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ORIGINAL ARTICLE

Efficacy of a Dexmedetomidine–Remifentanil Combination Compared with a Midazolam–Remifentanil Combination for Conscious Sedation During Therapeutic Endoscopic Retrograde Cholangio-Pancreatography: A Prospective, Randomized, Single-Blinded Preliminary Trial

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Abstract

Background Dexmedetomidine as a conscious sedative exhibits both analgesia and respiratory sparing effects.

Aims We evaluated and compared the sedative effect and the safety of a dexmedetomidine–remifentanil (DR) regimen with a midazolam–remifentanil (MR) combination during the endoscopic retrograde cholangio-pancreatography (ERCP) requiring conscious sedation.

Methods One-hundred and ninety-eight patients were randomized and divided into two groups. A bolus of midazolam (0.05 mg kg^{-1}) was injected intravenously for MR group, and dexmedetomidine (1 μg kg^{-1}) was pumping for 10 min for DR group. Next, an initial loading dose of 1 μg kg^{-1} and 0.05–0.2 μg kg^{-1} min^{-1} of remifentanil was administered in all patients. Hemodynamic and respiratory changes, Ramsay Sedation Scale, Visual Analogue Scale, endoscopist and patient satisfaction were assessed. Furthermore, adverse events as well as recovery time and discharge time were rated.

Results Patient satisfaction scores were significantly higher in the DR group compared with MR group. The occurrence of desaturation was statistically higher, and the operation time was longer in the MR group. Although no statistically significant values could be determined between the two groups about amnesia and need of additional drug, the DR group was found to require a significantly reduced amount of extra midazolam. Furthermore, nausea during catheterization of oropharynx was found to be more pronounced in the DR group.

Conclusions The dexmedetomidine–remifentanil protocol provided a parallel sedative efficacy and improved respiratory sparing effects. The higher patient satisfaction scores potentially offer a more reproducible ERCP quality. Adding dexmedetomidine to remifentanil can be used safely as a conscious sedation method during ERCP.

Keywords Endoscopic retrograde cholangio-pancreatography (ERCP) · Dexmedetomidine · Midazolam · Conscious sedation · Remifentanil

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Introduction

The endoscopic retrograde cholangio-pancreatography (ERCP) plays a crucial role in the diagnosis and treatment of pancreaticobiliary pathologies. It represents a minimally invasive technique providing fewer complications, generally shorter hospitalization times and lower medical costs compared to traditional surgery, particularly in sick and elderly patients suffering from hepatobiliary tract disorders. However, the overall procedure times may be as long as 60 min and the procedure is always performed in the prone or semiprone position [1]. Therefore, moderate sedation and analgesia are usually required to reduce discomfort and stress.

Nowadays, most patients are administered with some form of moderate sedation and/or analgesia, i.e., "conscious sedation" [1]. The sedation method is designed to attenuate pain, discomfort and stress in patients undergoing ERCP. Conscious sedation is widely applied in a clinical setting with changing drug combination regimens. In our Gastrointestinal Endoscopy Unit, ERCP is usually carried out involving benzodiazepines (midazolam) and opioids (remifentanil) under conscious sedation according to expert consensus approved by the Chinese Society of Digestive Endoscopy (CSDE). However, particularly worth mentioning in this context are common adverse side effects such as hypoxemia (oxygen desaturation < 85%) that may occur frequently in the combinatory administration of midazolam and remifentanil as sedatives during ERCP [1, 2]. Furthermore, the prone or semiprone position of patients during the surgical procedure may further complicate adequate ventilation. Desaturation and hypoventilation may bring about cardiac events such as myocardial ischemia and cardiac arrhythmias, complications that have been identified as the leading cause of endoscopy-related death [3].

