Efficacy of dexmedetomidine-ketamine *vs.* fentanyl-ketamine on saturated oxygen, hemodynamic responses and sedation in cystoscopy: a double-blinded randomized controlled clinical trial

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Abstract

Cystoscopy is a diagnostic and invasive procedure for treatment and follow-up of genitourinary system patients and could be performed with a variety of anesthesia techniques. The study aimed to assess the efficacy of dexmedetomidine-ketamine *vs*. fentanyl-ketamine on sedation and analgesia for cystoscopy. This double-blind randomized controlled clinical trial enrolled 60 patients undergoing cystoscopy in two groups. Patients were assigned randomly by block random allocation method into dexmedetomidine-ketamine group (1 μg/kg dexmedetomidine) and fentanyl-ketamine group (2 μg/kg fentanyl) receiving ketamine (0.5 mg/kg). Subsequently, mean blood pressure, heart rate, saturated oxygen, respiratory rate, pain intensity, Ramsay score for sedation level, cystoscopy duration, and urologic satisfaction were measured and compared between two groups. Both the groups were similar regarding age, sex and baseline hemodynamic parameters ($P > 0.05$). Lower heart rate and pain score were revealed in the dexmedetomidine-ketamine group at 25–50 and 30–60 minutes, respectively, after cystoscopy ($P < 0.05$). Moreover, repeated measure test showed that there was significant difference in trend of respiratory rate and pain score between two groups ($P = 0.017$) and was lower in dexmedetomidine-ketamine group. The dexmedetomidine-ketamine group relieves pain 30 minutes after cystoscopy with stable hemodynamic parameters during operation. Therefore, dexmedetomidine-ketamine is recommended to be employed for pain relief in subjects undergoing cystoscopy. The study was approved by Ethical Committee of Arak University of Medical Sciences with IR.ARAKMU.REC.1397.108 on July 2, 2018, and registered in Iranian Registry Clinical Trial center with code IRCT20141209020258N105 on April 21, 2019.

Key words: analgesia; cystoscopy, dexmedetomidine; fentanyl; ketamine; sedation

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Introduction

Cystoscopy has been highlighted as one diagnostic, invasive procedure on genitourinary system, being frequently employed in evaluating and treating urinary tract diseases.[1] This does remain easy and effective for the diagnosis and follow-up of patients with hematuria, urinary tract symptoms, and bladder tumors and is routinely utilized in outpatient clinics.[2] Sedation and analgesia with intravenous sedoanalgesia drugs have been recognized as a safe, cost-effective alternative to either general or regional anesthesia.[3,4] Ketamine is a phencyclidine derivative that creates displaying analgesic, metabolism mediated through hepatic microsomal enzymes and amnesic effects as an intravenous anesthetic.[5-7] Norketamine is a metabolite of ketamine with anesthetic potency equal to 20–30%.[6,7] One pharmacokinetic feature of ketamine is rapid release and have short half-life. Therefore, ketamine is not administered alone, but combined with other anesthetics.[8,9] Dexmedetomidine is an α2-adrenergic agonist and diminishes heart rate (HR), systemic vascular resistance, and blood pressure after administration by injection. Therefore, the use of dexmedetomidine helps in maintaining the patient's hemodynamic status, and has a potent anesthetic effect reducing the need for opioids, complications, and stress response, as well as improving recovery.[10,11] The dexmedetomidine analgesic effects are attributed to the activation of α2 adrenergic receptors in the dorsal horn of the spinal cord and the inhibitory effect on substance P-release.[12] Parallel studies investigating the dexmedetomidine efficacy on sedation of patients undergoing cystoscopy and showed its pain relief effect.[12-14] Fentanyl is a potent opioid 75 to 125 times stronger than morphine and used in various ways for analgesia and anesthesia. The preoperative injection of fentanyl can reduce postoperative opioid doses and opioid intake. It has a faster onset and a shorter duration than morphine that indicates a higher solubility in fat, facilitating its passage through the blood-brain barrier.[9,15]

However, cystoscopy is being performed with a variety of anesthesia techniques like local, regional, and general anesthesia.[1,16] It is recognized as a painful procedure which in suprasegmentally reflex responses to pain and increasing the sympathetic tone, catecholamine, and catabolic hormone secretion, as well as, reducing anabolic hormone levels.[16] This mechanisms causes a hyper-metabolic state and augments

their own oxygen consumption in patients and because stress response may lead to poor wound healing and immune function depression.[16,17] Therefore, pain management is reasonably evident and some medications are targeted to alleviate and to treat anxiety with probable kidney side effects in patients. A combination with balanced dose helps enhance the therapeutic efficacy besides decreasing their side effects.[3,4,18] Since, no study has compared the combination of our drugs and that former studies have been exploring the efficacy of either propofol or dexmedetomidine alone, the authors decided to conduct a study to address the efficacy of dexmedetomidine-ketamine (DEX-KET) and fentanyl-ketamine (FEN-KET) on sedation and analgesia for cystoscopy.

