

Effectiveness of Dexmedetomidine as an Adjunct Agent for Sedation during ERCP

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Abstract

Objectives: To evaluate dexmedetomidine as an adjunct drug to propofol for sedation during ERCP, and its effects on perfusion index (PI) which could be used as an indicator for analgesia level.

Methods: 76 patients ASA (I-III) scheduled for ERCP procedure were randomly classified to either dexmedetomidine/propofol group or propofol group. In dexmedetomidine/propofol group, sedation was induced by dexmedetomidine (0.7 µg/kg) and propofol (50 mg) followed by infusion of dexmedetomidine (0.4 µg/kg/h) and propofol (0.5-1 mg/kg/h). In propofol group, sedation was induced by propofol (50 mg) followed by propofol infusion (0.5-1 mg/kg/h). HR, SBP, DBP, RR, SPO₂ and PI were continuously monitored and recorded at the time points (T0 to T8).

Results: Comparing dexmedetomidine/propofol group versus propofol group; PI values showed significant increase at T2 to T7 (p<0.001), HR values showed significant decrease at T1 to T8 (p 0.013 at T1 and 0.001 at T2 to T8), SBP values showed significant decrease at T1 to T8 (p=0.002 at T1, 0.001 at T2 to T7 and 0.004 at T8) and DBP values showed significant decrease at T4 to T6 (p value 0.008, 0.002 and 0.003 at T4, T5 and T6). RR and SPO₂ values were comparable in both groups. In dexmedetomidine/propofol group, the propofol dosage was significantly lower (p value 0.001) and the recovery time was significantly higher (p value 0.001) than that of propofol group, while the procedure time was comparable between both groups. Dexmedetomidine/propofol group showed higher incidence of bradycardia than propofol group (p value 0.035) while propofol group showed more cases with tachycardia (p value 0.016) and more cases with airway obstruction (p value 0.026).

Conclusion: dexmedetomidine is a useful adjunct drug for sedation during ERCP procedure.

Keywords: Dexmedetomidine; Sedation; Perfusion index; ERCP

Abbreviations

ERCP: Endoscopic retrograde cholangio-pancreatography; PI: Perfusion Index; HR: Heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; RR: Respiratory rate; SPO₂: Oxygen saturation

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) procedure is used for diagnosis and management of several biliary and pancreatic diseases. It is a complex painful procedure that necessitates adequate sedation and analgesia, as agitation and discomfort have been reported to be within the factors causing post ERCP complications [1].

The patient category scheduled for ERCP procedures are usually the elderly, as the incidence of biliary complications is more frequent in the older age groups, who could be complaining of some co-morbid diseases adding additional risks to the procedure [1,2]. So cautious choice of a sedative agent, as well as monitoring of its hemodynamic effects are required.

Propofol is the most commonly used agent for sedation during ERCP procedures. It is a potent hypnotic agent with rapid onset of action and rapid recovery. It has dose dependent cardiac effect which together with the respiratory depression and insufficient analgesia present the common adverse effects observed with it [3]. So adding an adjunct drug may result in a decrease in propofol dose and consequently its adverse effects while increasing the level of analgesia.

Dexmedetomidine is a highly selective α-2 adrenergic agonist with sedative and analgesic properties. It causes sympatholysis and hemodynamic stability. It lacks respiratory depression. So it is considered a safe alternative sedative sole agent and an useful adjunct agent in many clinical situations [4,5].

Peripheral perfusion is regulated with autonomic nervous system. This regulation is affected by anesthetic agents as most of them cause vasodilatation [6-8]. In addition, pain stimuli change the circulating catecholamines level which may be reflected on the tissue perfusion [9].

Now new generation pulse oximeters can measure the perfusion index (PI) noninvasively. Perfusion Index is a numerical value that indicates the strength of the infrared signal returning from the monitoring site. It measures the ratio of pulsatile to non-pulsatile components of the infrared signal which reflects the pulsatile and the

non-pulsatile amounts of blood. This relationship between the pulsatile and the non-pulsatile amounts of blood at any particular site corresponds to PI at that site. It ranges from 0.02% (very weak pulse strength) to 20% (very strong pulse strength) [6-10].

