Dexmedetomidine infusion for prevention of emergence agitation in patients undergoing percutaneous nephrolithotomy under sevoflurane anesthesia: a prospective double-blinded randomized placebo study

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Introduction Percutaneous nephrolithotomy (PCNL) under general anesthesia is more susceptible for developing emergence agitation (EA).

Aim This randomized double-blinded, prospective, comparative, clinical study was aimed to evaluate dexmedetomidine efficacy for EA prevention in patients undergoing PCNL.

Patients and methods A total of 44 patients with American Society of Anesthesiologists grades I–II aged between 21 and 70 years, experiencing an elective PCNL under general anesthesia, were included in the study. Patients were randomly allocated to one of two groups: group C and group D. Placebo was given to group C, whereas a bolus dose of dexmedetomidine 1.0 μg/kg was given to group D patients, followed by 0.4 μg/kg/h after anesthesia induction. Adjustment was made to end-tidal sevoflurane to keep bispectral index at 45–55. Sevoflurane and the study drug were stopped when surgical dressing was applied. Evaluation of EA was made from extubation until the patients was transferred to postanesthesia care unit. EA incidence was the primary outcome, whereas sevoflurane requirement, hemodynamic stability, and recovery from anesthesia were the secondary outcomes.

Results There was a significant reduction of EA incidence (group C 54.5%; group D 9.1%) with dexmedetomidine infusion to 90.9% (P=0.0001). There was also significant lowering of the end-tidal sevoflurane concentration and an average 38.87% reduction in required concentration in group D, in contrast to group C ($P<0.001$). There was significantly higher average mean arterial blood pressure and heart rate in group C compared with group D ($P<0.001$). There is significantly lesser time to extubation, lesser time to achieve bispectral index 90, and lesser time in reacting to verbal command in group C when compared with group D ($P<0.0001$).

Conclusion The EA incidence and sevoflurane requirement among patients experiencing PCNL are significantly decreased by dexmedetomidine infusion. Moreover, dexmedetomidine was associated with delayed extubation time, residual sedation, and prolonged postanesthesia care unit stay.

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Introduction

Inhaled anesthetic agents comprise the basis of modern anesthetic practice. The introduction of newer inhalational agents is aimed at identifying the perfect agent that rapidly induces anesthesia, has pleasant smells, provides more safety, with less adverse effects [1].

However, even with the recent agents like sevoflurane, still there are some adverse effects that shield it from being the 'perfect' anesthetic agent [2]. Sevoflurane appears to have many advantages such as decreasing time to awakening with faster eye opening, response to verbal command, and orientation to person, place, and time [3]. However, the utilization of inhalational analgesics may cause emergence agitation (EA) during recovery from general anesthesia. EA has also been specified to emergence delirium, and sometimes it is accompanied with negative postoperative behaviors [4].

Although it occurs for short duration, it may require pharmacological intervention. Various agents including ketamine, propofol, clonidine, and opioids have been used to prevent EA. However, these medications may be accompanied with sedation after anesthesia, causing slow arousing, and in a few patients are associated with unwanted adverse effects, such as nausea or vomiting [5].

Dexmedetomidine acts on α-2 adrenergic receptors producing sedation, hypnosis, with anxiolytic effects without significant depressive effects on respiration. It has been extensively used in children to decrease the incidence of EA [6].

Rim *et al*. [7] found that EA in the postanesthesia care unit (PACU) occurred in ~10% of patients undergoing urological surgery. Percutaneous nephrolithotomy (PCNL) is still used as the first-line treatment in large stones, even though there are many recent retrograde 'per vias naturales' techniques that are becoming more popular in bigger large renal stone [8].

This study hypothesizes that dexmedetomidine infusion during the maintenance of anesthesia leads to diminished rate of EA in adult patients posted for PCNL under sevoflurane anesthesia. This randomized, double-blinded, controlled, and clinical trial aimed to evaluate the effect of dexmedetomidine on incidence of EA as the primary outcome. Other outcomes included intraoperative requirement of sevoflurane, intraoperative hemodynamics, and recovery after general anesthesia.

Patients and methods

This double-blind, randomized, clinical study was approved by our local ethics and research committee at Al-Hussein Hospital, and written informed consents were obtained. The study included 44 patients, aged 21–70 years of age, with American Society of Anesthesiologists physical status I–II scheduled for elective PCNL of more than 1 h duration under sevoflurane anesthesia.

