Original Article

Comparing the Efficacy and Safety of Dexmedetomidine-Lidocaine and Propofol-Fentanyl-Midazolam Combinations during Endoscopic Retrograde Cholangiopancreatography

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Abstract

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Background: Propofol is commonly used for providing sedation in endoscopic retrograde cholangiopancreatography (ERCP). It's simple to use and effective but presents cardiovascular and respiratory adverse effects. Recently, dexmedetomidine has been tried but very little evidence exists to support its use. The aim of this study was to compare the efficacy and safety of combination of dexmedetomidine and lidocaine (DL) with the standard propofol-fentanyl (PF) regimen.

Materials and Methods: After approval of the hospital ethics committee, 63 patients (18-60 years of age) were randomly divided into 2 groups. Thirty-one patients received a PF combination (group PF), and 32 patients received DL combination (group DL). The level of sedation was adjusted to achieve a Ramasy Sedation Scale (RSS) score of 3 (moderate sedation) in both groups of patients. Arterial pressure (MAP), heart rate (HR), and peripheral oxygen saturation (SpO_2) during ERCP and recovery was continuously assessed.

Results: The oxygen saturation (SpO_2) showed high statistical significant differences between both groups throughout the procedure with stability in DL group ($p<0.01$). There was no statistical difference in HR and MAP between the two groups ($p>0.05$). Post-procedural recovery time was significantly shorter in PF group (15.97 ± 3.27 min) compared with (19.38 ± 5.64 min) DL group ($p<0.01$). PONV was 3.2% in PF group, while it was absent in DL group. No drug adverse effect or cardiovascular complications were observed in both groups.

Conclusion: Dexmedetomidine and lidocaine combination as total intravenous anesthesia (TIVA) during ERCP not only did not reported any oxygen desaturation ($SpO2<90\%$) but also showed better stability of oxygen saturation (SpO_2) and less PONV when compared with propofol and fentanyl combination.

Keywords: Dexmedetomidine, Lidocaine, Sedation, ERCP, oxygen saturation.

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Introduction

Endoscopic retrograde cholangio-pancreatography (ERCP) has revolutionized the management of many pancreatic and biliary problems with its utility ranging from a diagnostic solution to complex diagnosis and therapeutic intervention (1, 2). It is a complex procedure which requires technical expertise as well as adequate sedation and anesthesia. The procedure time ranges from 30 to 60 minutes, and it is performed with the patient in the prone or semi-prone position. Moderate to deep levels of sedation and analgesia are required to minimize patient discomfort and to facilitate the operation (3).

ERCP is a complicated and long procedure. It requires moderate to deep sedation, and even general anesthesia. The level of sedation depends on the type of ERCP procedure as diagnostic or therapeutic and patient characteristics (4-6). There are various agents available to provide sedation. Current drugs include benzodiazepines (7) with an opioid; most commonly midazolam and diazepam (8), with or without propofol often combine with fentanyl or remifentanil (9). Ketamine has also been used in low doses for moderate sedation. Newer agents such as dexmedetomidine (10) and fospropofol are also being used (11). Combination with Lidocaine never been used. The anti inflammatory and analgesic properties of Lidocaine has also shown in new studies (29).

Recently dexmedetomidine has been used as TIVA in conscious sedation. A few studies have reported the success of dexmedetomidine in combination with ketamine and propofol as safe and effective sedative agent (12, 13). PF-based sedation techniques are effective for ERCP procedures but are not without cardiovascular and respiratory adverse effects (13). The use of dexmedetomidine as the sole anesthetic agent and as the adjuvantanalgesicagenthasbeenpublishedbuthasnotbeeneffective as propofol combined with fentanyl for conscious sedation during ERCP (14). This study was designed to compare the efficacy and safety profile of dexmedetomidine-lidocaine (DL) combination with the standard propofol and fentanyl (PF).

Methods

This study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences at the Taleghani Hospital. The sample was drawn from patients admitted to undergo ERCP. We excluded patients who had ASA physical status Grade III and more, baseline $SpO_2 < 90\%$, mechanically ventilated patients, patients with comorbid conditions such as diabetes mellitus, hypertension (HTN) or hepatic or renal insufficiency to see the pure effect of both these drugs and to avoid any interaction with any simultaneous drug intake, which could have altered the results. Sixty-three patients with American Society of Anesthesiologist (ASA) classification I and II, aged 18 to 60 years, admitted for diagnostic and therapeutic ERCPs, were enrolled in the study. Patients provided written informed consent for participation in the study.

