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Research article

Dexmedetomidine added to propofol for drug-induced sleep endoscopy in adult patients with obstructive sleep apnea: Randomized controlled trial

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ABSTRACT

Background: The aim of this study was to evaluate if the addition of dexmedetomidine to propofol could improve the success and reduce the complications during drug induced sleep endoscopy in obstructive sleep apnea patients.

Patient and methods: Fifty adult patients scheduled for drug induced sleep endoscopy were randomly allocated to one of two groups. Group P (25 patients) received propofol loading dose of 0.5 mg/kg over 3 min then continuous infusion in a dose of 25–75 mcg/kg/min. Group PD (25 patients) received propofol infusion as group P and dexmedetomidine intravenous infusion with a loading dose of 0.5 mcg/kg over 5 min then continuous infusion in a dose of 0.2–0.7 mcg/kg/h. The primary outcome was successful completion of the procedure. The secondary outcomes included the time to start endoscopy, procedure duration, the incidence of adverse events and surgeons and patients satisfaction.

Results: Successful completion of the procedure was significantly higher in group PD (96%) compared to group P (72%). The total propofol dose needed/patient (mg) was significantly more in group P compared to group PD (173.5 ± 41.6 versus98.4 ± 19.8 with shorter recovery time in group PD. Both surgeons and patients satisfaction were significantly higher in group PD compared to group P. The incidence of cough and gag reflexes were significantly higher in group P compared to group PD. Heart rate (HR) was significantly lower in group PD compared to group P at 5, 10, 15, 20, 25 and 30 min from the start of the studied drugs. Respiratory rate (RR) was significantly lower in group P compared to group PD at 5, 10, 15 and 20 min from the start of the studied drugs ($p < 0.05$).

Conclusion: Addition of dexmedetomidine to propofol is associated with higher incidence of successful completion of the procedure with faster recovery. Cough and gag reflexes were significantly lower with the addition of dexmedetomidine with higher surgeons and patients satisfaction.

1. Introduction

Obstructive sleep apnea (OSA) is a sleep disorder that affects 2–4% of adult populations [1]. It is characterized by episodes of apnea and hypopnea as a result of upper airway obstruction [2] and can be associated with multiple comorbidities and adverse cardiovascular events [3]. Drug-induced sleep endoscopy (DISE) was proposed by Croft and Pringle in 1991 [4] and is considered an important tool for evaluation of the degree and sites of upper airway obstruction in patients with obstructive sleep apnea [5,6].

Many sedative agents were used either alone or in combination for sedation during drug-induced sleep endoscopy. The most commonly used sedatives for DISE include midazolam, propofol and dexmedetomidine [7].

Propofol is a commonly used sedative for many procedures due to its rapid onset with easy titration and short half-life [8]. It can be used in small repeated intravenous boluses, continuous intravenous infusion or target controlled infusion [9]. The main disadvantage of propofol is respiratory depression and decrease of the muscle tone that can lead to improper evaluation of the airway obstruction [10].

Dexmedetomidine is a highly selective α-2 adrenoreceptor agonist with sedative, hypnotic and analgesic properties. It preserves the muscles tone with minimal or no respiratory depression [11,12]. Its use as a sole sedative may require a high dose that can cause marked hemodynamic instability and delayed recovery [13].

We selected propofol because it is the most commonly used sedative during DISE and it produces a similar state to the non-rapid eye movement (NREM) sleep [14]. We hypothesized that addition of

