Egyptian Journal of Anaesthesia (2015) **31**, 35–41

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Egyptian Journal of Anaesthesia

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Research Article

Comparative study between dexmedetomidine-ketamine and fentanyl-ketamine combinations for sedation in patients undergoing extracorporeal shock wave lithotripsy. A randomized double blinded study

Ayman A. El sayed [a,*], **Osama M. Assad** [b], **Mohamad S. El tahawy** [a]

[a] *Department of Anesthesia, Ain Shams University, Egypt*
[b] *Department of Anesthesia, Cairo University, Faculty of Medicine, Egypt*

Received 7 July 2014; revised 29 September 2014; accepted 2 November 2014
Available online 12 December 2014

KEYWORDS

ESWL;
Dexmedetomidine;
Fentanyl and Ketamine

Abstract *Background and objectives*
Extracorporeal shock wave lithotripsy (ESWL) is used safely for management of urinary stones. The aim of this randomized double blinded study was to compare the effects of dexmedetomidine-ketamine and fentanyl-ketamine combinations on analgesia, sedation, hemodynamics and respiratory effects in patients underwent ESWL.
Methods: Sixty patients aged between 20 and 50 years, ASA I or II physical status were randomly assigned into two groups. In Group Fentanyl-ketamine (FK) (n = 27): Patients received fentanyl at a 1 μg/kg over 10 min before the procedure and 0.5 mg/kg bolus of ketamine. In Group Dexmedetomidine-ketamine DK (n = 30): patients received dexmedetomidine 1 μg/kg over 10 min before the procedure and a 0.5 mg/kg bolus of ketamine. A blinded researcher assessed the patient's pain level (primary outcome), sedation level, and awareness via visual analogue scale (VAS), modified Observer's Assessment Alertness/sedation, and bispectral index respectively.
Results: There was a significant increase in VAS in the recovery period in FK group. There was a significant decrease in hemodynamics (HR, MAP) in the recovery period in DK group. There was a significant increase in bispectral index values in FK group during the postoperative period. The first

* Corresponding author at: Department of Anaesthesia, Ain Shams University, Egypt. Tel.: +201116929668.
E-mail addresses: draymanahmedm@yahoo.com, mai_nabil80@hotmail.com (A.A. El sayed).

Peer review under responsibility of Egyptian Society of Anesthesiologists.

http://dx.doi.org/10.1016/j.egja.2014.11.001

analgesia required was significantly longer in DK. There was a significant increase in sedation score in the recovery period in FK group. There was no significant difference between the two groups as regards the adverse effects except nausea and vomiting (significant in FK group).

Conclusion: Dexmedetomidine/ketamine combination was accompanied by more prolonged analgesia in the recovery period, prolonged sedation, and delayed request of first dose analgesia with less nausea and vomiting than fentanyl/ketamine combination.

1. Introduction

Extracorporeal shock wave lithotripsy (ESWL) is used safely for management of urinary stones. It is a simple, noninvasive and can be used safely in pediatric patients [1]. The newer generations of lithotripsy machines are less painful. The anesthetic agent should achieve adequate analgesia, sedation, immobility and hemodynamic stability [2]. A relaxed, cooperative patient is a main key in maintaining stones in place for optimal fragmentation. Thus, it is essential to choose a proper combination of drugs with minimal adverse effects to achieve a proper target [3].

Anesthetic techniques were changed from general or regional anesthesia to analgesic sedative techniques [4]. Different analgesic agents including NSAIDS (ketorolac or diclofenac), opioids (pethedine or morphine) and other analgesic techniques (cutaneous creams or local anesthetic agents) [5] have been used. NSAIDS are effective for pain relief with fewer side effects than narcotics; however, it is associated with hypersensitivity reactions, gastrointestinal disturbances, and sometimes coagulation disorders [6]. Regional anesthesia like intrathecal sufentanil and lidocaine can be used. However, these techniques are more time consuming to perform with prolonged recovery [7]. The EMLA cream, an eutectic mixture of prilocaine (2.5%) and lignocaine (2.5%) for topical use, has also used in ESWL. However, it should be used appropriately as an occlusive dressing for long period (60 min) before the procedure, and in combination with other analgesic agents [8]. Ketamine is one of the most commonly used drugs to achieve sedation and analgesia in ESWL. It can be used as a single agent or in combination with other drugs to achieve deep sedation with fewer side effects [2]. Dexmedetomidine is highly selective α2-adrenergic receptor agonist that has sedative analgesic properties with minimal side effects on ventilation [9]. Being an agonist for α2-adrenergic receptors, it decreases the release of catecholamines and it posseses sympatholytic action which results in bradycardia and hypotension [10]. Because of these effects, dexmedetomidine may be effective agent for conscious sedation in ESWL [11]. Fentanyl is a strong synthetic narcotic. But unfortunately it has significant adverse effects like respiratory depression, drowsiness, nausea and vomiting [12].

