.05$ was considered statistically significant. Data were analyzed using Statistical Package for Social Sciences software version 16 (SPSS Inc., Chicago, IL, USA).

Results. Seventy-five patients (59 males and 16 females) were included in the study. The groups did not significantly differ in terms of age or gender. The duration of surgery and anesthesia were also similar across groups. Catheter-related bladder discomfort incidence did not significantly differ between the groups at t_0, t_1, and t_3. At t_2 and t_4, CRBD incidence in Group D and Group K were significantly lower (p=0.042) than that in the control group (p=0.044) (**Table 1**). The severity of CRBD among groups were similar (**Table 2**). There were significant differences regarding patient satisfaction scores among groups (p=0.002). The scores in Group K and Group S were similar, but the results for patient satisfaction were significantly higher in Group D compared with Group K (p=0.020) and Group S (p=0.000). Sedation scores significantly differed between the groups at t_0 and t_1 (p=0.009, p=0.001). The sedation scores at t_0 in Group D and Group K were significantly higher than that of the Group S (p=0.004, p=0.017). Sedation scores were significantly higher in Group K at t_1 (p<0.001). Overall incidence of nausea was 28%. Postoperative nausea and vomiting incidences were similar among groups (**Table 3**). As expected, the groups were significantly differed in the rate of hallucinations at t_0 (p=0.002). While patient groups were similar with reference to the rate of hallucinations experienced at t_1, no patients

Table 1 - Catheter-related bladder discomfort incidence among groups included in this study.

Severity	Pain	Group D	Group K	Group S	*P*-value
T_0	+	17	14	15	0.675
	-	8	11	10	
T_1	+	10	7	9	0.662
	-	15	18	16	
T_2	+	8	7	15	0.042
	-	17	18	10	
T_3	+	8	7	12	0.297
	-	17	18	13	
T_4	+	7	5	13	0.044
	-	18	20	12	

T_0 - pain at the end of the operation 0, T_1 - 15 minutes, T_2 - 60 minutes, T_3 - 120 minutes, T_4 - 360 minutes. Group D - received 1 μg/kg dexmedetomidine, Group K - received 250 μg/kg intravenous ketamine, Group S - received normal saline, + = positive, - = negative

Table 2 - Comparison of severity of catheter-related bladder discomfort between groups.

Groups	T_0	T_1	T_2	T_3	T_4
Group D	2.04 ± 1.01	1.56 ± 0.82	1.36 ± 0.56	1.32 ± 0.47	1.28 ± 0.45
Group K	1.8 ± 0.95	1.32 ± 0.55	1.28 ± 0.45	1.28 ± 0.45	1.2 ± 0.40
Group S	1.8 ± 0.81	1.36 ± 0.48	1.60 ± 0.50	1.36 ± 0.48	1.28 ± 0.45
P-value	0.602	0.582	0.055	0.834	0.757

Data are expressed as mean ± standard deviation. T_0 - pain at the end of the operation 0, T_1 - 15 minutes, T_2 - 60 minutes, T_3 - 120 minutes, T_4 - 360 minutes. Group D - received 1 μg/kg dexmedetomidine, Group K - received 250 μg/kg intravenous ketamine, Group S - received normal saline

Table 3 - Number of patients who experienced postoperative nausea and vomiting (PONV) in groups.

PONV	Group D	Group K	Group S	*P*-value
Early nausea (0-6 hours)	8	6	7	0.820
Late nausea (6-24 hours)	1	1	0	1.000
Early vomiting	1	1	0	1.000
Late vomiting	1	1	0	1.000

Group D - received 1 μg/kg dexmedetomidine, Group K - received 250 μg/kg intravenous ketamine, Group S - received normal saline

experienced hallucinations at t_2, t_3, or t_4. Significantly more patients experienced hallucinations at t_0 in Group K than in Group D (p=0.034) and Group S (p=0.005). The number of patients who had bad dreams at t_0 and t_1 did not differ significantly between the groups, and none of the patients experienced bad dreams at t_2, t_3, or t_4. The number of patients with diplopia at t_0 significantly differed between groups (p=0.022). Paired comparisons revealed that the number of patients with diplopia at t_0 in Group D was significantly higher than that in Group S (p=0.017). Although the number of patients who had diplopia was higher in Group K, this difference in diplopia frequency was not significant. The number of patients who experienced diplopia at t_1 was significantly higher in Group K compared with Group S (p=0.002). No patients in any group experienced diplopia at t_2, t_3, or t_4. Respiratory depression was observed in one patient in Group K at t_0. No patients experienced respiratory depression at other time points.