Dexmedetomidine, a highly selective alpha-2 adrenoreceptor agonist, has been used for sedation in adults in different scenarios since it was approved by the US Food and Drug Administration in 1999 for the use in intensive care units. The drug features anxiolytic, sedative, analgesic and antiemetic properties providing advantages that differentiate it from propofol or midazolam. In particular, no respiratory depression at clinically deep levels of sedation are observed using dexmedetomidine. Furthermore, dexmedetomidine facilitates a decrease in salivary secretion, a particularly desirable effect during gastroendoscope intubation [4]. A growing pool of evidence suggests that dexmedetomidine may be successfully used in various clinical scenarios [5, 6]. Therefore, we hypothesize that the combinatory use of dexmedetomidine–remifentanil (DR) may offer a safe sedative method, contributing to the safety of patients in terms of respiratory sparing effects and further reducing the incidence of adverse effects.

The study described here was designed to compare the efficacy and safety of the DR combination with the midazolam–remifentanil (MR) combination during ERCP. The corresponding results are described in subsequent sections.

Patients and Methods

Ethics

Written consent was obtained from all patients, and the study was approved by the Hospital Ethics Committee. The trial was registered in China at the Central Trial Registry of Hospital (2014/KY/048).

Inclusion and Exclusion

All 208 patients, age ranging between 18 and 85 years, were classified to be anesthesia risk group I–III according to the American Society of Anesthesiologists (ASA). The patients were enrolled in this prospective, randomized, single-blind study. Exclusion criteria were: ASA physical classes IV and V, refusal to anticipate, comorbid uncontrolled internal problems, pregnant or breast-feeding women, history of long-term sedative or narcotic analgesic drug or alcohol abuse, baseline peripheral oxygen saturation (SaO_2) < 90%, age > 85 years and severe hypertension.

Randomization and Blinding

The randomization was using an Internet-based randomization software (http://www.randomization.com). One-hundred and ninety-eight patients, uninformed of treatment assignment, were randomly categorized to the DR group or the MR group using a computer-generated table of random numbers. Sealed envelopes were provided to all patients as they reported for the procedure. Importantly, all investigators remained blinded to the group allocation until the end of the study and the finalization of the statistical analysis.

All patients fasted overnight and received no premedication. The patients were administered with infusions of Ringer's solution at a rate of 5 ml min^{-1} via a 20-G intravenous catheter that was inserted into the left or right antecubital region during the procedure and continued in the recovery room.

The procedure was performed in the endoscopy suite by one of the two endoscopists at the institution. Each endoscopist had a plethora of experience and performed at least 500 ERCPs. The preparation, storage, and dispensing of the drugs were administered independently by a senior anesthesiologist, and the clinical data were collected by an anesthesiology resident who remained blinded to the group allocation at that time. The endoscopists and the

anesthesiology resident were uninformed of the study drugs; however, the senior anesthesiologist was informed of the actual drugs used since the drug characteristics were markedly different.

Anesthesia Procedure

The patients received 10 ml of oral dyclonine hydrochloride mucilage, dispelling the chamber passage bubble, 10 min prior to the start of the sedation in order to gain clear vision during the endoscope procedure. All patients were placed in prone position and were provided with intranasal supplemental oxygen (6 L min^{-1}). The DR group received a 1 μg kg^{-1} dexmedetomidine bolus (0.5 μg kg^{-1} for patients over 65 years) over 10 min and the MR group received 0.05 mg kg^{-1} midazolam (the dose was titrated slowly with 1 mg mL^{-1} diluted formula), followed by an infusion of remifentanil at 0.05–0.2 μg kg^{-1} min^{-1} in each divided group.

Outcomes and Data Collection

The demographic data of the patients were noted. The heart rates (HR), noninvasive systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), oxygen saturation (SpO_2) and respiration rate (RR, detected by impedance pneumography) were monitored in all patients. Desaturation was defined as $SpO_2 < 90\%$ for > 10 s. Hypotension was defined as MAP < 70 mm Hg, and bradycardia was defined as HR < 50 beats per minute.

The Ramsay Sedation Scale (RSS; 1–6) was used to evaluate the depth of sedation, and a score of 4 or higher were used as the trigger of the procedure. In case of sudden patient movement and difficulties in maneuvering the endoscope, a midazolam dose of 0.02 mg kg^{-1} was administered and the infusion velocity of remifentanil was increased at the same time to maintain adequate sedation. If the SpO_2 decreased to < 90%, the nasal oxygen supply was increased by 2 L min^{-1} until returning to normal oxygen saturation. Furthermore, the procedure was interrupted and the endoscope was withdrawn until a normal oxygen saturation was achieved. The procedure was reattempted or terminated after reassessment of the senior anesthesiologist.