The exclusion criteria were hypersensitivity to study medications, a history of alcohol or drug abuse, conditions associated with severe systemic diseases (cardiac, hepatic, renal, pulmonary, endocrinal, neurological, or psychiatric disease), got an opioid analgesic prescription within a 24-h period before the operation, BMI more than 35 kg/m^2, and on medications such as α-2 agonists, clonidine, beta-blockers, and tricyclic antidepressant.

Preanesthetic visit included thoroughly evaluation of the patients a day before scheduled operation. Anesthesia administration was performed similarly for both groups utilizing a standard protocol. Patients were premedicated with intravenous midazolam (0.05 mg/kg for lean body weight) in the preoperative holding area, and the patients were then transferred to the operating room.

In the operating room, standard monitoring included five-lead electrocardiograph, heart rate, arterial oxygen saturation (SpO_2,) measured by pulse oximeter, and noninvasive blood pressure (Datex Ohmeda-GE, S5, patient monitor; GE, San Diego Ca., USA). Moreover, bispectral index (BIS, BIS VIEW, BIS VIEW$_{TM}$, Aspect Medical Systems, Norwood, MA, USA) electrodes were applied, and baseline vital signs were then recorded. Two intravenous accesses were secured for all patients: one for infusion of study drug and the other for intravenous fluids. Following preoxygenation, anesthesia was induced with propofol 2.0–2.5 mg/kg intravenous, and fentanyl 2 μg/kg intravenous slowly, targeting BIS score of 45–50, and atracurium 0.5 mg/kg intravenous was used to facilitate tracheal intubation.

Patients were randomly allocated to two groups: group C (n=22) received sevoflurane in air and oxygen (50 : 50) with a bolus dose of normal saline (0.9%) for 10 min and then infusion was maintained after intubation, and group D (n=22) received sevoflurane in air and oxygen (50 : 50) with dexmedetomidine infusion 1 μg/kg for 10 min as a bolus dose followed by 0.4 μg/kg/h after intubation.

The sample size of this study was calculated according to the primary outcome measure, that is, Kim *et al*. [7] reported 10% incidence of EA in patients experienced urological surgery. The study assumes that the 60% reduction in incidence of EA with dexmedetomidine under sevoflurane anesthesia would be of clinically relevant. The sample size calculation for the two-sided test (α) of 5% and with power (1–β) of 80% would be 22 patients in each group for proportional outcome [8]. We enrolled 22 patients in each group.

Randomization depended on computer-generated codes, which were maintained in successively random numbered opaque envelopes. The envelopes were opened just before the surgery. The study drug was labeled as test and prepared in 50-ml syringe. The drug dilution was based on weight of the patient, and all patients received loading infusion at 120 ml/h for the first 10 min and followed by 8 ml/h till the end of surgery (when surgical dressing was applied). The attending anesthesiologist, recovery nurses, and patients were blinded to randomization schedule.

During the surgery, sevoflurane concentration was titrated to keep BIS 45–55, and end-tidal sevoflurane concentration was recorded every 10 min in both the studied groups. End-tidal CO_2 concentration was kept at 35–40 mmHg by ventilating the lungs with 6–8 ml/kg tidal volume, and 12 breaths per minute was the respiratory rate.

Intraoperative mean values of mean arterial blood pressure and heart rate were recorded at the following times: baseline (T1), induction of

anesthesia (T2), beginning of surgery (T3), discontinuation of anesthetics (T4), arrival at PACU (P1), 10 min after arrival at PACU (P2), and 20 min after arrival at PACU (P3).

Paracetamol 1 g intravenous (injectmol 10 mg/ml; Al-Amreya, Alexandria, Egypt) over 30 min and 0.1 mg/kg intravenous ondansetron was given half an hour before the end of the surgical procedure. Sevoflurane and the study drug were stopped when surgical dressing was applied.

Neuromuscular blockade was reversed using intravenous atropine 0.01 mg/kg and neostigmine 0.05 mg/kg. Then trachea was extubated with adequate power of muscles. Emergence time was defined as the time interval from surgical dressing till the patient was transferred to PACU once the patient tells his/her name. At that period, evaluation of agitation level utilizing the Riker sedation-agitation scale was done (Table 1) [9], and EA and pain measurements were repeated every 2 min to gain the peak score. Patients with EA score of 5 and 6 required intervention in the form of frequent verbal reminding, whereas 1 mg/kg propofol was given to patient with 7 EA score.