Subjects and Methods

This double-blinded randomized controlled trial enrolled 60 patients undergoing cystoscopy who were admitted Vali-Asr Hospital Clinic, Arak, Iran, after obtaining written consent and verification of inclusion/exclusion criteria. Sample size calculation by MedCal 15 software (MedCalc Software Ltd., Ostend, Belgium) was conducted based on power 80% and $\alpha = 0.05$ and minimum difference of sedation score between two groups based on results of other studies. The minimum sample size for each group was estimated to be 29.

Subjects

Inclusion criteria were 18–65 years of age, both genders, American Society of Anesthesiologist status I–II, being candidate for cystoscopy, lack of sensitivity to medications used, no history of heart, lung, liver and kidney diseases, no body mass index > 36 kg/m^2, no history of obstructive sleep apnea, no history of addiction to drug or other psychotropic substances, as well as alcohol, and no history of psychological disease. Exclusion criteria were including patient dissatisfaction with participation in the study or non-cooperation of eligible subjects.

Patients were assigned into two groups by block randomization method[19] and all kept nil per os from the night before surgery. Patients received 10 mL/kg of Ringer's lactate solution along with 3–4 L/min of oxygen via nasal cannula throughout the cystoscopy. No other sedation medication was intraoperatively used. The DEX-KET group received 0.5 mg/kg ketamine (Rotexmedica GmbH Arzneimittelwerk Co., Bunsenstrasse, Germany) and 1 μg/kg dexmedetomidine (Exir Co., Tehran, Iran), while the FEN-KET group did 0.5 mg/kg ketamine and 2 μg/kg fentanyl (Caspian Tamin Co., Rasht, Iran). The drug varying in each group, i.e., fentanyl *vs*. dexmedetomidine, was first administered intravenously in a volume of 10 mL over 10 minutes. Afterward ketamine, as the base drug, was done at the desired dose. HR, mean blood pressure, and saturated oxygen (SaO_2), respiratory rate (RR), and pain score was measured via visual analog scale,[20] based on which 0 and 10 mean the lowest and highest severe pain experienced by the patients.

Measurements

The sedation level was quantified by Ramsay score,[21] as follows: 1 = Patient is restless and agitated; 2 = patient is tranquil, cooperative, orientated, and agitated; 3 = patient is sedated while he/she responds only to commands; 4 = patient responds well to optical and tactile stimulus stimuli; 5 = patient responds to optical and tactile stimuli with laziness and inactivity; 6 = patient does not respond at all. These were recorded for all patients at baseline and after induction of analgesia and sedation every 5 minutes during the surgery up to 60 minutes later. After the cystoscopy, the monitoring continued to achieve full patient consciousness, whereas the side effects of the medications were recorded during cystoscopy and up to 2 hours thereafter.

The side effects were defined as a decrease in mean blood pressure by more than 20% of baseline or as a decrease in SaO_2 below 90%, despite receiving 4 L/min oxygen via face mask, or as a decrease in HR by more than 20% of baseline. The recovery score (Aldrete score[22]) was recorded for patients during the cystoscopy when a score > 8 was considered as patient transferability score. Urologist satisfaction with cystoscopy was recorded at the end of cystoscopy, as follows: 0: comfort and full satisfaction; 1: moderate or partial satisfaction; 2: difficulty or dissatisfaction with cystoscopic conditions. Data was measured and recorded by an anesthesiologist who was unaware of patient allocation. Moreover, the patients were not aware of the group they were assigned.

Ethical consideration

The written informed consent was obtained from all eligible subjects and the study protocol was approved by Ethical Committee of Arak University of Medical Sciences with IR.ARAKMU.REC.1397.108 on July 2, 2018 (**Additional file 1**). Moreover, the study protocol is registered in Iranian Registry Clinical Trial center with code IRCT20141209020258N105 on April 21, 2019.