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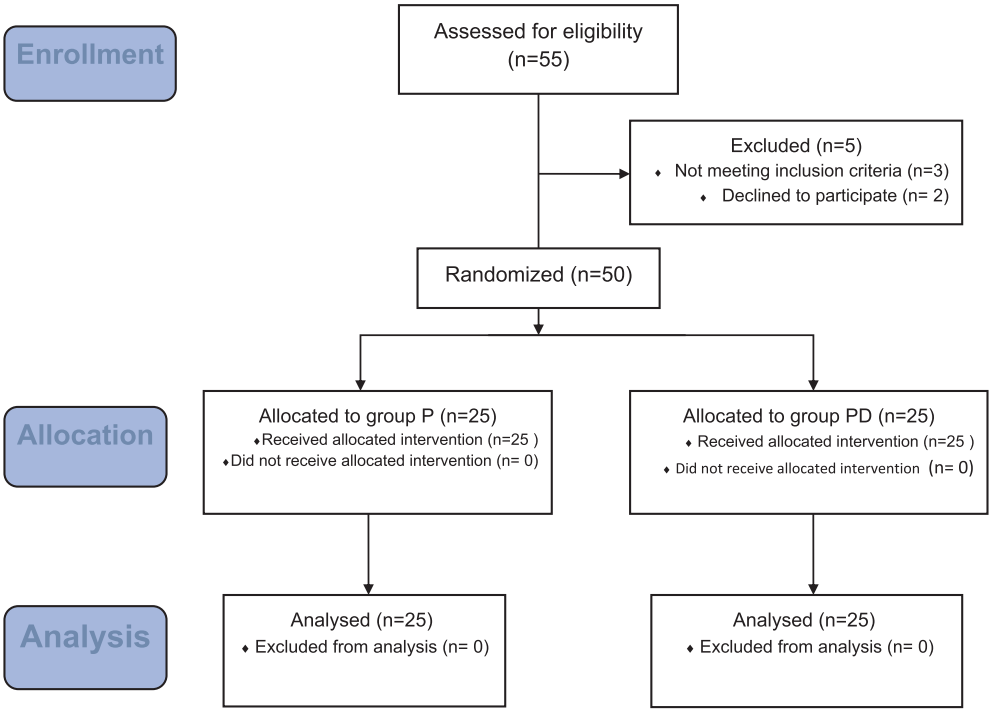

Fig. 1. Patient's flowchart demonstrating the number of patients eligible for inclusion into the study, enrollment, allocation and analysis.

Table 1
Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) [15].

Responsiveness	Score
Agitated	6
Responds readily to name spoken in normal tone (alert)	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1
Does not respond to deep stimulus	0

dexmedetomidine to propofol could improve the success of the procedure and reduce the incidence of respiratory depression and airway complications.

2. Patients and methods

2.1. Study design

This prospective, randomized double-blinded controlled study was carried out in Zagazig University Hospitals from April 2017 to April 2018 after approval of institutional review board (IRB) and obtaining written informed consent from all patients. The study was registered in Clinical Trials. gov (NCT03091894).

Fifty adult patients with obstructive sleep apnea of American Society of Anesthesiologists (ASA) physical status II and III aged more than 18 years were randomly allocated into one of two groups (Fig. 1). Randomization of patients was performed according to a computer-generated random number with use of sealed opaque envelopes for allocation concealment into one of two groups. All the study medications were prepared by anesthetist who did not participate in the study. All procedures were performed by the same surgical and anesthesia team who were blinded about the study medications.

Group P (25 patients) received propofol intravenous infusion 10 mg/ml (Diprivan, AstraZeneca, Egypt) in 50 ml syringe (syringe A) via one syringe pump with a loading dose of 0.5 mg/kg over 3 min followed by continuous infusion in a dose of 25–75 mcg/kg/min. Another 50 ml syringe (syringe B) containing 50 ml normal saline (placebo) was given via another syringe pump with the same rate of syringe B in group PD for proper blindness.

Group PD (25 patients) received propofol intravenous infusion 10 mg/ml in 50 ml syringe (syringe A) via one syringe pump with a loading dose of 0.5 mg/kg over 3 min then continuous infusion in a dose of 25–75 mcg/kg/min. Dexmedetomidine intravenous infusion (Precedex, hospira, Egypt) in 50 ml syringe (syringe B) (4 mcg/ml) was given via another syringe pump with a loading dose of 0.5 mcg/kg over 5 min then continuous infusion in a dose of 0.2–0.7 mcg/kg/h.

The primary outcome was successful completion of the procedure (with diagnosis of site and degree of obstruction). The secondary outcomes were the time until sufficient sedation to start endoscopy as evaluated by Modified observer's assessment of alertness sedation (MOAA/S) score (Table 1) [15]. The total procedure duration, the incidence of oxygen desaturation, other adverse events and surgeons and patients satisfaction were also recorded.

Patients were excluded from the study if they had the following Criteria: (1) patient refusal, (2) ASA physical status > III, (3) known or suspected allergy to the studied drugs or its components, allergy to eggs or soy beans (4) morbid obesity, (5) patients with moderate to severe chronic obstructive pulmonary disease or uncontrolled asthma, congestive heart failure, seizures, or cerebrovascular disease (6) pregnancy.