It was reported that peripheral perfusion improves during inhalational anesthesia, total intravenous anesthesia [6-8], or neuroaxial anesthesia [11,12]. The resulting changes in PI could be useful for monitoring changes in peripheral vasodilatation and sympathetic tone in anesthetized patients, which could reflect the level of analgesia and sedation.

A previous study evaluated dexmedetomidine as a sole agent during ERCP procedures. It declared that dexmedetomidine was not as effective as propofol for sedation during ERCP [13]. So, we designed this study to evaluate its efficacy as an adjunct drug to propofol for sedation during ERCP procedures. We investigated its effects on peripheral perfusion and studied its other hemodynamic respiratory and adverse effects.

Methods

After obtaining approval of the research and ethics committee and informed consent of the patients. 76 patients ASA I-III scheduled for ERCP procedure were included in this prospective study.

We excluded patients with ASA class more than III together with any patient had compromised airway, hemodynamic instability, gastrointestinal reflux disease or history of allergic reaction to planned medications. Emergency cases (eg. for Cholangitis or bleeding) and pregnant women were also excluded.

Patients were distributed randomly according to a computer generated randomization code in blocks of four to one of two groups; dexmedetomidine/propofol (DP) group (n=37), and propofol (P) group (n=39).

There were two IV lines in each patient in both groups, one for propofol and another for Dex (in propofol/Dex group) or Saline (placebo in propofol group) to achieve blinding. Propofol boluses were given in propofol line. The study was blinded for the patient and the data collector but was not blinded for the anesthetist.

No pre-medications were given, patients were put in the prone position and monitored with ECG, NIBP, pulse oximetry and PI (Masimo setversion, Masimo Co., Irvin, California, USA), Masimo sensor was placed on a finger for all patients.

All patients were breathing spontaneously and received supplemental oxygen (2 L/min) by nasal catheter.

In (DP) group sedation was induced with dexmedetomidine (percedex; Hospira, Inc., Lake Forest, IL 60045 US) 0.7 µ/kg infused over 10 minutes and 50 mg bolus dose of propofol (B. Braun Melsungen AG 34209 Melsungen, Germany) to achieve a Modified Observer's Assessment of Alertness and Sedation scale (MOAA/S) equal 1 or 2 (Table 1) [14], followed by infusion of dexmedetomidine 0.4 µ/kg/h and propofol 0.5-1 mg/kg/h for maintenance of sedation.

In (P) group, sedation was induced by 50 mg bolus dose of propofol to achieve MOAA/S equal 1 or 2 followed by infusion of propofol 0.5-1 mg/kg/h. In patients of both groups, if any discomfort, agitation or unexpected movement occurred, incremental bolus of propofol (10-20) mg was given.

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

Table 1: Modified Observer's Assessment of Alertness/Sedation Scale [14].

Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate (RR), oxygen saturation (SPO₂), and perfusion index (PI) were continuously monitored and recorded at the following time points; (T0) before induction of sedation, (T1) after induction of sedation just before insertion of the endoscope, (T2) 5 minutes after the insertion of endoscope, at 10 minutes intervals throughout the procedure until withdrawal of endoscope and stoppage of drug infusion (T3-T6), and at 15 minutes intervals during the recovery period (T7,T8).

Respiration	
Able to take deep breath and cough	2
Dyspnea/shallow breathing	1
Apnea	0
Oxygen saturation	
SaO ₂ >95% on room air	2
SaO ₂ =90-95% on room air	1
SaO ₂ <90% even with supplemental O ₂	0
Consciousness	
Fully awake	2
Arousable on calling	1
Not responding	0
Circulation	
BP ± 20 mmHg baseline	2
BP ± 20-50 mm Hg baseline	1
BP +/- 50 mm Hg baseline	0
Activity	
Able to move 4 extremities	2
Able to move 2 extremities	1
Able to move 0 extremities	0

Table 2: Modified Aldrete Scoring System [15].