Statistical analysis

Data analysis was conducted using SPSS version 20 (IBM, Armonk, NY, USA) by independent samples *t*-test, chi-square test and analysis of variance for repeated measures.

Results

The included subjects ($n = 60$) undergoing cystoscopy who were hospitalized at Valiasr Hospital and were randomly assigned into two groups of DEX-KET and FEN-KET. The mean age of patients was 40.28 ± 9.43 years with the minimum and maximum age of 23 and 60 years, respectively. According to **Table 1**, there was no significant difference in mean age of DEX-KET and FEN-KET groups ($P = 0.968$). Moreover, sex distribution was similar between two groups ($P = 0.780$). In addition, the mean blood pressure, HR, RR, SaO_2 and pain score by visual analog scale were similar statistically before starting of cystoscopy ($P > 0.05$).

Based on the **Figure 1A**, the mean blood pressure was lower in the DEX-KET group than in the FEN-KET group at 20–40 minutes from the starting of cystoscopy ($P < 0.05$). But no statistically significant difference was found in mean blood pressure between two groups at other times studied ($P > 0.05$). However, repeated measure test showed that no significant difference was in trend of mean blood pressure between two groups ($P > 0.05$). As shown in **Figure 1B**, no statistically significant difference was observed in RR between the two groups at all times after cystoscopy ($P > 0.05$). In addition,

Table 1: Age and gender distribution in cystoscopy patients with dexmedetomidine-ketamine or fentanyl-ketamine anesthesia

	Dexmedetomidine-ketamine group	Fentanyl-ketamine group	*P*-value
Age (yr)	40.23±9.57	40.33±9.45	0.968
Gender			0.780
Female	14(48)	15(50)	
Male	16(52)	15(50)	

Note: Data in age are expressed as the mean ± SD, and analyzed by independent samples *t*-test. Data in gender are expressed as the number (percent), and analyzed by chi-square test.

the repeated measure test showed no significant difference in trend of RR between two groups ($P = 0.687$). The results showed no significant difference in SaO_2 between the two groups ($P > 0.05$). Moreover, similar trend of SaO_2 observed in two groups based on repeated measure analysis of variance test ($P = 0.652$; **Figure 1C**).

The results in **Table 2** declared a statistically significant difference in HR between both groups since 25th to 50th minutes from starting of cystoscopy ($P < 0.05$) and lower HR in the DEX-KET group, while no statistically significant difference was seen in HR between both groups at other times ($P > 0.05$). Moreover, repeated measure analysis of variance test showed that there was significant difference in trend of RR between two groups ($P = 0.017$).

Given the results in **Table 3**, a statistically significant difference was observed in the pain score between groups from 30th to 60th minutes after starting of cystoscopy ($P < 0.05$). Based on our results, the mean of pain score was lower in DEX-KET group than that in FEN-KET group. Moreover, the repeated measure test showed that the trend of increasing of pain score was different between groups and was higher in FEN-KET group ($P = 0.035$). According to our results, the mean of cystoscopy duration was not statistically significant between the two groups ($P = 0.731$). Moreover, no statistically significant difference was found in the Aldrete score for discharge from the recovery room between them ($P = 0.356$; **Table 4**).

Comparing Ramsay score as sedation level between groups showed that the mean of Ramsay score was higher in DEX-KET than that in FEN-KET group from the 5th to 15th minutes after starting of cystoscopy and at other times it was similar in two groups (2.010 ± 0.012 *vs*. 0.016 ± 0.001, $P < 0.001$). No statistically significant difference was seen in Ramsay score between both groups in all times after start of cystoscopy ($P < 0.05$). Moreover, no statistically significant difference was observed in the urologist satisfaction score in DEX-KET and FEN-KET groups (0.13 ± 0.35 *vs*. 0.17±0.38, $P = 0.723$). Full satisfaction rate was observed in 26 patients (87%) of DEX-KET group and 25 patients (83%) of FEN-KET group and no dissatisfaction reported in each group ($P = 0.500$).

The incidence of side effects in DEX-KET and FEN-KET was observed in 4 patients (13%) and 3 patients (10%), respectively. This difference was not statistically significant between the two groups ($P = 0.500$).

Discussion

According to our results, no significant difference was observed in age, gender, duration of surgery, BP, RR, SaO_2, Aldrete score, urologist satisfaction and side effects between two study groups including DEX-KET and FEN-KET, while HR and pain score were less in the DEX-KET group after cystoscopy. In the other hand, the DEX-KET group relieves pain score 30 minutes after cystoscopy.