All patients were fasting for 8 h and proper preanesthesia evaluation with recording of their *ASA physical status* and Apnea hypopnea index (events/h) was done. Atropine 0.5 mg was given intramuscularly 30 min before the procedure and two eighteen gauge intravenous cannulas were inserted and baseline parameters were recorded. All patients were monitored by non-invasive blood pressure, Pulse oximetry, capnography, respiratory rate and ECG (Datex-ohmeda. GE healthcare co. U.S.A).

The drugs infusion started and (MOAA/S) score was assessed every 3 min. Propofol continuous infusion was started in a dose of 25 mcg/kg/min and titrated every 3 min in a dose of 10 mcg/kg/min with a maximum dose of 75 mcg/kg/min. Dexmedetomidine continuous infusion was started in a dose of 0.2 mcg/kg/h and titrated every 3 min in a dose of 0.1 mcg/kg/h with a maximum dose of 0.7 mcg/kg/h. When the

(MOAA/S) score 1 was obtained the flexible endoscope was passed through the nose for endoscopic airway evaluation. Time to start endoscopy is defined as the duration between start of the studied drugs until (MOAA/S) score 1 was obtained. The total propofol and dexmedetomidine dose needed/patient was calculated. Adverse events (hypotension, bradycardia, arrhythmia, laryngospasm, cough, gag reflex, apnea or aspiration) were recorded during the procedure. Bradycardia was diagnosed if heart rate dropped below 60 beats/min and atropine 0.01 mg/kg was given if HR decreased below 50 beats/min. Hypotension was diagnosed if mean arterial blood pressure (MAP) decreased by more than 30% from baseline or below 60 mmHg and was managed by intravenous crystalloids and ephedrine 6 mg intravenous increments if needed.

All patients received oxygen 2 L/min via nasal cannula. If oxygen saturation dropped below 90% oxygen flow was increased to 4–6 L/min and if desaturation persisted, patients were managed by head tilt and chin lift or jaw thrust. Ventilation via face mask was performed for patients with persistent desaturation or apnea.

At the end of the endoscopy, all the studied drugs infusion were stopped and time till Recovery (time between stop of the study drugs until MOAA/S of 4 was obtained) was calculated and Patients were shifted to recovery room. Post procedural complications, sedation score (MOAA/S), Aldrete's recovery scores [16] were recorded in the recovery room at 5, 10, 15 and 30 min. After complete recovery, both patients' and surgeon were asked why they were satisfied/dissatisfied with the sedation received during the procedure. Both patients' and surgeon satisfaction were recorded using a 7-point Likert-like verbal rating scale [17] (Fig. 2).

2.2. Sample size calculation

Power analysis was done using Student's *t*-test for independent samples on successful completion of the procedure because it is the primary outcome in the current study. A pilot study was done before starting this study showed that the percentage of patients with successful completion of the procedure was 68% in group P and 96% in group PD. Taking a power of 0.8 and alpha error of 0.05, a minimum sample size of 23 patients was calculated for each group. Twenty-five patients were included for each group to compensate for possible dropouts. (MedCalc 13 for windows, MedCalc Software bvba, Ostend, Belgium).

3. Statistical analysis

All data were collected and statistically analyzed using SPSS version 19.

Continuous Quantitative variables were expressed as the mean ± SD and categorical qualitative variables were expressed as absolute frequencies (number) & relative frequencies (percentage). Continuous data were checked for normality by using kolmogorov-smirnov test. Independent samples Student's *t*-test was used to compare two groups of normally distributed data. Mann-Whitney U test was used for comparison of continuous variables with asymmetric distribution. Categorical data were compared using Chi-square test. All tests were two sided. P-value < 0.05 was considered statistically significant (S), p-value < 0.001 was considered highly statistically significant (HS), and p-value ≥ 0.05 was considered statistically insignificant (NS).

Table 2
Comparison between the studied groups as regard patients characteristics and baseline parameters.