The aim of this randomized double blinded study was to compare the effects of dexmedetomidine-ketamine and fentanyl-ketamine combinations on analgesia, sedation, hemodynamics and respiratory effects (secondary outcome) in patients underwent ESWL. We hypothesized that dexmedetomidine group would provide better analgesia with less side effects than the fentanyl group.

2. Patients and methods

2.1. Patient recruitment

This randomized, double blinded study was done after the approval of local ethics committee. All patients were conducted in Dr. Erfan and Bagedo general hospital in Jeddah-KSA. A written informed consent was obtained from each patient. Sixty patients aged between 20 and 50 years, who were scheduled for elective ESWL, were enrolled in our study. All patients had American Society of Anasthiologist (ASA) I or II physical status. All patients had a single renal stone less than or equal 10 mm and first time to do ESWL procedure. Exclusion criteria were allergy to any medications used in the study, heart block (2nd or 3rd degree), respiratory disorder or chronic use of drugs known to alter the anesthetic or analgesic requirements. Also, chronic users of any α2-agonists were excluded.

2.2. Anesthetic techniques and study protocol

After arrival at the ESWL unit, a 20G IV cannula was inserted in non dominant hand. All patients were monitored with noninvasive blood pressure (NIBP), oxygen saturation (SpO2), ECG, and respiratory rate (RR). A bispectral (BIS) sensor was attached to the forehead and connected to an Aspect A2000 monitor version. Then we started an infusion of Ringer lactate solution at the rate of 80 ml/kg/day in all patients.

Sedation level was evaluated by using the modified Observer's Assessment Alertness/sedation (MOAA/S) scale [13]:

1 = Not responsive to mild shaking (unarousable).
2 = Responsive to mild shaking.
3 = Responsive only to his name when spoken repeatedly or loudly.
4 = Responsive to the name spoken in normal tone.
5 = Awake and alert.
6 = Agitated.

Pain intensity was evaluated on 0–10 cm visual analog scale (VAS) [14].

The VAS and MOAA/S were evaluated by another person who was blinded to all groups.

The patients were divided in a randomized manner into two groups by a closed envelop method.

Nurses who did not participate in the study prepared all syringes with dexmedetomidine or fentanyl drugs according to the table of randomization. The calculated dose of fentanyl and dexmedetomidine for each patient was prepared in a total volume of 50 ml normal saline and was infused over a period

of 10 min. Drugs administration and data collection were performed in a double-blind fashion in which neither the patient nor the medical team were aware about the injected drugs. Three patients in Fentanyl group refused to complete the study. So those patients were excluded.

In Group Fentanyl-ketamine (FK) (n = 27): Patients received fentanyl at a 1 μg/kg over 10 min before the procedure and 0.5 mg/kg bolus of ketamine. In Group Dexmedetomidine-ketamine DK (n = 30): patients received dexmedetomidine 1 μg/kg over 10 min before the procedure and a 0.5 mg/kg bolus of ketamine. All patients received average 2300 shocks/session at the same power intensity with intensity level 6 and pulse energy (42 mJ), asynchronous using the Dornier Lithotripter SII, Med Tech, Germany. Additional ketamine was used when needed (when the patient experienced any pain or movement) at a dose 0.25 mg/kg in both groups. MOAA/S score of 3 was accepted to start the procedure. All patients were supplied by oxygen nasal cannula at rate 4 L/min. When ESWL completed, the recovery time was assessed with modified Aldrete score by another anesthetist, who did not participate in all the procedure. Modified Aldrete score is a system of scoring that evaluates the condition of the recovery and discharge of the patient by assessing 5 parameters (oxygenation, conscious, circulation, respiration, activity). BIS also was assessed by the same anesthetist. The main outcome for the recovery period was to achieve a modified Aldrete score of 9 or more and to achieve BIS 90 or more [15].