The endoscopist assessed the satisfaction measurement of performing ERCP at the end of the procedure as 4 = satisfactory and 1 = frustration. Furthermore, all patients were inquired about the satisfaction using the same score ratings. The Steward Recovery Score (SRS; 0–6) was used to assess recovery and was noted every 5 min, starting from the time of endoscope removal [5–7]. The complete recovery time was also measured from the completion of the ERCP procedures to achievement of a modified RSS score of 2. Criteria for discharge from the endoscopy recovery unit to the inpatient ward were when the patient reached a modified SRS of 6. According to consensus guidelines, adverse effects such as nausea, vomiting, gagging, and shivering were noted for 3 h following the procedure [8].

Statistical Analysis

In a previously conducted study comparing midazolam–meperidine–dexmedetomidine with midazolam–meperidine saturation during ERCP, a 17% difference between groups in terms of desaturation was found [9]. In an effort to detect such a difference in desaturation incidence between the groups, we calculated that 83 patients in each group would be needed to achieve a statistical power of 90% ($\alpha = 0.05$, $\beta = 0.1$).

The data were analyzed using SPSS software version 18 (SPSS Inc, Chicago, III). Where appropriate, the study results were noted as mean ± SD or percentage. We used an independent sample *t* test and nonparametric test for continuous variables. The Chi-square test and the Fisher exact test were used for categorical variables. Probability values of less than 0.05 were considered statistically significant.

Results

In our Gastrointestinal Endoscopy Unit, over the course of 3 months, 198 enrolled patients were scheduled for ERCP. All patients were randomized into two groups, the MR group containing 89 patients and the DR group containing 109 patients. Among all patients, three patients from the MR group and one patient in the DR were excluded as a consequence of procedure termination due to the unsuccessful catheterization of duodenal papilla, duodenal perforation, and severe respiration depression. Therefore, data were collected from 86 patients in the MR group and 108 patients in the DR group (Fig. 1).

Intraoperative Parameters

Patient characteristics and the total amount of drugs used for sedation are shown in Table 1. The mean patient age was 60.6 years in the MR group and 60.5 years in the DR group. The patients in both groups were comparable in their physical characteristics as well as total amount of drugs ($P > 0.05$). The overall procedure time was much longer in patients of the MR group than patients in the DR group ($P = 0.021$). Furthermore, the additional dosage of midazolam in the MR group was found to be significantly increased ($P < 0.001$).

MAP, HR, SpO_2, and respiratory rate are provided in Table 2 as mean ± SD. Significant differences were determined between the two groups in mean values of MAP, HR,