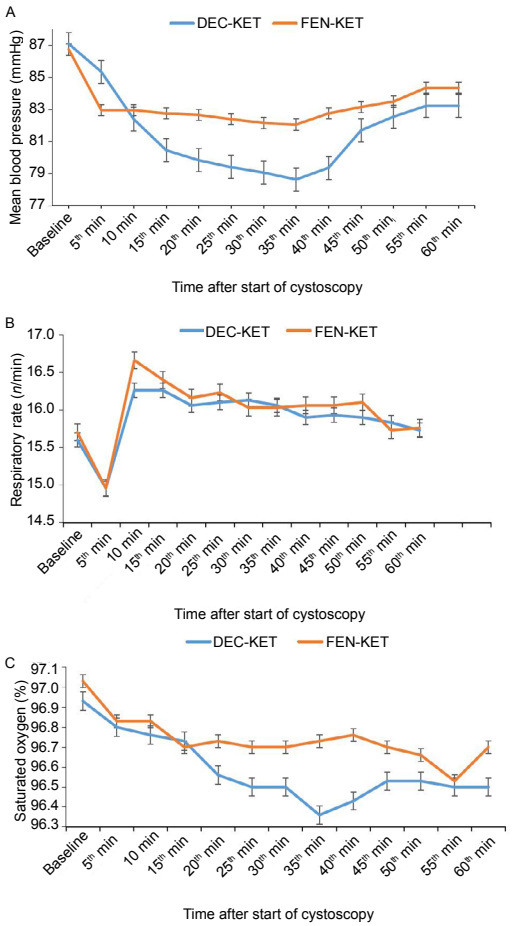

Figure 1: Comparison the DEX-KET and FEN-KET on mean blood pressure (A), respiratory rate (B), and saturated oxygen (C) in patients after cystoscopy. Note: Data are expressed as the mean ± SD, and analyzed by independent samples *t*-test. DEX-KET: Dexmedetomidine-ketamine group; FEN-KET: fentanyl-ketamine group.

Akça et al.'s study[13] comparing the prophylactic effect of ketamine and dexmedetomidine on catheter-related bladder discomfort reported that dexmedetomidine and ketamine equally relieve the pain and increases patient sedation, however, the side effects were greater in dexmedetomidine than ketamine. Our results indicated that DEX-KET relieved pain 30 minutes after cystoscopy, while no dexmedetomidine-related side effect was observed. Another study showed that ketofol creates more stable hemodynamic parameters and quality of sedation compared with alfentanil-propofol combination in elective colonoscopy, and required to less additional propofol.[23] However, it seems that the combination of alfentanil-propofol vs. ketamine-propofol reduced the pain ratings and increased duration of analgesia and has fewer complications in cystoscopy and that alfentanil is preferable to ketamine. Based on our study, DEX-KET relieved pain 30 minutes after cystoscopy. Another study by Heo et al.'s trial[24] compared the effect of remifentanil combined with dexmedetomidine for patients undergoing cystoscopy and suggested that both relieved pain dur-

Table 2: Comparison of HR of patients after cystoscopy in both DEX-KET and FEN-KET groups

	DEX-KET	FEN-KET	*P*-value
Baseline	87.43±8.03	88.96±8.34	0.471
5th min	86.53±7.34	88.43±7.99	0.342
10th min	85.93±7.08	88.26±7.88	0.233
15th min	85.40±6.71	88.06±7.81	0.162
20th min	84.50±6.59	87.96±7.82	0.069
25th min	83.80±6.82	87.86±7.85	0.036
30th min	83.26±7.26	87.66±7.93	0.029
35th min	82.90±7.66	87.56±7.99	0.025
40th min	83.63±7.26	87.76±7.88	0.039
45th min	84.60±6.81	88.83±7.30	0.024
50th min	85.10±6.22	89.00±7.26	0.029
55th min	85.76±5.64	89.00±7.26	0.059
60th min	85.76±5.64	89.00±7.26	0.059

Note: Data are expressed as the mean ± SD, and analyzed by independent samples *t*-test. DEX-KET: Dexmedetomidine-ketamine group; FEN-KET: fentanyl-ketamine group.