Time to extubation (time between surgical dressing and extubation), time to achieve BIS of 90 (time between surgical dressing and recording of BIS value 90), time to response to verbal commands (Tverbal) (time between surgical dressing and patient respond by telling his/her name), and time to discharge from PACU (Tdischarge) (time between surgical dressing and achievement of Aldrete score ≥9) (Table 2) [10] were noted and recorded.

Table 1 Riker sedation-agitation scale [9]

Scores	State	Behavior
7	Dangerous agitation	Trying to remove catheters, climbing over bedrail, thrashing side to side, or striking at staff
6	Very agitated	Requiring restraint and frequent verbal reminding of limits
5	Agitated	Anxious or physically agitated and calms to verbal instructions
4	Calm cooperative	Calm, easily arousable, and follows commands
3	Sedated	Difficult to arouse but awakens to verbal stimuli or gentle shaking, and follows simple commands
2	Very sedated	Arouse to physical stimuli but does not communicate or follow commands
1	Unarousable	Minimal or no response to noxious stimuli, and does not communicate or follow commands

Residual sedation was observed and monitored by a blinded observer using Ramsay sedation scale [11]. The intensity of pain was monitored, using numeric rating scale [12] (0=no pain, 10=unimaginably severe pain).

Analgesic requirement and nausea/vomiting were recorded. Paracetamol intravenous 15 mg/kg was given as rescue analgesia and administered in PACU on the patient request.

Data were tabulated and analyzed using SPSS IBM software, version 21 (IBM SPSS Advanced Statistics; IBM, Chicago, Illinois, USA). Categorical variables were expressed as percentages, whereas continuous data were checked for normal distribution by the Kolmogorov–Smirnov test and are reported as the means and SDs or the medians with 25th and 75th percentiles, when applicable. Categorical variables were analyzed by the χ^2 test. Comparisons of continuous data were performed by using the unpaired t test for normally distributed variables and the Mann–Whitney U test for nonnormally distributed variables.

Results

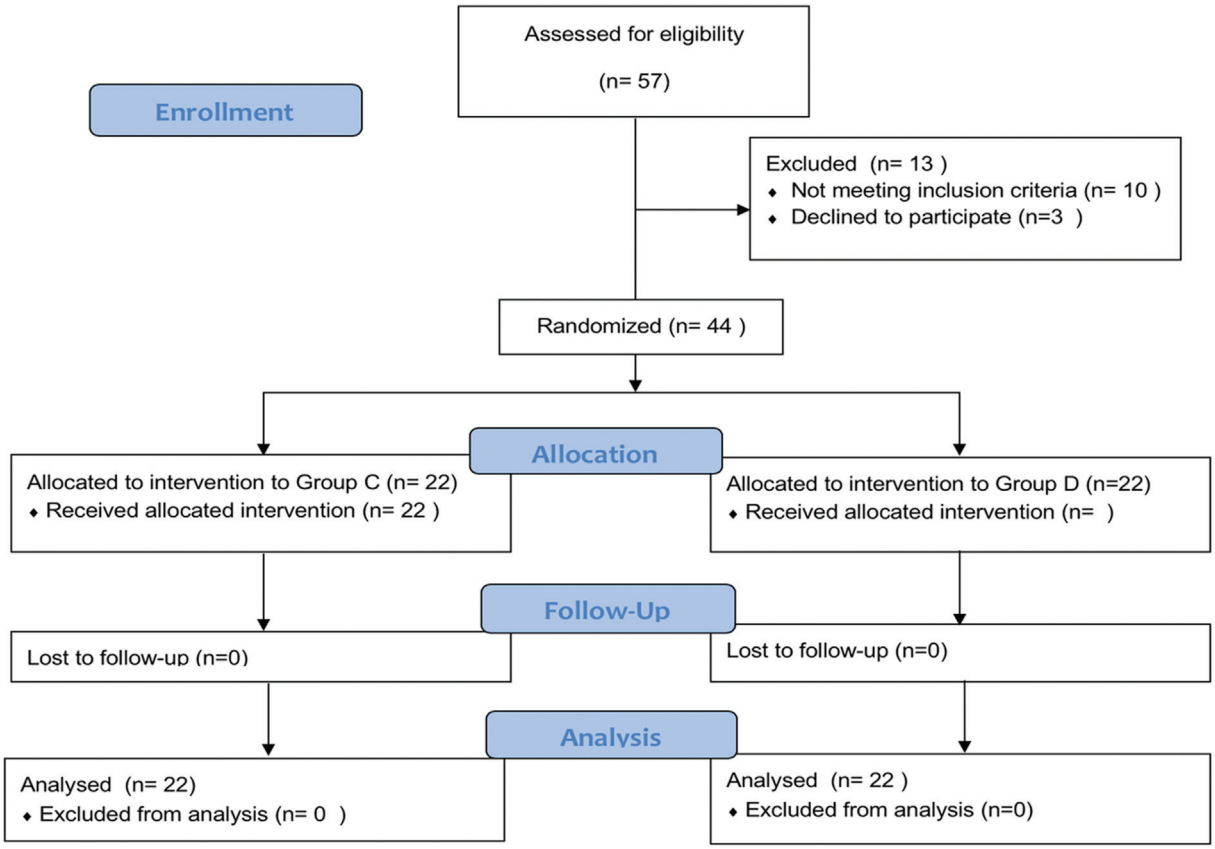
A total of 57 patients were screened; of them, 44 patients meeting the inclusion criteria were enlisted in the study (Fig. 1).