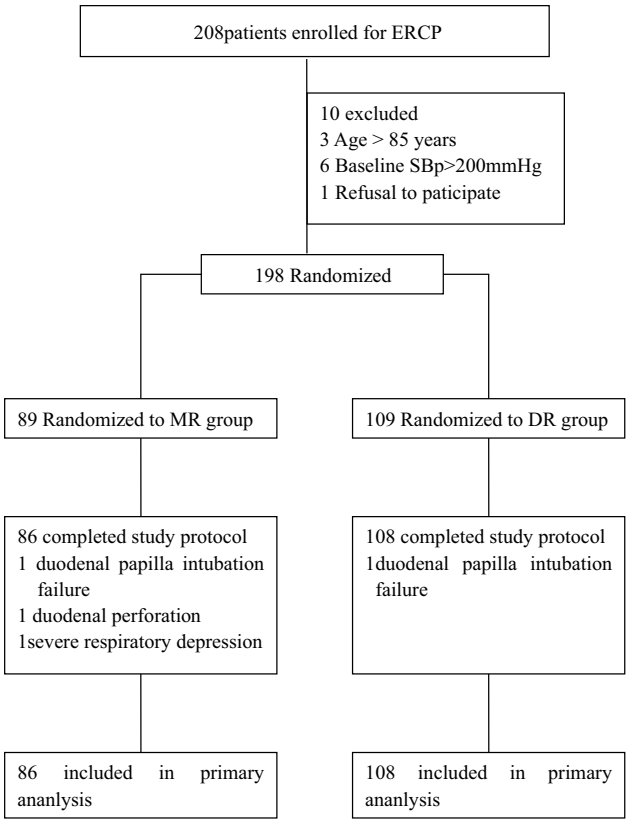

Fig. 1 Consort diagram showing disposition of all patients randomized

and respiratory rate recordings over the course of the procedure ($P < 0.05$). However, no hypotension or arrhythmia was observed in patients of both groups because all values were found to be within the normal physiological range and within 20% of the baseline values in both groups. Patients in the DR group exhibited a statistically significant lower MAP ($P < 0.05$) after infusion of loading dose and at 5, 10, 15 and 20 min until 70 min during ERCP (cf. Fig. 2), together with a lower HR during the procedure (cf. Fig. 3).

Outcome Variables

All sedation-related adverse events are shown in Table 3. Remarkable differences between the two groups in both pain and body movements were found. In particular, we observed a dramatically higher incidence of desaturation (19, 22%) in the MR group compared to the DR group (none) with $P < 0.05$. All 19 patients were asked to breathe deeply and the infusion rate of remifentanil was reduced without endoscope removal or additional mechanical ventilation. No episodes of respiratory depression were found to occur in the postoperative period. However, nausea and vomiting occurred in a small number of patients, significantly higher in the DR group. Satisfactory scores were rated from 0 (worst) to 4 (best). Although patient movement or slight tightness (resistance at the oral cavity) was described by the endoscopists, satisfaction numbers of patients and endoscopists were compared between the two groups; however, patient satisfaction scores were significantly higher in the DR group and no statistical differences were found in terms of the endoscopist's satisfaction between the two groups.

Table 4 shows the additional drug uses, time of activity, recovery times, and discharge times. A faster onset of sedation (RSS 3–4) in the MR group compared to the DR group could be observed. During the procedure, additional drugs such as midazolam, propofol, and remifentanil were administered if the endoscopists rated difficult cases due to patient movement of tightness. A small number of patients were applied with additional drugs to facilitate the operation, which was found to be no different in both groups. No statistically different recovery times and discharge times could be determined between the two groups, although the half-time of dexmedetomidine is longer than the half-life of midazolam.

Table 5 shows the sedative and analgesic effect after the procedure. No differences were observed between the two groups in VAS and Steward Recovery Score (SRS). However, the RSS in the DR group was found to be higher than that in the MR group ($P < 0.05$). Twenty-eight patients expressed amnesia in the MR group and 40 patients expressed amnesia during the procedure in the DR group, with no statistical difference.

Discussion

Generally, a favorable analgesic effect ensures a successful and safe ERCP process. Traditional sedation is carried out by administration of propofol or benzodiazepine, and common adverse effects are low arterial pressure and respiratory inhibition [10]. Interestingly, elderly patients are more responsive to sedative hypnotics for conscious endoscopic sedation. These patients usually feature a higher overall body fat content than younger patients which may delay the metabolism of lipid-soluble propofol, opioid, and benzodiazepine. Therefore, the occurrence of side effects is often increased. Dexmedetomidine, a highly selective α_2-adrenoceptor agonist, has been shown to improve the sedation of patients while maintaining consciousness and preserving sufficient oxygenation and circulation [11]. Endoscopic sedation based on balanced administration of dexmedetomidine and remifentanil during therapeutic ERCP has been shown to exhibit an improved sedation efficacy in terms of patient satisfaction, with decreased recovery time compared to midazolam–remifentanil sedation.