A detailed pre-operative check-up including general examination and systemic examination of the patient was carried out. On arrival in the Endoscopy Room, all vital parameters such as heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and oxygen saturation (SpO_2) were recorded. Readings were taken following the loading dose and every 5 min until the completion of the procedure.

This randomized, blind double-dummy clinical trial, with the rater blinded to the intervention, was conducted with patients who were undergoing an ERCP. The intervention was in the form that one group of patients was given dexmedetomidine with lidocaine (DL) and other group received propofol with fentanyl (PF) until achieving Ramasy sedation scale (RSS) score to 3 or 4 as moderate to deep sedation (Table 1). The DL group (n=32) received dexmedetomidine; (200 µg/ 2 ml) which prepared as 2 ml plus 48 ml normal saline total volume 50 ml. patients received loading dose of 1 µg/kg intravenous over 10 min and in 7 min lidocaine 1.5 ml/kg and then followed by 0.5 µg/kg/h infusion until RSS reached to 3-4. Group PF (n=31) received a single dose of midazolam (1mg) and additional fentanyl 1µg/kg and after 2 min patient received propofol 1 µg/kg/h in 60 sec and the followed by0.5 µg/kg/h infusion until RSS reached to 3-4. We used these doses of propofol and

dexmedetomidine to preserve sufficient consciousness to allow communication, but provided the necessary degree of sedation to enable surgical comfort and an adequate quality of recovery with no negative effects on hemodynamics and respiratory parameters.

The drug infusion was discontinued if one of the following adverse events was observed: hemodynamic and/or respiratory instability, i.e., hypotension (mean arterial pressure reduction of 30% of its initial value), or apnea longer than 30 seconds, or oxygen desaturation<90%. During the procedure, any of the following complications were noted, recorded and treated accordingly: oxygen desaturation was considered when SpO_2 less than 90% for more than 10s. Both groups were managed by supporting airway and/or assisting ventilation. Bradycardia was considered when HR was less than 50 beats/min and managed with atropine 20 mcg/kg intravenous Hypotension was considered when MAP decreased by >20% of the baseline MAP and managed by fluid bolus or vasopressors. Any cough or gagging was noted and recorded.

Outcome assessed

The primary outcome was defined as the sedation level recorded by the RASS and the requirement of additional sedatives or an analgesic to display signs of insufficient analgesia. The level of sedation was judged adequate when the score on RASS was above or equal to 3, whether the patient tolerated the introduction of the endoscope without the presence of pain, discomfort, or agitation. The secondary outcome was the respiratory maintenance pattern, which was assessed by oxygen saturation (SpO_2).Furthermore, the HR and mean arterial pressure (MAP) were measured by the automated oscillography method. The SpO_2 was monitored by a finger probe. The HR, MAP and SpO_2 were continuously monitored and recorded at 5 min interval. Postoperative nausea and vomiting (PONV) were recorded and managed accordingly. Times of induction, procedure, recovery, and adverse effects were also reported.

Statistical analysis

Data were entered and analyzed using statistical package for social sciences (SPSS) for windows version 21 software (SPSS Inc., Chicago, IL, USA). Data were statistically described in terms of mean± standard deviation (±SD), or frequencies (number of cases) and percentages when appropriate. Numerical data between both groups were done using Student's t-test or Mann-Whitney test, depending on the distribution for independent samples. Categorical data were compared by Chi-square test with continuity correction or Fisher's exact test as applicable. P values less than 0.05 were considered statistically significant.