Table 2 Aldrete score [10]

Parameters	Description of the patient	Score
Activity level	Moves all extremities voluntarily on command	2
	Moves 2 extremities	1
	Cannot move extremities	0
Respiration	Breathes deeply and coughs freely	2
	Is dyspneic, with shallow, limited breathing	1
	Is apneic	0
Circulation (blood pressure)	Is 20 mmHg > preanesthetic level	2
	Is 20–50 mmHg > preanesthetic level	1
	Is 50 mmHg > preanesthetic level	0
Consciousness	Is fully awake	2
	Is arousable on calling	1
	Is not responding	0
Oxygen saturation as determined by pulse oximetry	Has level >90% when breathing room air; requires supplemental oxygen to maintain level >90%	2
	Has level <90% with oxygen supplementation	1
		0

*Maximum total score is 10; a score of ≥9 is required for discharge.

Figure 1



Consort flow chart.

Table 3 Demographics, type and duration of surgery, and duration of anesthesia

	Group C	Group D	*P* value
Demographics			
Age (year)	43.12±13.72	40.86±11.84	0.34
Sex (M/F)	15/ 7	13/9	–
BMI (kg/m^2)	29.46±1.12	30.53±2.65	0.68
Duration of surgery (min)	102.24±20.76	99.88±18.64	0.46
Duration of anesthesia (min)	117.88±14.93	121.84±15.98	0.63

Data are expressed as *n* and mean±SD. Group D, dexmedetomidine group; group C, control group.

The demographic characteristics (age, weight, and sex), duration type of surgery, and duration of anesthesia were comparable between the groups ($P>0.05$) (Table 3).

Regarding EA, 12 (54.5%) patients in group C had EA, and one (4.5%) of the patients had dangerous agitation, whereas only two (9.1%) patients had EA and none of the patients had dangerous agitation in group D ($P=0.0001$) (Fig. 2). Dexmedetomidine was efficient in decreasing the incidence of EA by 90.9%.