Table 1 Patient characteristics and procedure details

	Group MR ($N=86$)	Group DR ($N=108$)	P value
Age, (years)	60.6 ± 13.1	60.5 ± 14.5	0.563
18–64 year	48	61	
> 64 year	38	47	0.521
Sex: male/female	47/39	55/53	0.665
Body mass index, mean ± SD, (kg m^{-2})	23.4 ± 3.2	23.2 ± 3.4	0.609
ASA status (I, II, III),	2/63/21	3/69/36	0.377
Type of surgery, (*n*) (%)			
ERCP + SI + ENBD (48)	28% (24)	22% (24)	0.925
ERCP + SE/STE (11)	7% (6)	5% (5)	0.587
ERCP/+ ENBD (28)	19% (16)	11% (12)	0.739
ERCP + SE + SI+ENBD(8)	6% (5)	3% (3)	0.363
ERCP + SE + ENBD (99)	40% (35)	59% (64)[a]	0.003
Procedure time, (min)	41.5 ± 19.6	35.5 ± 16.2[a]	0.021
Procedure time of type of surgery, (min)			
ERCP + SI + ENBD	45.5 ± 17.9	45 ± 18.8	0.5
ERCP + SE/STE	29.2 ± 7.9	35.4 ± 22.8	0.587
ERCP/+ ENBD	35.3 ± 16.9	33.2 ± 16.3	0.739
ERCP + SE + SI +ENBD	33.4 ± 13.3	48 ± 29.7	0.363
ERCP + SE + ENBD	44.8 ± 22.5	31.8 ± 12.4[a]	0.003
Total drugs used, remifentanil, (ug)	299.4 ± 128.5	267.6 ± 122.8	0.081
Midazolam, (mg)	1.37 ± 0.3	0.06 ± 0.3[a]	<0.001

Data expressed as mean ± SD, *n*, or % (*n*)

ERCP Endoscopic retrograde cholangio-pancreatography; *ENBD* Endoscopic nasobiliary drainage; *SI* stent implantation; *SE* stone extraction; *STE* stent extraction

[a] $P < 0.05$

Table 2 Hemodynamic and respiratory parameters

	Group MR ($N=86$)	Group DR ($N=108$)	P value
MAP, (mmHg)			
BV	102 ± 16	104 ± 18	0.075
Be V	96 ± 19	104 ± 17[a]	0.003
EV	99 ± 13	91 ± 10[a]	0.001
HR, (bpm)			
BV	83 ± 15	87 ± 19	0.107
Be V	101 ± 18	84 ± 18	0.887
EV	98 ± 14	84 ± 14[a]	0.008
SpO_2, (%)			
BV	98 ± 2	98 ± 2	0.602
Be V	97 ± 3	98 ± 3[a]	0.005
EV	98 ± 2	98 ± 3[a]	0.033
RR, (bpm)			
BV	16 ± 1	16 ± 1	0.163
Be V	16 ± 8	16 ± 8	0.158
EV	17 ± 2	16 ± 1[a]	0.001

Data expressed as mean ± SD

BV Baseline values; *Be V* beginning values of operation; *EV* ending values of operation

[a] $P < 0.05$

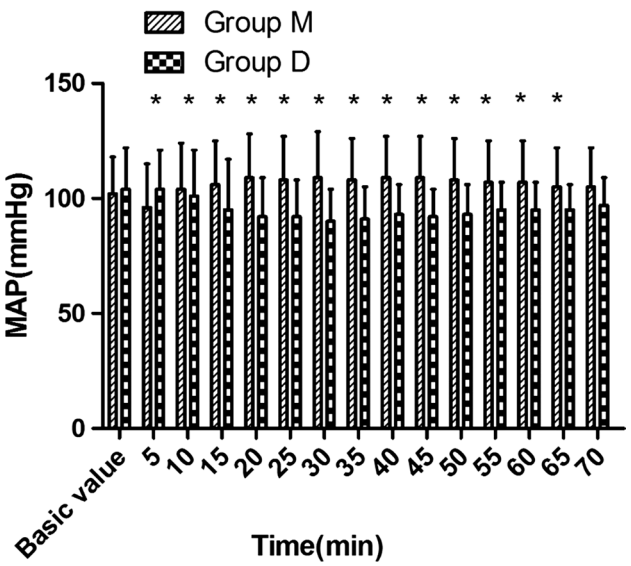

Fig. 2 Mean artery pressure (MAP) at different time intervals between two groups. Data are expressed as mean ± SD. *$P < 0.05$. *M* Midazolam–remifentanil; *D* dexmedetomidine–remifentanil