Results

The study recruited 64 patients scheduled for ERCP over a period of 6 months at a single institution. They were randomized into 2 groups, PF and DL, with 32 patients in each. The data were collected from 32 patients in group DL and 31 patients in group PF. One patient from group PF was excluded from the study because of missing data or procedure termination due to unrelated sedation reasons. Patient characteristics in two groups were shown in table 2. There were no significant differences in the demographic characteristics data between the two groups.
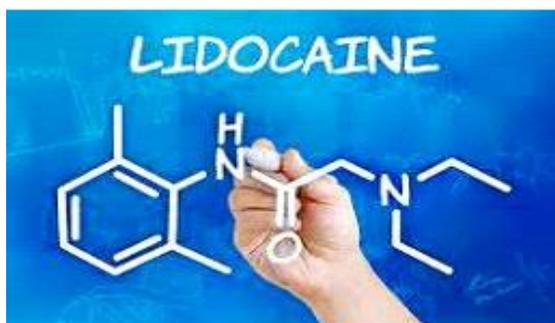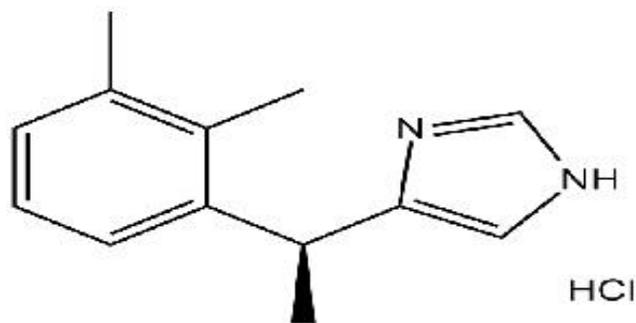
Figure 1.(A) Lidocaine Formula; (B) Dexmedtomidine Formula.

Table 1: Ramsay Sedation Scale.

Score	Term	Description
1	Drowsy	Not fully alert but has sustained awakening (eye opening) to voice (>10s)
2	Light sedation	Briefly awakens with eye contact to voice (< 10s)
3	Moderate sedation	Movement or eye opening to voice (but not eye contact)
4	Deep sedation	Not responsive to voice but movement or eye opening to physical stimulation
5	Unarusable	No response to voice or physical stimulation

Table 2: Characteristics of patients in two groups (n=63).

Variables	Group DL (n=32)	Group PF (n=31)	P-value
Gender (M/F)	19/13	17/14	0.716
Age	51.91±5.96	49.16±8.73	0.152
ASA type (I/ II)	19/13	18/13	0.916
Smoker	7 (21.9%)	13 (41.9%)	0.087

Data were expressed as mean±SD. P value> 0.05 was considered statistically not significant. Group DL; dexmedetomidine with lidocaine, group PF; propofol with fentanyl. ASA; American Society of Anesthesiologists

Table 3: Vital sign during ERCP and recovery time.

Variables	Group DL (n=32)	Group PF (n=31)	P-value
HR (beat/min)	80.31±9.88	77.92±11.85	0.341
MAP (mm Hg)	78.02±5.43	77.86±7.31	0.738
Spo_2	96.02±1.55	94.54±3.01	0.002*
Recovery time	19.38±5.64	15.97±3.27	0.011*
PONV	0 (0)	1 (3.2%)	0.492

HR: Heart rate, MAP: Mean arterial pressure, Spo_2: Oxygen saturation, PONV: Postoperative nausea-vomiting, P-value<0.05 was considered statistically significant

Table 4: Changes of HR between two groups during the ERCP procedure.

HR Time Variable (min)	Group DL (n=32)		Group PF (n=31)		P-value
	Mean±SD	Range (min-Max)	Mean±SD	Range (min-Max)	
First	86.25±11.29	70-120	82.26±14.54	65-110	0.220
0-5	86.81±11.29	70-110	82.74±13.77	65-115	0.136
5-10	84.06±9.95	70-105	79.81±14.43	60-120	0.082
10-15	82.41±11.45	70-105	77.58±12.84	60-105	0.144
15-20	81.09±10.91	65-110	76.94±12.29	60-105	0.128
20-25	79.22±9.85	65-110	76.61±10.98	55-100	0.395
25-30	77.81±8.03	65-90	76.29±10.72	60-100	0.292
30-35	75.16±8.93	60-95	76.13±10.22	55-100	0.692
35-40	75.94±8.65	60-95	77.26±9.56	65-100	0.715
Total	80.31±9.88	60-120	77.92±11.85	55-120	0.341

Group DL; dexmedetomidine with lidocaine, group PF; propofol with fentanyl, P-value<0.05 was considered statistically significant

HR, MAP, SpO2, recovery time and POVN were given as mean±SD in Table 3. Patients in DL group significantly showed more stability of SpO2 than patients in PF group (p=0.002).There were no significant differences in MAP and HR values between the two groups (p>0.05). Recovery times were significantly longer in the DL group (p=0.011). Nausea and Vomiting (PONV) were observed in one patient (3.2%) in group PF, while it was absent in DL group but there were no significant statistically

Table 5: Changes of MAP between two groups during the ERCP procedure.