2.3. Outcome measures

The primary measure of the study was to assess the VAS score. The VAS score was recorded at 5 min intervals after the initial measurement till the end of the procedure, and every 5 min for 15 min in the recovery period.

The secondary measures include hemodynamics, sedation and analgesia requirement. The basal values for respiratory rate (RR), mean arterial blood pressure (MAP), heart rate (HR), MOAA/S and BIS were recorded immediately before giving the study drug. The MOAA/S score, hemodynamics (HR, MAP), respiratory rate (RR) and BIS variables were recorded at 5 min intervals after the initial measurements till the end of the ESWL procedure. All the previous parameters were measured again every 5 min for 15 min in the recovery period.

Other secondary measures included adverse effects like hypotension (MAP < 50 mmHg), nausea, vomiting and bradycardia (HR < 50/min) were recorded during the procedure. Normal saline 0.9% infusion at 1–2 ml/kg/h was used for hypotension till MAP value was 50 mmHg. Atropine 0.01 mg/kg IV was given to treat bradycardia. Ondansetron 4 mg IV was considered for management of nausea and vomiting. When upper airway obstruction was noted, jaw thrust was applied and nasopharyngeal airway was inserted. It was important for us to keep suction ready for use when excessive salivation occurred.

2.4. Statistical methods

Data were analyzed using SPSS version 15.0 computer software (Chicago, IL, USA). Numerical variables were presented as mean and standard deviation (SD). Independent T test was used for inter-group comparisons of numerical variables, while categorical variables were presented as frequency (%). Chi-square test was used for comparisons of categorical variables. P value $\leqslant 0.01$ is highly significant and P value $\leqslant 0.05$ is significant. Sample size calculation was performed by GPower® version 3.1.5 computer software [Franz Faul, Universität Kiel, Germany, 2012]. It revealed that at least 30 patients were needed in each group for detection of a difference in VAS of at least 25%, assuming its pooled value is 4 cm (effect size = 0.7) with a power of 0.85 and significance level (α error) of 0.05 [16].

3. Results

During the period of the study, 60 patients with required ESWL were identified. Three patients in fentanyl group refused to complete the study and they were excluded from the analysis. ASA physical status and the demographic parameters of the patients in the two groups were similar. As regards total operative time, it was comparable. No significant difference between the two groups as regards number of shocks and total ketamine dosage which was given (Table 1).

There were no statistically significant differences between the 2 groups as regards the RR, MAP and HR preoperatively. There was reduction in the hemodynamic parameters (HR, MAP) after 5 min and all over the procedure in both groups, this reduction was within 15% from the baseline values (not significant), and it was not important clinically. There was a highly significant decrease in HR after 40, 45, 50 min (recovery period) in DK group in comparison with FK group (P = 0.005, 0.001, and 0.006 respectively). Also, there was a significant decrease in MAP during recovery period in DK group in comparison with FK group (P = 0.001, 0.035 and 0.012 respectively). On the other hand, there were no significant decreases in RR in the first 5 min and all over the procedure in comparison with base line. Also, there was no significant difference between the two groups at the different time points (Table 2).

As regards BIS values, there was no significant difference between the two groups throughout the procedure while there was a significant increase in FK group during the postoperative period 40, 45 and 50 min) (P = 0.001, 0.02 and 0.01 respectively) (Fig. 1).

As regards VAS values, there was no significant difference between the two groups throughout the procedure while there was a significant increase in FK group during the postoperative period (40, 45 and 50 min) (P = 0.034, 0.045, 0.047 respectively) (Fig. 2).

As regards MOAA/S sedation score values, there was no significant difference between the two groups throughout the procedure while there was a significant increase in sedation score after 40, 45, 50 min (recovery period) in FK group in comparison with DK group (P = 0.022, 0.012 and 0.041 respectively) (Fig. 3).

There was no significant difference between the two groups as regards adverse effects like hypotension, hypertension, bradycardia, tachyarrhythmia, or additional ketamine needed. While there was a significant difference between the two groups regarding nausea and vomiting as 20% (6/30) of patients in DK group got nausea and vomiting while 51% (14/27) of patients in FK group developed nausea and vomiting.

Table 1 Demographics, total ketamine used, operative and ESWL data.