	Group P (N = 25)	Group PD (N = 25)	p-Value
Age (years)	44.5 ± 10.2	43.2 ± 9.5	0.642*
Gender			
Male: number (%)	20 (80%)	22(88%)	0.440§
Female: number (%)	5 (20%)	3(12%)	
Body mass index (kg/m^2)	27.9 ± 6.1	29.0 ± 5.4	0.499*
ASA physical status			
ASA II: number (%)	21(84%)	20(80%)	0.712§
ASA III: number (%)	4(16%)	5(20%)	
Apnea hypopnea Index (events/h)	32.9 ± 14.8	34.1 ± 15.6	0.781*
Baseline parameters			
HR (beats/min)	81.4 ± 10.2	79.5 ± 9.6	0.610*
MAP (mmHg)	84.9 ± 7.6	86.1 ± 8.1	0.590*
SpO_2 (%)	96 ± 3.9	95 ± 4.6	0.415*
RR (breath/min)	17.3 ± 4.2	18.1 ± 3.9	0.487*

N = Total number of patients in each group.
Quantitative data were expressed as mean ± SD.
Qualitative data were expressed as a number (percentage).
HR = Heart rate. MAP = Mean arterial pressure.
SpO_2 = Oxygen saturation. RR = Respiratory rate.
* Independent samples Student's *t*-test.
§ Chi-square test; $p < 0.05$ is significant.

4. Results

Patients' characteristics and baseline parameters were comparable in the two studied groups ($p > 0.05$) (Table2).

Successful completion of the procedure was significantly higher ($p < 0.05$) in group PD (96%) compared to group P (72%). There was no statistically significant difference between the two studied groups as regard the Time to start endoscopy or the total procedure duration ($p > 0.05$). The total propofol dose needed/patient (mg) was significantly more in group P compared to group PD ($p < 0.001$). The time till patients recovery was significantly longer in group P compared to group PD ($p > 0.05$). The surgeon satisfaction was significantly higher in group PD compared to group P ($P < 0.001$). Patient satisfaction was significantly higher in group PD compared to group P ($P < 0.001$) (Table 3).

The incidence of oxygen desaturation below 90% and the lowest oxygen saturation recorded during the procedure were comparable in both groups ($p > 0.05$). The incidence of laryngospasm during the procedure was higher in group P (2 patients) compared to group PD (no patients) but it was statistically insignificant ($p > 0.05$). The incidence of cough during the procedure was significantly higher in group P (6 patients) compared to group PD (no patients) ($p < 0.05$). Significantly more patients in group P (8 patients) developed gag reflex during the procedure compared to group PD (2 patients) ($p < 0.05$). There was no significant difference among the two studied groups as regard the incidence of other complication during the procedure (bradycardia, hypotension, arrhythmia, apnea and pulmonary aspiration) (Table 4).

No significant difference was found between the two groups with respect to post procedural sedation score and Aldrete's score at 5, 10, 15 and 30 min in the recovery room ($p > 0.05$). There was no significant

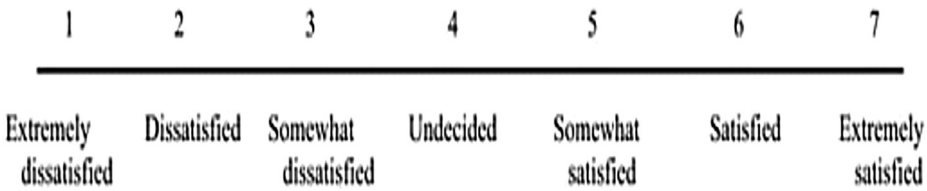

Fig. 2. A 7-point Likert-like verbal rating scales for assessment of Patients' and surgeons' satisfaction [17].

Table 3
Comparison between the studied groups as regard procedure data, surgeon satisfaction and patient satisfaction.

	Group P (N = 25)	Group PD (N = 25)	p-Value
Successful completion of procedure: number (%)	18 (72%)	24 (96%)	0.02§
Time to start endoscopy (time to MOAA/S 1) (min)	19.9 ± 4.7	21.1 ± 5.1	0.389*
Total procedure duration (min)	32.8 ± 3.0	34.1 ± 3.2	0.14*
Total Propofol dose/patient (mg)	173.5 ± 41.6	98.4 ± 19.8	< 0.001*
Total Dexmedetomidine dose/patient (mcg)	–	61.2 ± 13.5	–
Time till Recovery (time to MOAA/S 4) (min)	6.8 ± 3.9	3.6 ± 1.5	0.006*
Surgeon satisfaction	5.02 ± 0.01	6.08 ± 0.91	< 0.001*
Patient satisfaction	5.04 ± 0.03	6.05 ± 0.92	< 0.001*

N = Total number of patients in each group.
MOAA/S = Modified observer's assessment of alertness sedation.
Quantitative data were expressed as mean ± SD.
Qualitative data were expressed as a number (percentage).
P < 0.05 is significant. P < 0.01 is highly significant.
* Independent samples Student's *t*-test.
§ Chi-square test.