Table 3: Comparison of pain of patients after cystoscopy in both DEX-KET and FEN-KET groups

	DEX-KET	FEN-KET	*P*-value
Baseline	00.00±00.00	00.00±00.00	1
5th min	2.13±0.345	2.13±0.345	1
10th min	2.33±0.479	2.26±0.449	0.581
15th min	2.33±0.479	2.63±0.439	0.581
20th min	2.50±0.508	2.63±0.614	0.364
25th min	2.60±0.508	2.73±0.615	0.261
30th min	2.73±0.639	3.06±0.520	0.031
35th min	2.73±0.639	3.06±0.520	0.031
40th min	2.73±0.639	3.06±0.520	0.031
45th min	3.20±0.406	3.53±0.507	0.007
50th min	3.20±0.406	3.53±0.507	0.007
55th min	3.20±0.406	3.53±0.507	0.007
60th min	3.20±0.406	3.53±0.507	0.007

Note: Data are expressed as the mean ± SD, and analyzed by independent samples *t*-test. DEX-KET: Dexmedetomidine-ketamine group; FEN-KET: fentanyl-ketamine group.

Table 4: Comparison of cystoscopy duration and Aldrete score for discharge from the recovery room in both DEX-KET and FEN-KET groups

	DEX-KET	FEN-KET	*P*-value
Duration of cystoscopy (min)	13.23±1.85	13.06±1.89	0.731
Aldrete score (recovery level)	9.73±0.45	9.83±0.38	0.356

Note: Data are expressed as the mean ± SD, and analyzed by independent samples *t*-test. DEX-KET: Dexmedetomidine-ketamine group; FEN-KET: fentanyl-ketamine group.

ing the cystoscopic procedure, whose results were in line with ours. Moreover, in Arpaci et al.'s study,[25] the sedation effect of remifentanil-dexmedetomidine and remifentanil-midazolam combinations during cystoscopy was compared and the faster and more satisfactory effect of remifentanil-dexmedetomidine was shown. Those results were consistent with ours in which no difference was found in urologist satisfaction between the groups. Another studies showed that the effect of dexmedetomidine on cystoscopy and indicated better sedation score and analgesic effects in the dexmedetomidine group, suggesting dexmedetomidine as a safe effective drug for cystoscopy.[14,25] Their results were in line with our study. In addition, Sajedi et al.[26] performed a single-dose study of propofol combined with fentanyl to induce anesthesia during cystoscopy and reported that propofol had a greater effect on deep sedation in patients undergoing cystoscopy, while did not pose a risk to patients. Our DEX-KET relieved pain 30 minutes after cystoscopy.

In summary, the DEX-KET relieves pain 30 minutes after cystoscopy with stable hemodynamic parameters. Thus, the DEX-KET combination can be used as a choice for sedation in cystoscopy, with absence of side effects which requiring treatment. Future studies should use other diverse drug combinations as well as higher sample sizes to assess the efficacy of other alternative pharmaceutical options. Nevertheless, long follow-up of patients for consequences was not conducted in this study, which was its limitation.

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Author contributions
Study conception or design: HM, EM, TK, AM; data acquisition and analysis: BY, DG; data collection and entry: AM; data interpretation: HM, TK; manuscript drafting: BY, DG. All authors revised the manuscript and approved the final version.

Conflicts of interest
There is no conflict of interest.

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Institutional review board statement
The study protocol was approved by Ethical Committee of Arak University of Medical Sciences with IR.ARAKMU.REC.1397.108 code on July 2, 2018. Moreover, the study protocol is registered in Iranian Registry Clinical Trial center with code IRCT20141209020258N105 on April 21, 2019.

Declaration of patient consent
The authors certify that they have obtained patients consent forms. In the form, patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published.

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The writing and editing of the article were performed in accordance with the CONsolidated Standards Of Reporting Trials (CONSORT) statement.

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The statistical methods of this study were reviewed by the epidemiologist of Qom University of Medical Sciences, Iran.

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Data sharing statement
Datasets analyzed during the current study are available from the corresponding author on reasonable request.

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Additional file 1: Hospital Ethics Approval.

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Research Ethics Certificate

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Status:	Approved		
Approval Statement:	The project was found to be in accordance to the ethical principles and the national norms and standards for conducting Medical Research in Iran. Notice: 1. Although the proposal has been approved by the research ethics committee, meeting the professional and legal requirements is the sole responsibility of the PI and other project collaborators. 2. This certificate is reliant on the proposal/documents received by this committee on 2018-07-02. The committee must be notified by the PI as soon as the proposal/documents are modified.		
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