The procedure time (time from insertion of endoscope till its withdrawal) and the recovery time (time from stoppage of drug intake until achievement of modified Aldrete score of 10) were recorded (Table 2) [15].

Any adverse effects as hypotension (decreased blood pressure >20% from the baseline value), bradycardia (HR<50), and oxygen desaturation (SPO₂<90% for more than 10 seconds), airway obstruction, laryngospasm, apnea (stoppage of respiratory activity for more than 10 seconds), nausea, and vomiting were reported.

Statistical methods

Sample size was calculated using Epi info version 6.04. Confidence interval 95%, with study power was 80%. Accordingly the total calculated sample size was about 76 patients.

Parameters	Dexmedetomidine/ propofol (n=37)	Propofol (n=39)	P value
Age (years) mean ± SD	52.92 ± 9.49	55.21 ± 10.75	0.33
Weight (kg) mean ± SD	82.16 ± 8.43	78.42 ± 8.85	0.063
Gender (M/F)	23/14	22/17	0.61
Propofol dosage (mg/kg/h) mean ± SD	6.93 ± 1.45 [*]	9.33 ± 1.27	0.001
ASA class (%)			0.91
I	16 (43.2%)	18 (46.2%)	
II	15 (40.5%)	16 (41%)	
III	6 (16.2%)	5 (12.8%)	
Indications for ERCP			0.992
-Calcular	14 (37.8%)	16 (41%)	
-Malignant biliary stricture	13 (35.14%)	12 (30.8%)	
-Bening biliary stricture	4 (10.8%)	4 (10.3)	
-Pancreatic	3 (8.1%)	3 (7.7)	
-others	3 (8.1%)	4 (10.3)	

Table 3: Age, weight, gender, propofol dosage, ASA class and indications for ERCP. Age, weight and propofol dosage data are presented as means ± standard deviations, gender data is presented as number of patients while ASA class and indications for ERCP data are presented as number of patients (%). *denotes significance between both groups, p value <0.05

Continuous variables were presented as mean ± SD, while categorical variables were presented as number and/or percentage of total. Independent samples t-test was used to test the differences between the two groups regarding; age, weight, propofol dosage, procedure and recovery times, PI, HR, SBP, DBP, RR, and SPO₂. While changes in data within the same group (PI, HR, SBP, DBP, RR, & SPO₂) were analyzed using a repeated measure of analysis of variance. Data about gender, ASA Class, indications of ERCP procedure, and incidence of side effects were analyzed with chi-square test or Fisher's

exact test as appropriate. A p value <0.05 was considered statistically significant and all analyses were done using SPSS software version 20.

Results

There were no significant differences regarding the demographic data, ASA classification and indications for ERCP as shown in Table 3.

The perfusion index (PI) values, (Figure 1) showed significant increase in dexmedetomidine/propofol group versus propofol group at the time points from T2 to T7 with p value <0.001. Within the dexmedetomidine/propofol group, PI values increased significantly at T1 to T7 from the baseline value (T0) with p value <0.001. PI values within the propofol group, increased significantly at T1 to T5 than T0 with p value <0.001.