Table 4
Comparison between the studied groups as regard procedural complications.

	Group P (N = 25)	Group PD (N = 25)	p-Value
Oxygen desaturation < 90%: number (%)	9 (36%)	7 (28%)	0.544§
Lowest oxygen saturation	85.7 ± 4.2	86.8 ± 3.9	0.342*
Laryngospasm: number (%)	2 (8%)	0	0.149§
Cough: number (%)	6 (24%)	0	0.022§
Gag reflex: number (%)	8 (32%)	2 (8%)	0.034§
Bradycardia: number (%)	0	0	1.00§
Hypotension: number (%)	2 (8%)	0	0.149§
Arrhythmia: number (%)	1 (4%)	1 (4%)	1.00§
Apnea: number (%)	4 (16%)	1 (4%)	0.157§
Pulmonary aspiration: number (%)	0	0	1.00§

N = Total number of patients in each group.
Quantitative data were expressed as the mean ± SD.
Qualitative data were expressed as a number (%).
* Independent samples Student's *t*-test.
§ Chi-square test. P < 0.05 is significant.

Table 5
Comparison between the studied groups as regard post procedural scores and complications.

	Group P (N = 25)	Group PD (N = 25)	p-Value
Sedation score (MOAA/S):			
After 5 min	4 (4–5)	4 (4–5)	0.124U
After 10 min	5 (4–5)	5 (4–5)	0.259U
After 15 min	5	5 (4–5)	0.317U
After 30 min	5	5	1.00U
Aldrete's score:			
After 5 min	9 (8–9)	8 (7–9)	0.635U
After 10 min	9 (9–10)	10 (9–10)	0.441U
After 15 min	10 (9–10)	10 (9–10)	0.917U
After 30 min	10	10	1.00U
Nausea: number (%)	2 (8%)	2 (8%)	1.00§
Vomiting: number (%)	1 (4%)	0	0.314§
Bradycardia: number (%)	0	0	1.00§
Hypotension: number (%)	0	0	1.00§
Delirium: number (%)	0	0	1.00§

N = Total number of patients in each group.
MOAA/S = Modified observer's assessment of alertness sedation.
MOAA/S and Aldrete's score were expressed as Median (range).
Qualitative data were expressed as a number (%).
U Mann-Whitney U test.
§ Chi-square test. P < 0.05 is significant.

difference among both groups regarding the incidence of post procedural complications (p > 0.05) (Table 5).

Heart rate (HR) was significantly lower in group PD compared to group P at 5, 10, 15, 20, 25 and 30 min from the start of the studied drugs (p < 0.05) (Fig. 3).

No significant difference was found between both groups as regard the mean arterial pressure (MAP) neither during the procedure nor in the recovery room (p > 0.05) (Fig. 4).

Respiratory rate (RR) was significantly lower in group P compared to group PD at 5, 10, 15 and 20 min from the start of the studied drugs (p < 0.05) (Fig. 5).

5. Discussion

Drug induced sleep endoscopy (DISE) is a procedure used for dynamic assessment of both site and degree of airway obstruction during induced sleep-like state. The findings obtained from DISE can be used as a guide for planning of proper management in patients with OSA [18,19].

Many sedative agents were used during DISE, but still no standard protocol or ideal drug for sedation [20]. The proper sedative dose required for appropriate depth of sedation during DISE is a challenge. Sedative overdose can cause oxygen desaturation and hemodynamic instability while under-dosing may lead to inadequate sedation with longer procedure duration.

Successful completion of the procedure with diagnosis of sites and degree of obstruction was the main outcome of the current study. The percentage of successful completion of the procedure was significantly higher in group PD (96%) compared to group P (72%). This higher success rate in group PD can be attributed to the addition of dexmedetomidine which significantly reduced the total propofol dose needed to achieve the satisfactory sedation level. The incidence of cough and gag reflex were significantly lower with addition of dexmedetomidine to propofol during the procedure.

The higher incidence of cough and gag reflex in group P despite of proper sedation level as indicated by the MOAA/S can be explained by inability of propofol to prevent these reflexes and its lack of analgesic properties. Cho et al. found that the incidence of cough was 23% when propofol was used as a single agent for sedation during DISE [21].

Although the total procedure duration and the time needed to start the endoscopy were comparable in both groups, the time taken till recovery was significantly shorter in group PD. Again this can be attributed to the lower total propofol dose needed in group PD compared to group P.