MAP Time Variable (min)	Group DL (n=32) Mean±SD	Range (min-Max)	Group PF (n=31) Mean±SD	Range (min-Max)	P-value
First	82.97±4.37	75-95	81.94±4.60	70-90	0.717
0-5	81.41±5.42	70-95	81.61±5.23	70-95	0.947
5-10	80.19±6.68	65-100	80.48±6.63	70-100	0.861
10-15	79.00±6.96	60-95	78.06±9.10	60-100	0.431
15-20	77.81±6.59	60-95	75.64±7.61	60-95	0.098
20-25	76.56±4.99	60-90	75.48±7.46	65-100	0.158
25-30	76.56±4.99	70-90	76.45±7.09	70-100	0.477
30-35	76.09±3.75	70-80	76.94±8.03	65-100	0.828
35-40	76.56±4.10	70-85	78.23±7.37	65-100	0.415
Total	78.02±5.43	60-100	77.86±7.31	60-100	0.738

Group DL; dexmedetomidine with lidocaine, group PF; propofol with fentanyl, P-value<0.05 was considered statistically significant

Table 6: Changes of SpO_2 between two groups during the ERCP procedure.

SpO2 Time Variable (min)	Group DL (n=32) Mean±SD	Range (min-Max)	Group PF (n=31) Mean±SD	Range (min-Max)	P-value
First	96.53±1.74	99-100	96.26±1.29	94-99	0.401
0-5	96.13±1.74	93-100	95.81±1.70	92-99	0.465
5-10	96.16±1.71	93-99	94.87±3.06	88-99	0.274
10-15	96.16±1.72	92-99	93.81±4.26	85-98	0.064
15-20	96.03±1.69	92-99	93.39±4.24	86-98	0.032
20-25	96.09±1.42	92-99	93.29±3.58	86-98	0.006
25-30	95.94±1.56	92-99	94.06±2.87	88-98	0.015
30-35	95.78±1.36	93-98	95.23±2.67	86-98	0.809
35-40	95.94±1.27	93-98	95.87±1.75	92-99	0.849
Total	96.02±1.55	92-100	94.54±3.01	85-99	0.002

Group DL; dexmedetomidine with lidocaine, group PF; propofol with fentanyl, P-value<0.05 was considered statistically significant
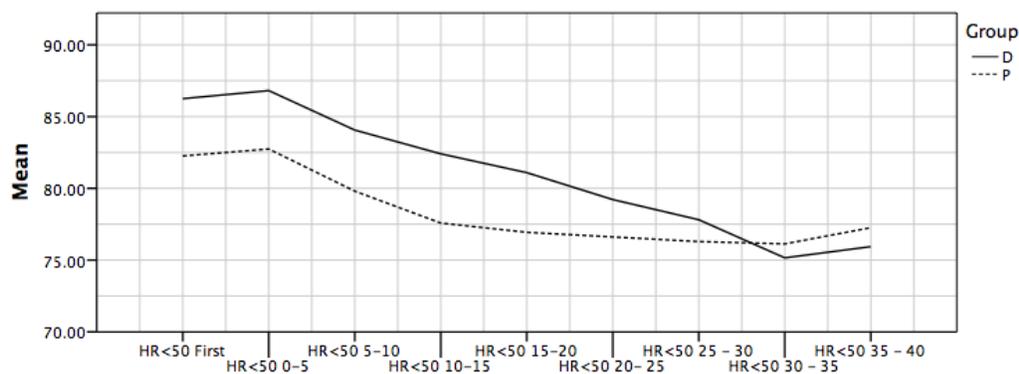

Figure 1.HR during the procedure between two groups.

(p=0.492). there was no event of drug adverse or cardiovascular complication observed in both regimens.