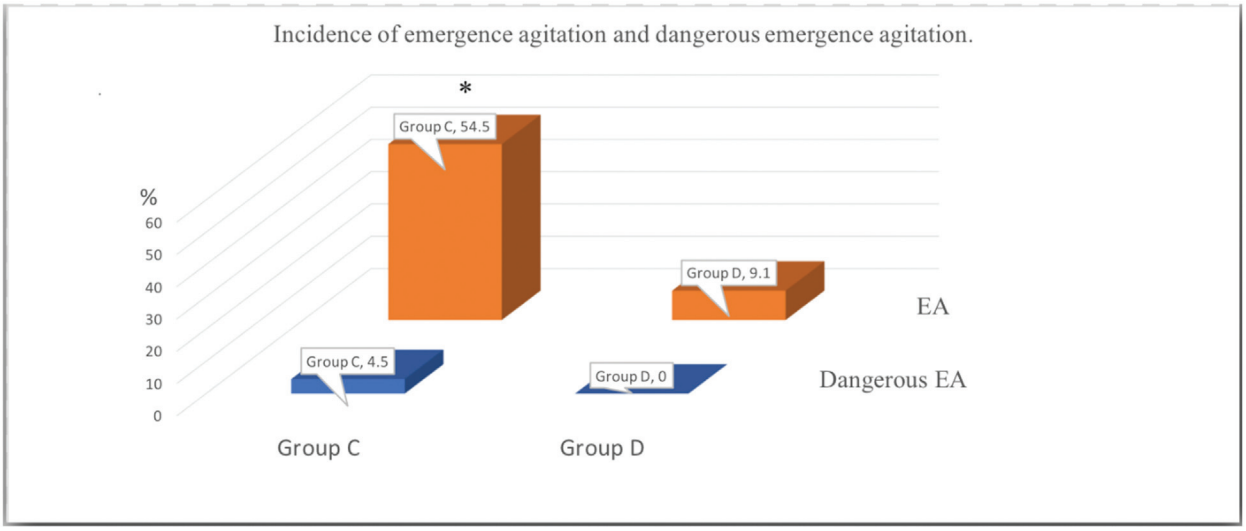
The end-tidal sevoflurane concentration was significantly lower, and there was an average 38.87% reduction in requirement of sevoflurane in group D compared with group C ($P<0.001$) (Table 4).

Regarding intraoperative mean arterial blood pressure and heart rate, there were higher significant differences in mean arterial blood pressure (Fig. 3) and heart rate (Fig. 4) in group C compared with group D at all times during the observation period ($P<0.001$).

In group C, time to extubation, time to achieve BIS90, and Tverbal (6.43±0.41, 6.76±0.19, and 6.94±0.16 min, respectively) was significantly shorter compared with group D (9.83±0.37, 10.45±0.91, and 11.2±0.3 min, respectively) ($P<0.0001$) (Table 4). The Tdischarge in group C was significantly less compared with group D (11.45±1.64 vs. 17.85±3.31 min) ($P<0.01$) (Table 5).

Regarding sedation, antiemetic requirement, and analgesic requirement, patients in group C had

Figure 2



Incidence of emergence agitation (EA) and dangerous EA. Group D, dexmedetomidine; group C, control with normal saline. *P value of 0.0001.

Table 4 End-tidal sevoflurane recorded at different time intervals in both groups

	Group C	Group D	P value
At 10 min	2±0.2	2.1±0.2	0.884
At 20 min	2.03±0.2	0.81±0.2	0.001*
At 30 min	2.1±0.1	0.7±0.2	0.003*
At 40 min	1.98±0.2	0.67±0.2	0.001*
At 50 min	1.85±0.2	0.83±0.2	0.023*
At 60 min	2±0.2	0.9±0.3	0.001*
At 70 min	2.3±0.2	0.85±0.4	0.013*
At 80 min	2.12±0.2	0.92±0.1	0.001*
At 90 min	2.72±0.2	0.96±0.2	0.001*
At 100 min	1.95±0.2	0.73±0.1	0.001*
At 110 min	1.8±0.2	0.8±0.2	0.01*
At 120 min	1.7±0.2	0.6±0.1	0.004*

Data are expressed as mean±SD. Group D, dexmedetomidine group; group C, control group. *Significance at P value less than 0.05.

significantly less residual sedation compared with group D (P=0.006). The antiemetic requirement in groups C and D was 14 and 9.1%, respectively (P=0.15). The analgesic requirement in groups C and D was 18.2 and 9.1%, respectively (P=0.3). Both the groups displayed acceptable level of analgesia evaluated using numeric rating scale, without any significant difference in the mean score (P=0.124) (Table 5).

Discussion

EA is defined as a condition of restlessness without focus and lack of cooperation, as well as inconsolability, often resulting in crying and screaming, as well as in thrashing and confusion [13]. In spite of agitation being observed more regularly when it comes to pediatric patients, there has been 4.7 or 21.3% of such incidence reported in adults. Utilizing different scoring scale for EA evaluation is what possibly led to the broad variation in the reported incidence [14].