Consistent with our results, Abbas et al. [22] reported that time to recovery was significantly shorter when dexmedetomidine was added to propofol during sedation for upper gastrointestinal endoscopy. Khare

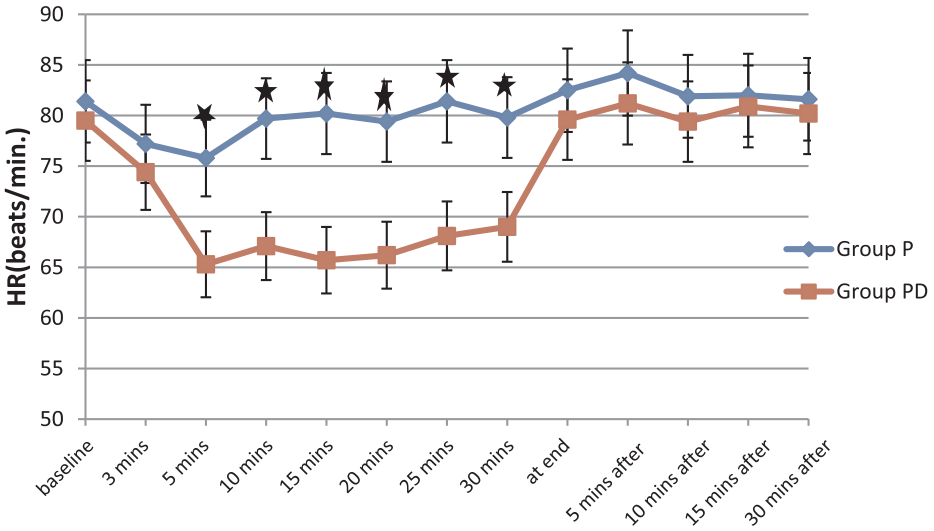

Fig. 3. Marker & error bar chart shows HR (beats/min) at various times of measurements of the studied groups; markers represent mean; Y-error bar represent 95% confidence interval of mean, HR = Heart rate. ★ Indicates significant difference between the studied groups.

et al. [23] found that recovery time was significantly less when dexmedetomidine was added to propofol infusion during laparoscopic cholecystectomy. Another study showed that recovery from anesthesia was faster when dexmedetomidine was used as adjunct during general anesthesia [24].

In the current study, surgeon and patient satisfaction were significantly higher in group PD compared to group P. Consistent with our results, Kim et al. [25] found that patients and surgeons satisfaction were higher when dexmedetomidine was added to propofol for monitored anesthesia care. Another study showed similar Patients and surgeons satisfaction when dexmedetomidine was compared to propofol for DISE [26].

The higher surgeon satisfaction with group PD was due to the higher incidence of procedure completion with lower incidence of cough and gag reflex and less interruption of the procedure. The higher patients' satisfaction with group PD was attributed to the natural sleep like sedation with dexmedetomidine and the faster recovery compared to propofol group.

Post procedural sedation and recovery score and the incidence of post procedural complications were comparable among both groups. No significant difference was noted among the two studied groups as regard the mean arterial pressure (MAP). The heart rate was significantly lower in group PD compared to group P at 5 min from starting the studied drugs until 30 min from starting drugs infusion. Bradycardia can occur with dexmedetomidine due to its sympatholytic effects [27,28]. In the current study, none of the patients developed bradycardia and no patients needed atropine. Kim et al. [25] found that bradycardia and need of atropine were significantly higher with dexmedetomidine compared to combination of dexmedetomidine and propofol.

Propofol can cause respiratory depression [29] while dexmedetomidine has a respiratory preserving effect [30]. In the current study, the respiratory rate was significantly lower in propofol group compared to group PD at 5, 10, 15 and 20 min from starting the studied drugs. Four patients in propofol group developed apnea compared to only one patient in group PD. The apnea was transient with no patients needed endotracheal intubation. No significant difference between both groups as regard the oxygen desaturation < 90% or the lowest oxygen saturation. In a study by Kim et al. [25], they found no significant difference in respiratory rate among the studied groups, but they used target control infusion to reach MOAA/S score of 3.