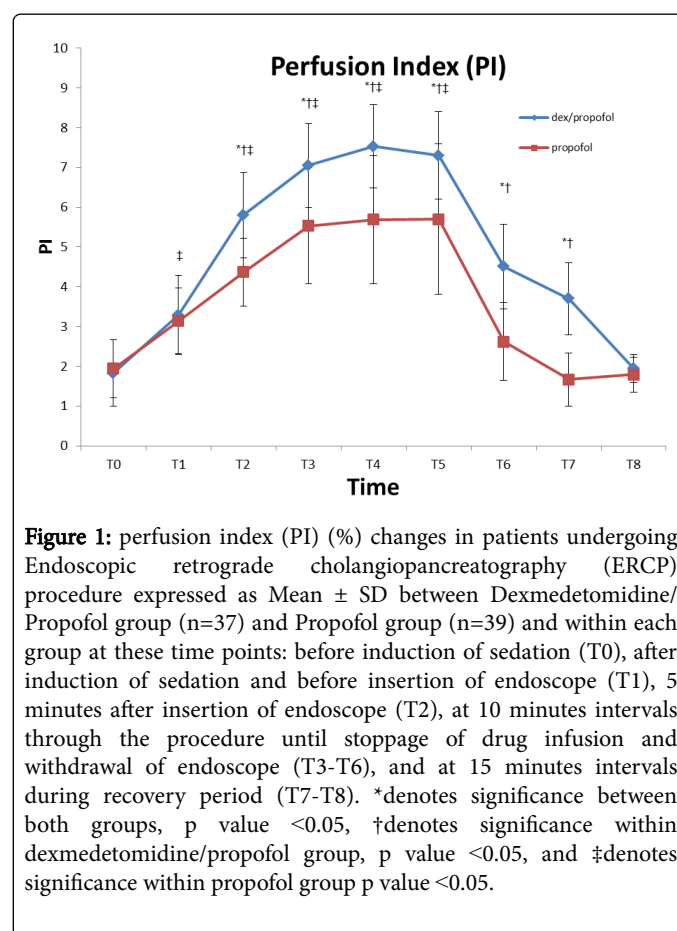


Figure 1: perfusion index (PI) (%) changes in patients undergoing Endoscopic retrograde cholangiopancreatography (ERCP) procedure expressed as Mean ± SD between Dexmedetomidine/ Propofol group (n=37) and Propofol group (n=39) and within each group at these time points: before induction of sedation (T0), after induction of sedation and before insertion of endoscope (T1), 5 minutes after insertion of endoscope (T2), at 10 minutes intervals through the procedure until stoppage of drug infusion and withdrawal of endoscope (T3-T6), and at 15 minutes intervals during recovery period (T7-T8). *denotes significance between both groups, p value <0.05, †denotes significance within dexmedetomidine/propofol group, p value <0.05, and ‡denotes significance within propofol group p value <0.05.

Heart rate (HR) values, (Figure 2) showed significant decrease in dexmedetomidine/propofol group versus propofol group at T1 to T8 with p value at T1 is 0.013 and at T2 to T8 is <0.001. Within the dexmedetomidine/propofol group, HR values decreased significantly at T1 to T8 versus T0 with p value <0.001. In the propofol group, HR values decreased significantly at T1 versus T0 with p value <0.001 then increased significantly at T2 to T7 versus T0 with p value <0.001 at T2 to T6 and 0.004 at T7.

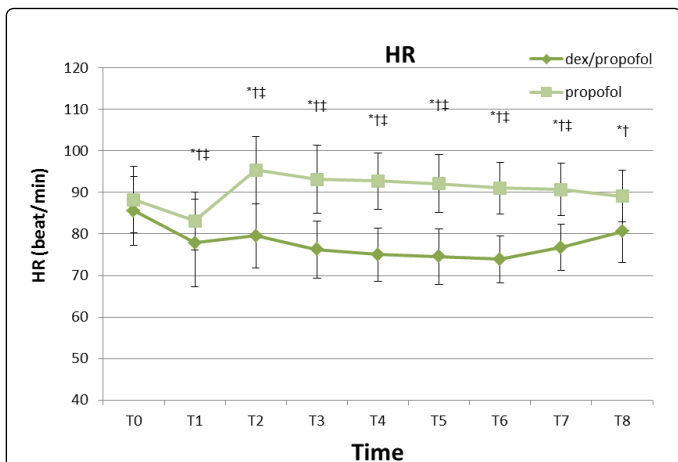


Figure 2: heart rate (HR) (beat/min) changes in patients undergoing Endoscopic retrograde cholangiopancreatography (ERCP) procedure expressed as Mean ± SD between Dexmedetomidine/Propofol group (n=37) and Propofol group (n=39) and within each group. *denotes significance between both groups, p value <0.05, †denotes significance within dexmedetomidine/Propofol group, p value <0.05, and ‡denotes significance within propofol group p value <0.05.