There were no significant differences in HR and MAP between two groups after loading dose in 5,10,15,20,25,30,35 and 40 min during ERCP procedure (Table 4 and 5). The case of oxygen desaturation (SpO2 <90%) was observed in PF groups after the loading dose at 5 to 35 minutes during ERCP procedure. While, it was absent in DL group and no cases in this group presented oxygen desaturation (SpO2 <90%). There is a significant difference in the
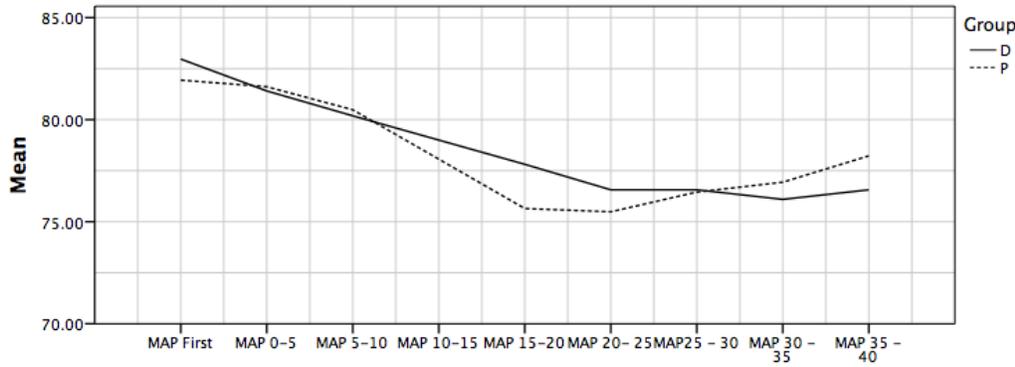
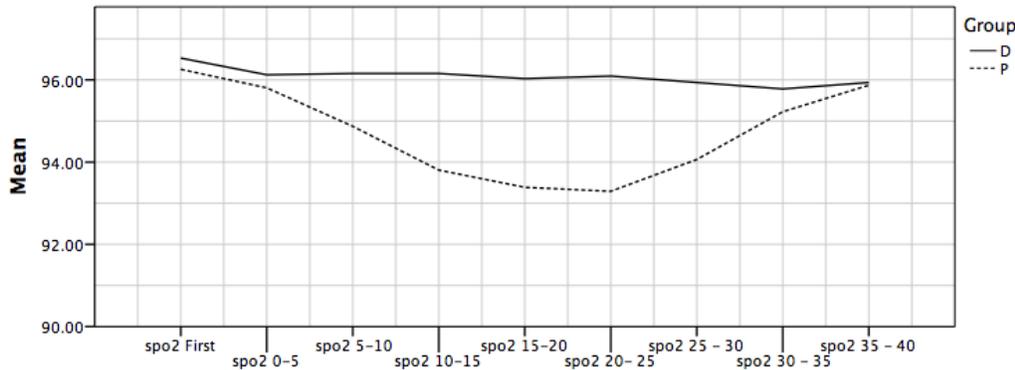**Figure 2.**MAP during the procedure between two groups.

Figure 3. SpO₂ during the procedure between two groups.

oxygen saturation (SpO2) level between the two groups in the 15, 20 and 25 minute of ERCP process (p=0.03, p=0.006 and p=0.015) respectively. Patients in DL group significantly showed more stability (p=0.002) of SpO2 after the loading dose at 5, 10, 15, 20, 25, 30, 35 and 40 min during ERCP procedure (Table 6).

Figures 1 to 3;HR (beats/min), MAP (mmHg), and SpO2 (as Mean±SD), determined at different stages of the study, including baseline (at least 5 minutes before the first drug administration), 5, 10, and 15 minutes after starting sedation, and from 15 minutes until the end of an ERCP (40 min).

Discussion

The goals of this study were to provide adequate steady state of sedation level while maintaining airway reflex, maintain cardiovascular and respiratory status, minimize side effects and pain and ensure patient comfort. Generally, propofol alone or in combination with midazolam or fentanyl is one of the most widely used regimens for sedation during the ERCP (15-17).However, the combination use of

sedatives with propofol may produce some additional risks (9, 18). In this study we compared the efficacy and safety of two different methods of moderate sedation; we used dexmedetomidine and lidocaine combination (DL) versus propofol and fentanyl combination (PF) during ERCP procedure.

Many previous studies use dexmedetomidine in combination or single as anesthetic agent during ERCP procedure and they reported different results. Eldesuky Ali Hassan et al. compared the hemodynamic stability, respiratory effect and recovery time in patient, who were randomly assigned in the two groups. Group D received dexmedetomidine as single aesthetic agent, and group K received a combination of ketamine and propofol (Ketofol) as aesthetic agent. MAP and HR in group D were significantly lesser than in the ketofol group. Additionally, time to achieve RSS score and total dose of rescue sedation in both groups were not significantly different. However, patient and endoscopist satisfaction in the ketofol group was significantly higher than in the dexmedetomidine group (4). Furthermore, Ceylan et al. (19) used dexmedetomidine (D) as single aesthetic agent and

then evaluated the effects of propofol and dexmedetomidine hemodynamics stability and satisfaction during ERCP procedure. The fifty patients with ASA physical status class Ⅰ and Ⅱ were randomized into the two groups. Group P and group D received propofol and dexmedetomidine respectively. All patients were sedated to attain a RSS of 3-4. The mental status examination before and after the procedure as well as pain was evaluated. The blood pressure and heart rate values in group D were significantly lesser than in group P. However, there were no significant differences in patient and endoscopist satisfaction among the two groups.