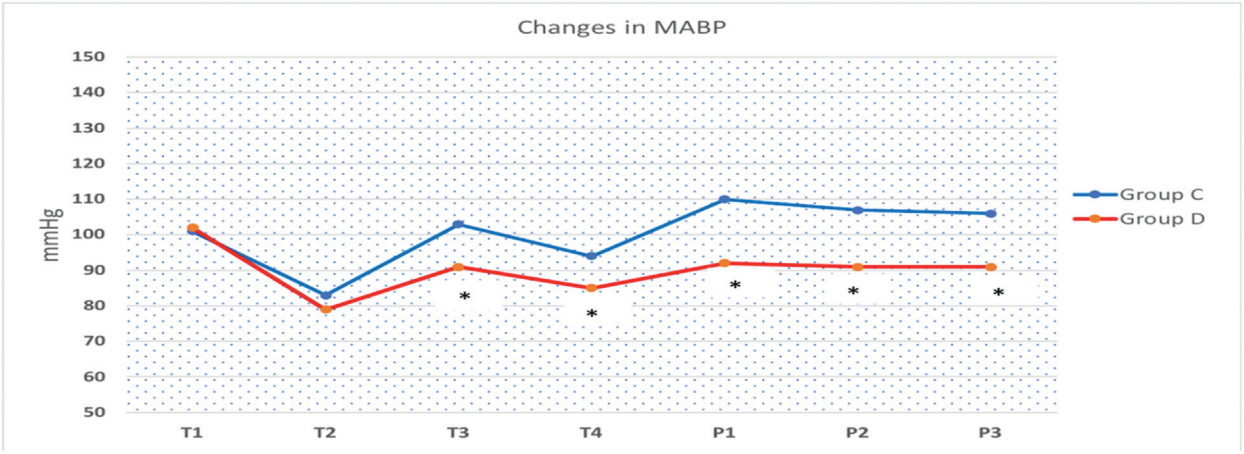
Noradrenaline release increase in the preoptic area of the rat brains, precisely in the locus coeruleus, has been described as a cause of EA [15]. Nonetheless, suggestion has been made for link with other factors like pain and inhalational anesthetics, as well as the use of preoperative benzodiazepine and male sex, together with age, preoperative anxiety, and type of surgery [16].

Results from this study showed the effectiveness of intraoperative infusion of dexmedetomidine (1 μg/kg against 10 min and followed by 0.4 μg/kg/h) in the reduction of EA incidence after undergoing PCNL surgery. Additional stable hemodynamics was produced during surgery and during extubation, and significant reduction in sevoflurane requirement took place. This was associated with delayed extubation and residual sedation, together with lengthy PACU stay.

There is a link between fast recovery from anesthesia and EA development, and this usually occurred when short-acting volatile anesthetic agents such as sevoflurane and desflurane are utilized [17]. It is also referenced as emergence delirium or emergence excitement, with the possibility of resulting in a dissociative state while having an altered cognitive awareness and excitation, as well as agitation when recovering from anesthesia.

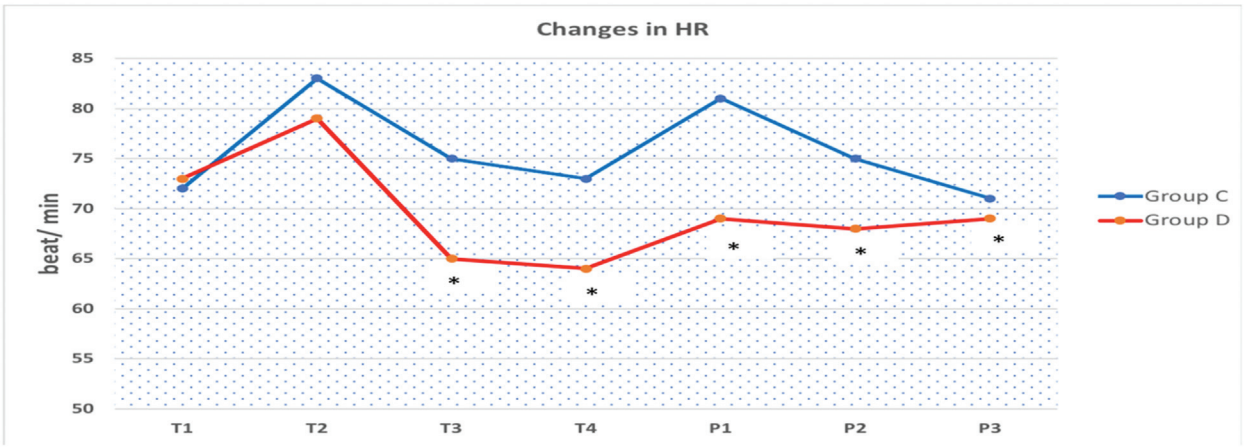
Reports emanating from different studies showed that 4.1% was the EA incidence in adult patients