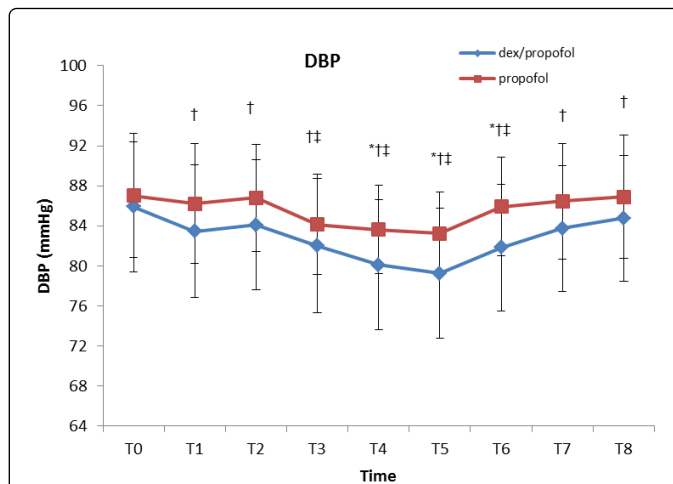


Figure 4: diastolic blood pressure (DBP) (mm Hg) changes in patients undergoing Endoscopic retrograde cholangiopancreatography (ERCP) procedure expressed as Mean ± SD between Dexmedetomidine/Propofol group (n=37) and Propofol group (n=39) and within each group. *denotes significance between both groups, p value <0.05, †denotes significance within dexmedetomidine/Propofol group, p value <0.05, and ‡denotes significance within propofol group p value <0.05.

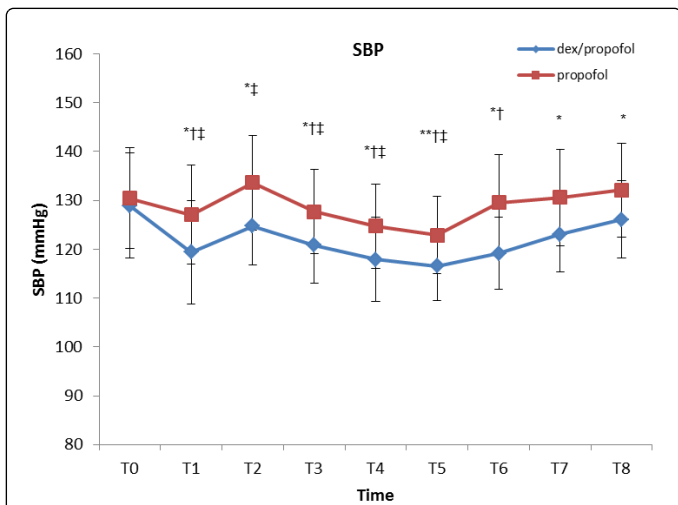


Figure 3: Systolic blood pressure (SBP) (mm Hg) changes in patients undergoing Endoscopic retrograde cholangiopancreatography (ERCP) procedure expressed as Mean ± SD between Dexmedetomidine/Propofol group (n=37) and Propofol group (n=39) and within each group. *denotes significance between both groups, p value <0.05, †denotes significance within dexmedetomidine/Propofol group, p value <0.05, and ‡denotes significance within propofol group p value <0.05.