	DK-group (n = 30)	FK-group (n = 27)
Age	40.36 ± 1.44	39.44 ± 4.52
Gender (male/female)	21/9 (70%/30%)	21/6 (77.8%/22.2%)
ASA status (I/II)	21/9 (70%/30%)	19/8 (70.4%/29.6%)
Operative time (min)	34.96 ± 2.39	34.18 ± 2.057
Number of shocks	2300 ± 180.03	2296 ± 275.23
Total ketamine used (mg)	56.3 ± 3.36	56.1 ± 3.35

Data are presented as mean ± SD and ratio for sex and ASA status.
ASA: American Society of Anesthesiology, DK group; Dexmedetomidine-ketamine group, FK group; Fentanyl-ketamine group.

Table 2 Hemodynamics and respiratory rate data.

	HR		MAP		RR	
DK-group (n = 30) FK-group (n = 27)	DK Group	FK Group	DK Group	FK Group	DK Group	FK Group
Baseline	85.5 ± 2.4	85.3 ± 2.8	82.3 ± 2.3	81.7 ± 2.3	21.4 ± 1.3	21.3 ± 1.5
5 min	66.5 ± 1.8	66.9 ± 1.5	74.7 ± 1.9	75.3 ± 1.8	18.4 ± 1.3	18.4 ± 1.3
10 min	64.8 ± 2.6	65.4 ± 2.1	67.2 ± 1.6	67.8 ± 2.1	19.2 ± 1.6	19.4 ± 1.6
15 min	64.03 ± 1.6	63.1 ± 2.6	63.8 ± 1.5	63.1 ± 1.6	19.5 ± 1.8	19.2 ± 2.1
20 min	60.9 ± 2.4	61.6 ± 2.3	59.4 ± 2.5	60.1 ± 2.3	18.6 ± 1.7	19.3 ± 1.6
25 min	61.4 ± 2.1	60.7 ± 1.8	64.9 ± 1.9	65.07 ± 1.7	18.6 ± 1.4	19.3 ± 1.6
30 min	59.7 ± 1.7	59.5 ± 1.8	59.7 ± 2.2	59.4 ± 2.1	19.03 ± 1.1	19.6 ± 1.4
35 min	59.6 ± 1.6	59.4 ± 1.5	65.4 ± 1.6	65.9 ± 1.4	18.2 ± 1.6	18.8 ± 2.7
40 min	64.3 ± 4.2**	67.9 ± 5.1	67.1 ± 2.5**	69.3 ± 2.5	18.6 ± 1.3	19.3 ± 1.4
45 min	72.8 ± 6.02**	78.2 ± 2.9	71.7 ± 7.4*	75.1 ± 2.9	18.7 ± 1.5	19.0 ± 1.6
50 min	82.7 ± 3.9**	85.3 ± 2.7	77.6 ± 3.4*	79.7 ± 2.7	19.1 ± 1.6	19.5 ± 1.6

Data are presented as mean ± SD; HR; heart rate, MAP; mean arterial pressure, RR; respiratory rate, DK group; Dexmedetomidine-ketamine group, FK group; Fentanyl-ketamine group.
* $P < 0.05$ = significance between groups.
** $P < 0.01$ = highly significance between groups.

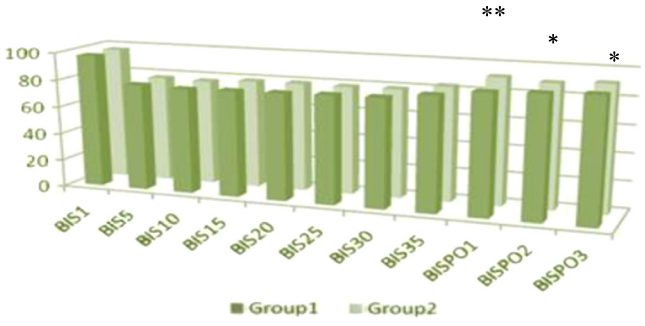

Figure 1 Bispectral index (BIS). Group 1; Dexmedetomidine-ketamine (DK), Group 2; Fentanyl-ketamine (FK). BIS-1, 5, 10, 15, 20, 25, 30, 35, BISPO-1, BISPO-2, BISPO-3; baseline, 5, 10, 15, 20, 25, 30, 35 min intraoperatively, postoperative-1 (40 min), postoperative-2 (45 min), postoperative-3 (50 min) respectively. * $P < 0.05$ = significance between groups, ** $P < 0.01$ = highly significance between groups.