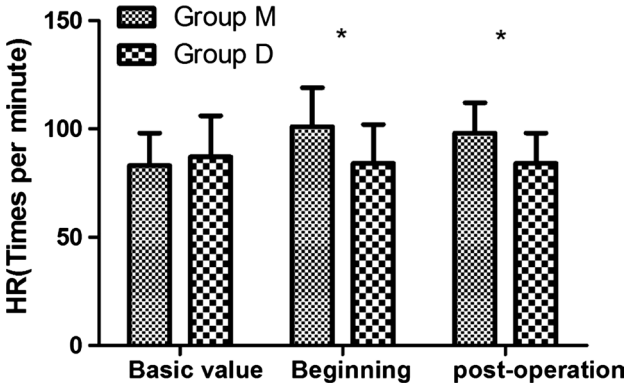

Fig. 3 Heart rate (HR) at different time point during the procedure between two groups. Data are expressed as mean ± SD. *$P < 0.05$. *M* Midazolam–remifentanil; *D* dexmedetomidine–remifentanil

Table 5 Amnesia during the procedure, VAS, RSS and Steward Recovery Score after the procedure

	Group MR ($N = 86$)	Group DR ($N = 108$)	*P* value
VAS	0.3 ± 1.1	0.1 ± 0.4	0.134
RSS	1.5 ± 1.3	1.8 ± 1.3	0.110
Steward	5.2 ± 1.00	4.9 ± 1.1	0.171
Amnesia during operation, *n* (%)	28 (32.6)	40 (37.0)[a]	0.001

Data expressed as mean ± SD or *n* (%)

VAS Visual Analogue Scale; *RSS* Ramsay Scale; *SRS* Steward Recovery Score

[a]$P < 0.05$

In this study, our data showed that the dexmedetomidine- and remifentanil-based sedation was safer and more effective than the midazolam- and remifentanil-based sedation, especially in the case of respiratory depression and without additional unfavorable effects.

To provide patient comfort and in order to facilitate the surgical manipulation, the conscious sedation represents a recommended strategy during ERCP procedure [1, 8]. However, it is necessary to ensure that protective reflexes are not suppressed and spontaneous respiration is reserved during conscious sedation [10]. Midazolam represents a modern drug that is frequently used in procedural sedation due to its rapid activity onset, short duration of action and protective effects on cardiovascular stability. The latter features were further verified by the shorter onset time in the MR group compared to that in the DR group. However, the process time was much longer in the MR group. While the type of surgery exhibited no effect on the overall clinical outcomes, we also found a tendency toward decreased SpO_2 (less than 90%) in patients after midazolam administration. This finding may be due to the additional release of midazolam during sudden patient movement where the compound may have accumulated in fatty issue [11]. However, the frequency of added midazolam exhibited no significant differences between the two groups.

Several recent controlled randomized trials [6, 12] have evaluated the efficacy of dexmedetomidine in comparison with midazolam for gastrointestinal endoscopy. The results showed that dexmedetomidine is usually used as an

Table 3 Sedation-related adverse events, satisfaction of patients and operator

	Group MR ($N = 86$)	Group DR ($N = 108$)	*P* value
Painful during procedure, no. (%)	6 (6.9)	2 (1.9)[a]	0.001
Body movement, no. (%)	5 (5.8)	2 (1.8)[a]	0.001
No. of patients with $SpO_2 < 90\%$, (%)	19 (22)	None[a]	0.001
Nausea and vomiting, no. (%)	2 (2.3)	7 (6.5)[a]	0.001
Satisfaction of patients, mean ± SD	3.6 ± 0.7	3.9 ± 0.3[a]	0.001
Satisfaction of operator, mean ± SD	3.9 ± 0.4	3.9 ± 0.4	0.403

Data expressed as mean ± SD or no. (%)

[a]$P < 0.05$

Table 4 Additional drug uses, time of activity, recovery time and discharge time

	Group MR ($N = 86$)	Group DR ($N = 108$)	*P* value
Additional drug uses, *n* (%)	5 (5.8)	6 (5.6)[a]	0.001
Onset time of sedation, (min)	4.8 ± 2.1	6.6 ± 1.3[a]	0.001
Recover time, (min)	0.9 ± 2.8	1.5 ± 3.6	0.247
Discharge time, (min)	11.4 ± 11.7	10.5 ± 3.3	0.498

Data expressed as mean ± SD or *n* (%)

[a]$P < 0.05$

alternative to midazolam for the sedation of nonintubated patients during surgery and other procedures owing to its anxiolysis and cooperative sedation without respiratory depression. These results are consistent with our study.