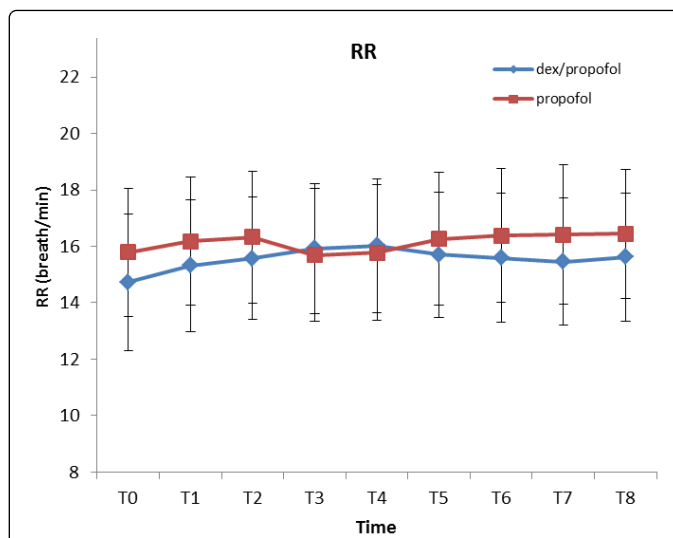


Figure 5: respiratory rate (RR) (breath/min) changes in patients undergoing Endoscopic retrograde cholangiopancreatography (ERCP) procedure expressed as Mean ± SD between Dexmedetomidine/Propofol group (n=37) and Propofol group (n=39).

The values of systolic blood pressure (SBP) showed significant decrease in dexmedetomidine/propofol group at T1 to T8 versus the propofol group (Figure 3) with p values (0.002 at T1, <0.001 at T2 to T7 and 0.004 at T8) respectively. Within the dexmedetomidine/propofol group, SBP values showed significant decrease at T1 and T3 to T7 with p values (0.003 at T1, <0.001 at T3 to T6 and 0.022 at T7) respectively. SBP values in propofol group showed significant decrease

at T1, T3 to T5 with p value <0.001 and significant increase at T2 with p value <0.001.

Diastolic blood pressure (DBP) values, (Figure 4) showed significant decrease in dexmedetomidine/propofol group versus the propofol group at T4 to T6 with p values (0.008, 0.002 and 0.003 at T4, T5 and T6 respectively). Within dexmedetomidine/propofol group, DBP values showed significant decrease from baseline value (T0) at T1 to T8 with p <0.001. In propofol group, DBP values showed significant decrease from T0 at T3 to T6 with p (0.002 at T3, <0.001 at T4, T5 and 0.023 at T6) respectively.

Respiratory rate (RR) and arterial oxygen saturation (SPO₂) values, (Figures 5 and 6) were comparable between both groups. The propofol dosage (Table 3) was significantly lower in dexmedetomidine/propofol group than propofol group with p value 0.001. Also, there was significant increase in the recovery time in dexmedetomidine/propofol group versus propofol group with p value 0.001, while the procedure time was comparable between both groups (Table 4).

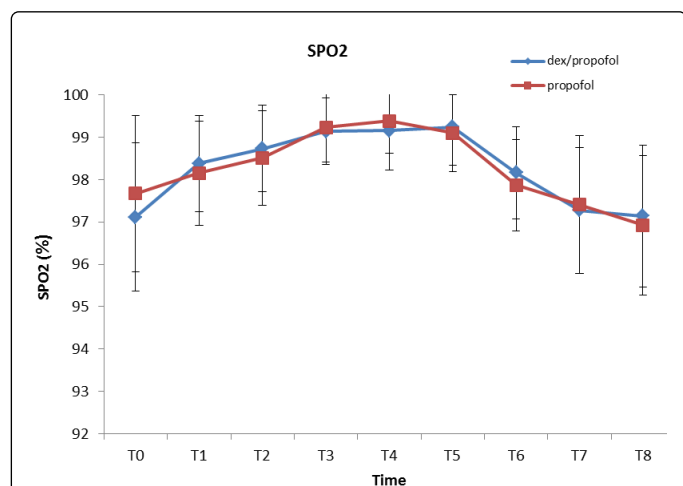


Figure 6: Oxygen saturation (SPO₂) (%) changes in patients undergoing Endoscopic retrograde cholangiopancreatography (ERCP) procedure expressed as Mean ± SD between Dexmedetomidine/Propofol group (n=37) and Propofol group (n=39).

Parameters	Dexmedetomidine/propofol (n=37)	Propofol (n=39)	P value
Procedure time (min)	36.86 ± 7.19	40.13 ± 7.39	0.055
Recovery time (min)	20.38 ± 4.92*	11.62 ± 4.37	0.001

Procedure time and recovery time data are presented as mean as ± standard deviation. *denotes significance between both groups, p value <0.05.