The current study has some limitations. First; no dexmedetomidine group was included in the study. Previous studies showed that dexmedetomidine alone was unsuccessful in providing adequate depth of

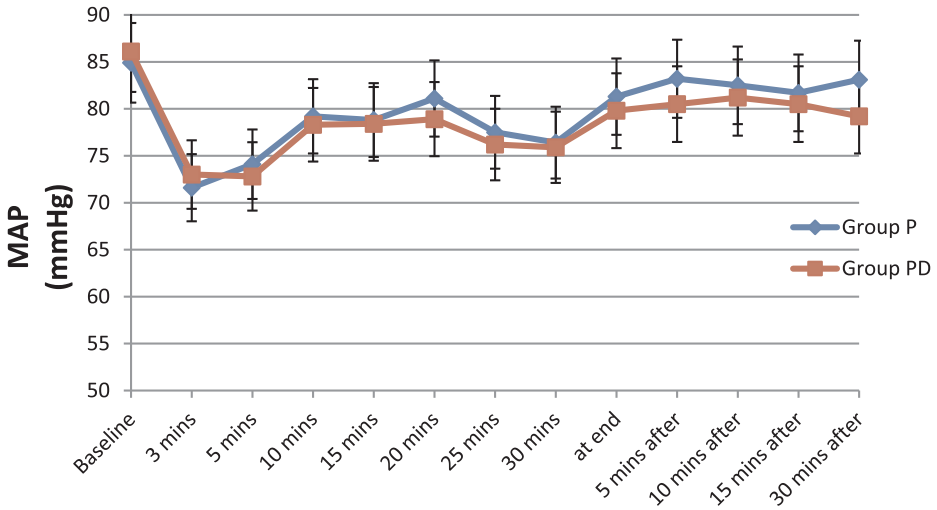

Fig. 4. Marker & error bar chart shows MAP (mmHg) at various times of measurements of the studied groups; markers represent mean; Y-error bar represent 95% confidence interval of mean, MAP = Mean arterial pressure.

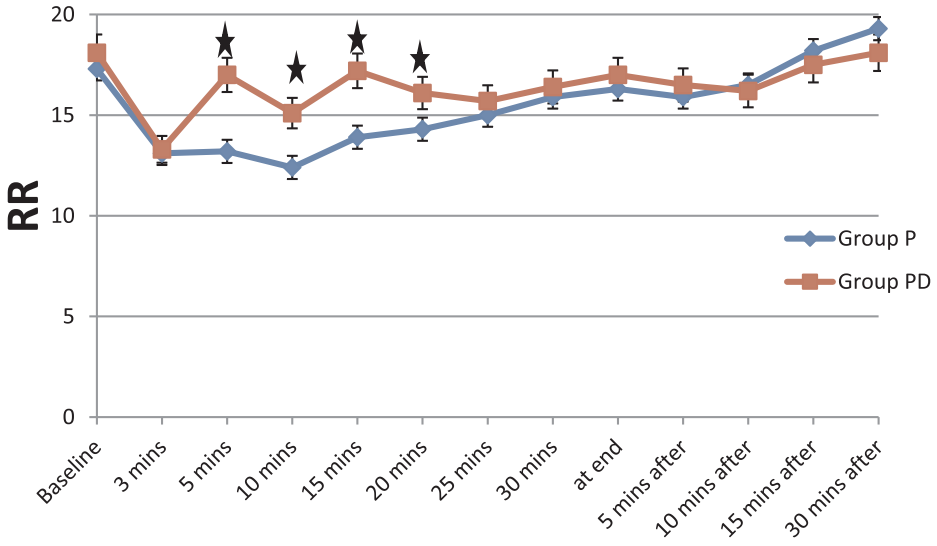

Fig. 5. Marker & error bar chart shows respiratory rate (breaths/min) at various times of measurements of the studied groups; markers represent mean; Y-error bar represent 95% confidence interval of mean, RR = respiratory rate. ★ Indicates significant difference between the studied groups.

sedation for invasive procedures [31] with up to 50% of patients failed to achieve enough sedation level [32]. Second, target controlled infusion and bispectral index (BIS) were not used in the current study because they were not available. Instead we used continuous infusion via syringe pump and the depth of sedation was assessed by Modified observer's assessment of alertness sedation (MOAA/S) score.

6. Conclusion

Addition of dexmedetomidine to propofol during DISE is associated with higher incidence of successful completion of the procedure with lower total propofol dose and faster recovery. The incidence of cough and gag reflexes were significantly lower with addition of dexmedetomidine with higher surgeons' and patients' satisfaction.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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