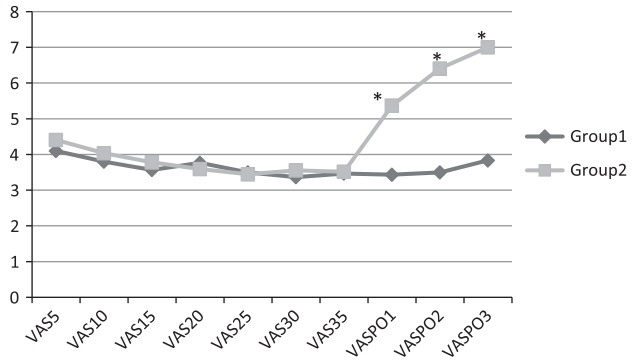

Figure 2 VAS; visual analog score. Group 1; Dexmedetomidine-ketamine (DK), Group 2; Fentanyl-ketamine (FK). VAS 5, 10, 15, 20, 25, 30, 35, PO1, PO2, PO3; 5, 10, 15, 20, 25, 30, 35 min intraoperatively, postoperative-1 (40 min), postoperative-2 (45 min), postoperative-3 (50 min) respectively. * $P < 0.05$ = significance between groups.

4. Discussion

ESWL is a safe and effective method to treat upper urinary tract stones, but it causes discomfort and pain in many patients [17]. Intravenous combination of dexmedetomidine 1 μg/kg over 10 min before the procedure and 0.5 mg/kg bolus of ketamine as well as same doses of fentanyl - combinations are effective and tolerated for patients undergoing ESWL. The dexmedetomidine/ketamine combination is associated with a more prolonged analgesia in the recovery period (primary outcome), delayed request of first dose analgesia, less

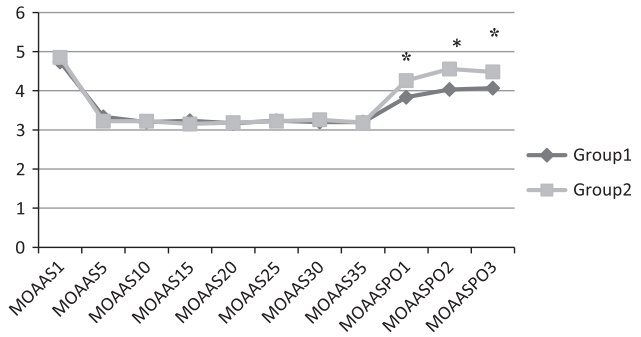

Figure 3 MOAA/S; modified Observer's Assessment Alertness/sedation scale. Group 1; Dexmedetomidine-ketamine (DK), Group 2; Fentanyl-ketamine (FK). MOAA/S 1, 5, 10, 15, 20, 25, 30, 35, MOAA/S-1, MOAA/S-2, MOAA/S-3; baseline, 5, 10, 15, 20, 25, 30, 35 min intraoperatively, postoperative-1 (40 min), postoperative-2 (45 min), postoperative-3 (50 min) respectively. $^{*}P < 0.05$ = significance between groups.

nausea and vomiting than and better hemodynamics compared to fentanyl/ketamine combination.

For the patient satisfaction, the most suitable drug for ESWL should provide adequate analgesia, sedation, rapid recovery and minimal side effects [18].

Dexmedetomidine displays specific and selective α2-adrenoreceptors agonists [19]. Activation of the receptors in the spinal cord and the brain inhibits firing of the neurons and causing hypotension, sedation, analgesia and bradycardia [20].

Ketamine is a sedative analgesic agent that does not interfere with the hemodynamics or respiration. It maintains the airway reflexes with better analgesia and sedation [21]. Monk et al. in his study, compared midazolam-ketamine and midazolam-alfentanil in the lithotripsy and stated that ketamine infusion provided better respiratory and hemodynamics stability. In spite of these benefits, there were prolonged recovery and emergence delirium when it was used in children [22]. The BIS monitor can be used as an effective and objective tool to guide the effective and safe doses of anesthetics. There are several advantages of the BIS as reduction of anesthetic doses, shorter recovery and early emergence [23].

As regards analgesia in our study, there was a significant difference only in the postoperative period as evident by increase in VAS score and decreased the mean time to the first required analgesia in FK group than DK group. This significant difference might be related to the prolonged analgesic effect of dexmedetomidine and fading effect of fentanyl. This finding is in accordance with the study of Gurbet et al. [24] who demonstrated that the infusion of dexmedetomidine intraoperatively decreased perioperative analgesia requirements. Similar to our findings, Aho and his colleagues [25] documented the analgesic properties of dexmedetomidine even when it was used as a sole agent after minor surgery. Another study done by Alhashemi and Kaki [26] showed that dexmedetomidine was an effective and safe drug to sedate the patients during ESWL without affection of respiration with better analgesia than propofol. However, our findings contradict the findings of Jalowieck et al. [27] who discussed the ability of dexmedetomidine to provide analgesia for colonoscopy but he found that it might induce hemodynamic instability and prolonged recovery.