Table 4: The times of procedure and recovery.

Table 5 compares the adverse effects between both groups, there were significant difference between both groups. Regarding bradycardia, 4 cases (10.8%) were reported in dexmedetomidine/propofol group, one of them needed IV atropine 0.5 mg versus no cases in propofol group with p value 0.035. Also, tachycardia was reported in 8 cases (20.5%) in propofol group versus one case (2.7%) in

dexmedetomidine/propofol group with p value 0.016. There were 6 cases (15.4%) in propofol group developed airway obstruction versus no cases in dexmedetomidine/propofol group with p value 0.026. Airway obstruction was mild and never necessitated more than chin lift or jaw thrust. It occurred mostly after boluses of propofol during the maintenance phase. There was no significant difference regarding the other adverse effects. Hypotension occurred to cases during the procedure was mild, transient and did not need any vasoconstrictors.

Parameters	Dexmedetomidine/propofol (n=37)	Propofol (n=39)	P value
Hypotension	3 (8.1%)	6 (15.4%)	0.326
Hypertension	3 (8.1%)	5 (12.8%)	0.503
Bradycardia	4 (10.8%)*	0	0.035
Tachycardia	1(2.7%)*	8 (20.5%)	0.016
Arrhythmia	0	1 (2.6%)	0.327
Oxygen desaturation	1 (2.7%)	4 (10.3)	0.184
Airway obstruction	0*	6 (15.4%)	0.026
Laryngospasm	0	1 (2.6%)	0.327
Nausea &/or vomiting	2 (5.4%)	3 (7.7%)	0.688

Data are presented as number of patients (%). * denotes significance between both groups, p value <0.05.

Table 5: Adverse effects between dexmedetomidine/propofol group and propofol group.

Discussion

Using dexmedetomidine as a sole agent for conscious sedation during ERCP resulted in less satisfactory sedation than propofol, as most of the patients needed additional sedatives to achieve a sufficient sedation level. However this may be attributed to the use of dexmedetomidine as a sole agent with a relatively small dose similar to those employed in intensive care for sedation and in anesthesia as an adjunct agent. In spite of that, patients received dexmedetomidine needed less fentanyl and had a longer recovery period during which they were more sedated than patients received propofol [13].

In our study, we used dexmedetomidine as an adjuvant agent to propofol. We found that the addition of dexmedetomidine to propofol resulted in lower HR, SBP and DBP values than in the propofol group. It offered lesser increases in hemodynamic values following endoscopic insertion. This could be explained by the central sympatholytic effect of dexmedetomidine in addition to employing a dose not high enough to produce initial vasoconstriction and BP increase.

Also, the addition of dexmedetomidine resulted in more PI values suggesting better level of sedation and analgesia. It could be explained by the dexmedetomidine sympatholytic effect and lack of catecholamines release that was reflected on peripheral perfusion.

Adding dexmedetomidine to propofol resulted in a reduction in amount of propofol used. SPO₂ and RR values were comparable between the two groups but the respiratory complications were more in propofol group. This may be rendered to the respiratory safety of dexmedetomidine and the lower amount of propofol used with it. Also,

the dexmedetomidine/propofol group was associated with a longer recovery time which could be due to the prolonged dexmedetomidine half-life.

Some previous studies compared the use of dexmedetomidine versus propofol for sedation in different settings. One study on healthy volunteers observed that using dexmedetomidine resulted in significant dose dependent reduction in HR, SBP and DBP, while using propofol resulted in lesser changes in BP but not in HR. The two agents were effective in producing the desired level of sedation [16].

Another study compared dexmedetomidine and propofol during electrophysiology study and demonstrated comparable sedation level with either drug. Mean arterial blood pressure values were significantly higher at 5, 15 min in dexmedetomidine group. RR values were significantly lower in dexmedetomidine group than in propofol group [17].