Figure 3



Perioperative mean arterial blood pressure changes. Group D, dexmedetomidine group; Group C, control group; T1, baseline; T2, induction of anesthesia; T3, beginning of surgery; T4, discontinuation of anesthetics; P1, arrival at postanesthetic care unit (PACU); P2, 10 min after arrival at PACU; P3, 20 min after arrival at PACU. *Significance at *P* value less than 0.05.

Figure 4



Perioperative heart rate changes. Group D, dexmedetomidine group; Group C, control group; T1, baseline; T2, induction of anesthesia; T3, beginning of surgery; T4, discontinuation of anesthetics; P1, arrival at postanesthetic care unit (PACU); P2, 10 min after arrival at PACU; P3, 20 min after arrival at PACU. *Significance at *P* value less than 0.05.

undergoing urological surgery [18]. An additional study that utilized a three-point scale in making an evaluation of EA came up with the report of 21.3% of patients developing postoperative EA in the PACU, with analysis of subgroup demonstrating the13.6% incidence in urology patients [19].

It is possible to explain these differences through variations in surgical site and through the scale used for assessing patient, as well as through interobserver agreement and the possibility of EA becoming specifically common upon undergoing urological surgery where agitation is experienced by 10% of patients [20]. It is possible to attribute higher incidence reported to a sense of suffocation experienced at the time the patient is coming out from anesthesia [21].

Many studies assessed the effectiveness of dexmedetomidine on postoperative EA and catheter-related bladder discomfort. Akça and colleagues evaluated the efficacy of prophylactic 1 μg/kg of dexmedetomidine intravenous 5 min before the end of surgery, whereas Kim and colleagues studied outcome of intraoperative dexmedetomidine 1.5 μg/kg loading, followed by 0.5 μg/kg/h infusion in the postoperative period. Both the studies described lower

Table 5 Time to extubation, time to achieve bispectral index 90, time to telling name on verbal command, incidence of emergence agitation, residual sedation, analgesic and antiemetic requirement in postanesthesia care unit, and time to discharge in both groups

Parameters	Group C	Group D	*P* value
Time to extubation (min)	6.43±0.41	9.83±0.37	<0.0001*
Time to achieve BIS90 (TBIS90) (min)	6.76±0.19	10.45±0.91	<0.0001*
Time to verbal response (Tverbal) (min)	6.94±0.16	11.2±0.3	<0.0001*
Time to discharge (min)	11.45±1.64	17.85±3.31	<0.0001*
Peak NRS score	5.3±1.4	5.34 ±0.65	0.124
Ramsay sedation score [median (95% confidence interval)]	1 (0.66–1.11)	2 (1.08–1.64)	0.006*
Analgesic in PACU	4 (18.2)	2 (9.1)	0.30
Antiemetic in PACU	3 (14.0)	2 (9.1)	0.15

Data are expressed as *n* (%) and mean±SD. BIS, bispectral index; group D, dexmedetomidine group; group C, control group; NRS, numeric rating scale; PACU, postanesthesia care unit.
*Significance at *P* value less than 0.05.

percentage of EA as compared with the control group [22].

The reduction in EA incidence is brought about by dexmedetomidine sedative property. Nonetheless, it also resulted in prolonging the time for extubation and the time for attaining BIS90, as well as the time in responding to verbal command.

In spite of the sedative property of dexmedetomidine, no patient developed respiratory depression, considering the fact that respiratory drive is not depressed by dexmedetomidine, thereby making the safety of dexmedetomidine infusion maintenance until extubation possible.

Intervention that comes in the form of verbal instruction only is required by patients with EA, whereas intervention in the form of propofol is required by patient with dangerous EA. No patient being provided with dexmedetomidine experienced dangerous agitation in the existing study, whereas two patients being given placebo experienced dangerous agitation. Dexmedetomidine sympatholytic property makes stable hemodynamic available when performing surgery and after extubation.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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