In our study, there was reduction in the hemodynamic parameters after 5 min and all over the procedure, this reduction was within 15% from the baseline values and it was not significant. This none significant decrease in hemodynamics may be explained by the hemodynamic stability of Ketamine. But there was intergroup significant difference during recovery period. It could be again due to prolonged effect of dexmedetomidine and fading effect of fentanyl and stop of ketamine. This was in agreement with the results of Feld and his colleagues [28] who compared the analgesic effects of dexmedetomidine to fentanyl in bariatric surgery and reported that dexmedetomidine provided both analgesia and stable hemodynamics, thus decreased the use of morphine in the postoperative period. In contrast to our study, Kaygusuz et al. [29] stated a significant reduction in MAP compared to the baseline when they used fentanyl/propofol for sedation in ESWL, this is may be related to propofol induced hypotension.

In the current study, there was no significant difference between the two groups as regards respiratory rate (RR) and no significant difference in comparison with the baseline. This none significant difference might be related to ketamine as it did not induce clinically important respiratory depression [21]. The effect of dexmedetomidine on RR is variable. Kaygusuz et al. [29] and Belleville et al. [30] stated a significant decrease in RR. While Hsu et al. [31] reported a significant increase in RR with dexmedetomidine. On the other hand, some authors reported that dexmedetomidine did not affect RR [32]. These wide changes might be related to variable methods of administration. Elbert et al. [33] used infusion of dexmedetomidine similar to Hsu et al. [31] and that study showed a significant increase in RR.

As regards sedation, we were not allowed to start procedure except when MOAA/S SCORE is 3 and the BIS value was less than 81. This is in accordance with the study of Yu et al. [34] who investigated the efficacy of BIS monitoring during balanced propofol sedation for colonoscopy and they found that the optimal cut-off value of BIS to maintain moderate sedation was 81. Also, in the study of Yeon, when patients experienced pain, MOAA/S and BIS were respectively, 3.9 ± 0.7 and 88.5 ± 6.4. While the patients who did not feel pain they were 2.7 ± 0.6 and 77.3 ± 5.1. There is agreement between the sedation level and BIS value, and many studies have proved that BIS is an objective method to monitor sedation [35]. In contrary to our study, Kronen et al. [36] who stated that the anesthetic period performed by fentanyl was accepted, but there was prolonged recovery with respiratory and central nervous depression.

One of the drawbacks which cause difference between the clinical scoring systems of sedation and BIS monitoring is the BIS timing measurement. When we use the clinical assessment in the form of painful or verbal stimuli, these stimuli lead to an increase in BIS value. So the BIS timing measurements change the BIS value [37].

The most common adverse effects of opioids are nausea and vomiting which reflected in our study by a significant increase in the incidence in FK group than DK group (51% vs. 20% respectively). This could be related to the renal pain, which was experienced as a result of the operation itself [8], or related to the effect of fentanyl to induce emesis (nausea and vomiting) which are the most common side effects of opioids as observed by Cepeda et al. study [38].

We had some limitations of our study as it is a single center study and the sample size required mainly based on the patient satisfaction which is a subjective tool. The only objective tool used was the BIS. It was obvious from our study that BIS was not superior to MOAA/S score in spite of its use may increase the cost burden. Also, this study was conducted on a specific category of patients (young age, ASA I, II and single renal stone) only.

In conclusion, both dexmedetomidine/ketamine and fentanyl/ketamine combinations at prescribed dose regimen were effective and tolerated for patients underwent ESWL. However, dexmedetomidine/ketamine was accompanied by more prolonged analgesia in the recovery period (primary outcome), delayed request of first dose analgesia with less nausea and vomiting than and fentanyl/ketamine. The addition of ketamine was important factor to keep the hemodynamics and respiration are stable. Also there is a good correlation between MOAA/S sedation score and BIS. Future studies are needed to compare the other sedation scores and BIS, and to compare the dexmedetomidine/ketamine with other commonly used agents during ESWL.

Conflict of interest

There is no conflict of interest.

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