Another study compared dexmedetomidine versus propofol for intraoperative sedation to supplement regional anesthesia. All patients achieved the targeted sedation level. Patients received dexmedetomidine (initial dose 1 μ /kg over 10 min then infusion of 0.4-0.7 μ /kg/h for maintenance) had slower onset of sedation, lower pain scores and less analgesic needs in the postoperative period suggesting good analgesic potential for dexmedetomidine. Respiratory parameters were comparable in both groups. Intraoperative MAP values were lower in the propofol group and the authors explained it by the powerful inhibitory effect of propofol on the sympathetic nervous system. Actually dexmedetomidine has a powerful inhibitory effect on the sympathetic nervous system. They hypothesized that this effect was opposed by the direct α -2 mediated vasoconstriction caused by dexmedetomidine when used in such a high dose [18].

This may help us in understanding the differences in hemodynamic findings between different studies. As dexmedetomidine was used with different doses, it was used either as a sole agent or as an adjuvant drug.

Another study compared dexmedetomidine/fentanyl versus propofol/ nalbuphine in plastic surgery found that though HR, SBP and DBP decreased intraoperatively in both groups but these decreases were more evident in the dexmedetomidine group. The recovery time was shorter in the propofol group. [19]

Other studies evaluated the combination of dexmedetomidine and propofol for sedation. Dutta et al in their study on healthy subjects found that the addition of dexmedetomidine decreased the mean propofol dose requirements by approximately one half [20]. This finding was augmented by the work done by Kang et al and concluded that adding dexmedetomidine as an adjuvant (1 μ /kg before anesthesia induction and 0.5 μ /kg/h infusion during maintenance) reduced propofol requirements by approximately 30% and produced more stable hemodynamics during remifentanyl based propofol supplemented anesthesia [21].

Another study demonstrated a significant decrease (>50%) in propofol infusion dosage when adding dexmedetomidine to it for conscious sedation during plastic surgery under local anesthesia. Patients in the (dexmedetomidine/propofol) group received continuous IV dexmedetomidine at a rate of 0.01 μ /kg/min, concomitant with propofol infusion. They had better hemodynamic stability and lesser time to eye opening as compared to those in the control (propofol only) group [22]. Also Wang et al, found that adding dexmedetomidine 1 μ /kg bolus over 10 minutes followed by its

infusion at 0.5 μ /kg/h decreased the bispectral index (BIS) value under stepwise propofol targeted controlled infusion (TCI) [23].

Perfusion index (PI) is a relative assessment of the pulse strength at the monitoring site. It is an indirect, noninvasive and continuous measure of peripheral perfusion [10]. Previous studies have demonstrated that an increase in PI is an early indicator that general [6-8] and epidural anesthesia [11,12] has initiated peripheral vasodilatation.

Hager et al. in their study on few healthy volunteers found that the PI could indicate painful stimuli under sevoflurane anesthesia, as painful stimulation significantly decreased PI, while there was weak correlation between end tidal sevoflurane concentration and PI and also between end tidal sevoflurane concentration and the decrease in PI values during painful stimulation [9].

In summary, our results found that the addition of dexmedetomidine to propofol for sedation during ERCP procedures resulted in lower propofol requirements. This is in agreement with most of the previous studies. Also, the resulted higher perfusion index (PI) could reflect more sufficient levels of sedation and analgesia.

With the use of dexmedetomidine, hemodynamics was less affected by the stressful periods during the procedure. That is considered beneficial especially for the elderly patients undergoing ERCP who could be potentially hypertensive or ischemic.

Our results demonstrated less respiratory complications when dexmedetomidine added to propofol. This is an important advantage during ERCP. This procedure may be associated with more respiratory complications especially during endoscopic insertion and throughout procedure due to either deep sedation or even light sedation in presence of secretions and endoscopic manipulations.

We conclude that using dexmedetomidine as an adjuvant drug to propofol for sedation during ERCP procedures resulted in a better sedation level, more efficient analgesia, in addition to the respiratory safety which is especially valuable in this type of procedures.

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