Discussion. Agarwal et al,[6] compared the effects of placebo and ketamine on CRBD in 44 patients undergoing percutaneous nephrolithotomy. The incidence of CRBD at t_3 and t_4 was significantly lower in patients treated with 250 μg/kg ketamine compared with the control group, and the intensity of pain at t_2 was reported to be significantly lower in the ketamine group.[6] In our study, the incidence of CRBD in the ketamine group at t_2 and t_4 was significantly lower than that in the control group; however, the severity of CRBD in patients was similar in groups.

Peroral use of tolterodine,[11] oxybutynin,[12] or gabapentin[13] one hour prior to anesthesia induction was shown to decrease the incidence and severity of CRBD in the postoperative period. Due to their various side effects, these drugs are only recommended for patients with moderate to severe discomfort. Binhas et al[3] evaluated the predictors of CRBD in 164 PACU patients, 47% patients complained of CRBD, and 27% reported the severity of pain as moderate and severe. Male gender was also found to be an independent predictor of moderate to very severe CRBD.[3] In another study,[14] that male gender is a predictor for CRBD. Length of urethra may be the cause of this relationship.[14] In our study, there was a male predominance in all groups, and the number of female patients was insufficient to show a relation between gender and CRBD.

Agarwal et al[11] evaluated the effects of tolterodine, a pure muscarinic receptor antagonist, in preventing catheter-related discomfort in 215 patients undergoing urological surgery requiring urinary catheterization. Fifty patients were treated with tolterodine one hour before the surgery at a dose of 2 mg administered orally, and the incidence of postoperative pain in the tolterodine group was significantly lower than that in the control group.[11] We also observed that dexmedetomidine and ketamine significantly reduced the incidence of pain by different mechanisms of action.

In a study evaluating tramadol, a muscarinic receptor antagonist and central opioid analgesic, for the prevention of catheter-related discomfort, 44 patients were included who had undergone percutaneous nephrolithotomy. Thirty minutes after extubation, the control group received 2 mL of saline, and the tramadol group received 45 mg/kg of tramadol. In the PACU, pain severity and incidence were lower in the tramadol group than the control group at all evaluation time points. Fentanyl requirement was also significantly lower in the tramadol group.[4] Agarwal et al[11] evaluated the preventive effects of gabapentin on CRBD in 108 patients undergoing percutaneous nephrolithotomy. They administered 600 mg peroral gabapentin one hour before surgery in the gabapentin group. The severity and incidence of pain, fentanyl requirement, and the number of patients requiring fentanyl were significantly lower in the gabapentin group (600 mg peroral gabapentin one hour before surgery) than the control group.[13] As cystoscopy is a relatively minor surgical intervention compared with percutaneous nephrolithotomy and the severity of postoperative pain is milder, patients were not under treatment with additional analgesics when CRBD severity and incidence were determined in the present study.

Dexmedetomidine has minimal effects on the respiratory system. It leads to a mild increase in partial pressure of carbon dioxide in spontaneously breathing dogs. This effect is an important advantage over anesthetic agents causing respiratory depression.[15] Hypotension and bradycardia are the most common adverse effects of dexmedetomidine.[10] In our study, no patients had catastrophic side effects in Group D. Ketamine has minimal effects on the central respiratory drive; 1-3 minutes after the administration of ketamine (2 mg/kg) there is a risk of decrease in the respiratory rate, and in rare instances, apnea may develop due to agents used in premedication, dosage, and speed of injection. In our study, one patient in the ketamine group experienced respiratory depression at t_0. Disturbing dreams and visual hallucinations are common in patients receiving ketamine anesthesia. In the postoperative period, patients typically complain of double vision (diplopia), altered body image, and a sensation of floating. In our study, the number of patients experiencing hallucinations at t_0 was significantly higher in the ketamine group than in the dexmedetomidine and control groups, which was interpreted as a ketamine-related side effect. In our study, although the tested drugs had similar effects to placebo in reducing the intensity of CRBD, they reduced the incidence of pain at t_2 and t_4 compared with the control group. However, the main limitation of our study is that we did not assess dose-response relationship between each drug in the control group. We only provided a comparison between 2 different drugs and control group using a single dose regimen.

In conclusion, dexmedetomidine and ketamine had similar analgesic effects in preventing CRBD; however, dexmedetomidine had a more acceptable side effect profile. To identify the optimal doses of dexmedetomidine and ketamine, more large-scale interventional studies are needed. CRBD can be a painful and upsetting discomforting, perturbational condition for patients in the postoperative period. Further studies using different medications are required to prevent this situation.

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