In combination form of dexmedetomidine, the efficacy of dexmedetomidine with propofol for anesthesia in ERCP procedure was evaluated by Abdalla et al. (20). Sixty patients with ASA physical status class Ⅱ or Ⅲ underwent ERCP procedures were randomly assigned into two groups. Group DF received combination of dexmedetomidine and propofol, group K, patients received a loading dose of ketamine 1 mg/kg and followed by 0.5 mg/kg per hour. Group DF during ERCP procedure showed better hemodynamic stability, less nausea and vomiting, as well as shorter recovery time when compared with the combination of ketamine and propofol. However, the negative results of the use of dexmedetomidine for ERCP procedure have been reported; for example, the study of Nagaraj et al. (21) compared the combination of dexmedetomidine and fentanyl with the combination of propofol and fentanyl for procedural sedation in ERCP procedure. The result of study showed that the combination of propofol and fentanyl achieved better overall conditions for ERCP compared to the combination of dexmedetomidine and fentanyl. Other studies used of dexmedetomidine with ketamine or propofol combination for sedation in ERCP procedures and reported that combination of dexmedetomidine gives more respiratory safety and hemodynamic stability (22, 23). The most of studies used dexmedetomidine with ketamine or propofol combination as induction agent for moderate to deep sedation but no study used it with lidocaine combination.

Therefore, in this study we used dexmedetomidine and lidocaine combination (DL) versus propofol and fentanyl combination (PF) during

ERCP procedure. In our study there was no event of drug adverse or cardiovascular complication observed in both regimens.

The case of oxygen desaturation (SpO2 <90%) was observed in PF groups after the loading dose at 5 to 35 minutes during ERCP procedure. While, it was absent in DL group and no cases in this group presented oxygen desaturation (SpO2 <90%). There is a significant difference in the oxygen saturation (SpO2) level between the two groups in the 15, 20 and 25 minute of ERCP process (P<0.05). Patients in DL group significantly showed more stability of SpO2. So, the results demonstrate that combination of DL gives more respiratory safety than propofol with fentanyl combination (P<0.01). In contrast to Muller et al. studies which reported, no statistical difference in SpO_2 between the dexmedetomidine as the sole anesthetic agent and propofol group (14). There were no significant differences in MAP, HR values at all-time points between the two groups (P>0.05). Recovery times were significantly longer in the DL group. Nausea and Vomiting (PONV) were observed in one patient (3.2%) in group PF, while it was absent in DL group, this result was consistent with previous study (24).

The most important result from this study was the persistence of oxygen saturation (SpO_2) in patients, who received dexmedetomidine and lidocaine combination (DL). No reported of oxygen desaturation (SpO2<90%) in DL group and more stability of SpO_2 during ERCP procedure in this group is very important because most patients who underwent ERCP are generally elderly and require sedation while in the prone position. This factor may be expected to prevent the risk of arterial hypoxemia (25). Arterial hypoxemia indicate impending respiratory failure or by itself may result in adverse physiological effects including acidosis, hyperkalemia, release of circulating catecholamines, myocardial excitation or depression, arrhythmias, arterial hypertension or hypotension, headache, intracranial hypertension, and agitation or narcosis (26-28).The limitation of this study was we don't measure respiratory rate, as the prone position makes it difficult to accurately count respiratory rate both artificially and automatically. So, the effect on respiratory function was judged only by SpO_2, which

may lead to missing subclinical respiratory depression.

Conclusion

Dexmedetomidine with lidocaine is a new combination that has been used in sedation or analgesia for short procedures as ERCP for first time in this study. Compared to other drugs and combinations, it provides similar effects; no event of hypotension or bradycardia but it has an added benefit with less number of postoperative side effects such as nausea and vomiting (PONV) and the most important result from this study was DL combination as total intravenous anesthesia (TIVA) during ERCP not only did not reported any oxygen desaturation (SpO2<90%) but also showed better stability of oxygen saturation (SpO2).

Acknowledgment

Conflicts of Interest

The authors declare that they have no conflict of interest.

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