Besides discomfort, pain from the intervention of sphincterotomy as well as biliary dilation must be attenuated. Remifentanil, characterized by its rapid onset and offset, represents a unique opioid class drug, and was therefore used throughout our study. Infusion of remifentanil quickly resulted in the desired target plasma levels and the activity was found to dissipate within 3–10 min after administration and regardless of the duration of infusion [13–15].

The DR combination has been tried for endoscopic submucosal dissection [16]; however, little evidence has been found to support its application for ERCP. Fortunately, in this study and compared with traditional MR regimen, no cases exhibited a desaturation episode in the DR group. However, hypoxia occurrence of up to 19% was found in the MR group, a finding that further supports a reasonable upper limit for safe dosage of DR in the conscious sedation during therapeutic ERCP procedures. This latter result is also in accordance with the results described in a previously conducted study by Lee et al. [9].

In the DR group, the induction dose was administered by infusion within 10 min, followed by maintenance. However, in the MR group, the drug was administered as a bolus. This explains the faster onset of sedation (RSS 3–4) in the MR group compared to the DR group (meantime: 4.8 vs. 6.6 min; $P < 0.05$) (cf. Table 4). Noteworthy, in the DR group the procedure time was also significantly shorter compared to the procedure time in the MR group due to the fact that patients experienced an increased coordination degree during ERCP (Table 4).

Our study exhibited significant differences in MAP, HR, and RR between the two groups, and the results are in accordance with results from a previous study conducted by Kilic et al. [17] and Alhashemi [18]. Furthermore, statistically significantly lower HRs in the dexmedetomidine group were found compared with the midazolam group.

Hypotension and bradycardia are recognized as two major adverse side effects associated with α_2-agonist agents. It has been suggested in the past that these effects are mediated by activation of α_2-adrenoceptors, imidazoline preferring receptors or both in the ventrolateral medulla and especially in the solitarius nucleus tract [19, 20]. In the present study, we observed a decrease in HR and comparatively stable BP values in the DR group. In the MR group, HR and BP values were found to be higher during the ERCP procedure compared with both baseline values and the DR group. This finding suggests that dexmedetomidine exhibits clinical advantages over midazolam with regard to controlling the hemodynamic variability.

Despite the promising results described above, our study exhibits several limitations: (1) the study was conducted in a single center and not blind to the investigators. Therefore, there is always an inherent risk of bias toward the intervention group; (2) the bispectral index and Narcotrend monitor were used in some studies to titrate the depth of sedation for ERCP [21, 22]. Jang et al. [23] have shown that a lower dose of propofol is required in the presence of bispectral index monitoring. The corresponding results are therefore limited without using this monitoring method during the procedure; (3) a combination of the compounds midazolam–remifentanil is frequently used in clinical applications and these agents are often identified as the medication most commonly used for sedation during ERCP [24, 25]. Furthermore, the combination has been shown to be appropriate to facilitate maintaining the blinded nature of the study. As a consequence, common alternatives such as ketamine were not tested. Given the growing interest in the use of ketamine sedation and favorable previous results in patients undergoing ERCP, [26, 27] further well-designed studies are warranted to compare the DR regimen with a ketamine or ketamine-based regimen.

In conclusion, DR provided high efficacy and a superior oxygenation profile during ERCP compared to a midazolam–remifentanil combination. Therefore, a dexmedetomidine substitute may be advantageous for oxygenation during sedation in therapeutic ERCP and may also be used as a valuable alternative to midazolam.

Author's contribution ZL wrote the manuscript; WL was responsible for statistical analysis; YQ and HC contributed to critical revision of the manuscript.

Compliance with ethical standards

Conflict of interest The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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