Dexmedetomidine versus midazolam for sedation during endoscopy: A meta-analysis

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Abstract. Patients undergoing endoscopy frequently require sedation, which commonly includes the administration of midazolam or dexmedetomidine. Previous meta-analyses have mainly focused on comparing the effects of these two drugs in intensive care unit patients. In the present study, randomized controlled trials (RCTs) that compared the sedative and clinical effectiveness of these two drugs in patients undergoing endoscopy were searched in a number of databases. The meta-analysis showed that dexmedetomidine demonstrated a significantly lower rate of respiratory depression and adverse events compared with those presented upon midazolam administration. A significant difference was also observed in the sedation potency of the sedatives. The current controlled data suggest that dexmedetomidine may be an alternative to midazolam in the sedation for endoscopy. However, more high-quality and well-designed studies are required to further evaluate this conclusion.

Introduction

Endoscopic procedures are of great importance for the diagnosis and treatment of various diseases, including upper gastrointestinal bleeding, esophageal dilatation and foreign body removal. However, anxiety, pain, fear and gastrointestinal reactions may cause patients to be less cooperative during endoscopy, and may even induce harmful cardiovascular adverse events (1); therefore, the role of sedation in endoscopy is significant. Higher doses of sedative drugs have been found to result in improved patient cooperation during the procedure and satisfaction (2,3). Although various sedative agents are commonly used, the 'ideal' agent for endoscopy sedation remains to be established.

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Midazolam, the most common agent used for sedation, is a benzodiazepine with rapid onset of action and short duration of sedative effect (4). It produces central nervous system depression effects through the stimulation of γ-amino butyric acid receptors (5). To date, midazolam remains the predominant intensive care unit (ICU) sedative agent (6). However, it has certain undesirable side effects, such as delayed recovery of memory, long-term behavioral changes such as long-term cognitive dysfunction and respiratory depression.

Dexmedetomidine is a new-type, highly selective α_2-adrenoceptor agonist, which has sedative, amnestic, sympatholytic and analgesic effects (7). It was first approved for use in ICU in 1999, and its use has been rapidly extended to various other clinical situations (8). A previous study has reported that dexmedetomidine may be a possible alternative to midazolam in sedation (9). As the use of dexmedetomidine has increased, associated adverse effects, such as hypotension and bradycardia, have been reported (10). Dexmedetomidine is increasingly used in the sedation of patients in different clinical situations.

Therefore, a meta-analysis was performed in the present study in order to compare the effects of the two drugs, midazolam and dexmedetomidine, in sedation during endoscopy by analyzing the most recently-published controlled trials.

Materials and methods

Result reliability. To ensure the reliability of the present meta-analysis, the results were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (11).

Literature search strategy. The following digital databases were searched for the identification of studies: PubMed (www.ncbi.nlm.nih.gov/pubmed), Cochrane Library (www.cochranelibrary.com/), Ovid (ovidsp.ovid.com/autologin.cgi) and ClinicalTrails (https://clinicaltrials.gov/) databases. In addition, Chinese databases were searched, including CQVIP (http://en.cqvip.com/), WanFang Data (www.wanfangdata.com/) and Chinese Biomedical Literature databases (www.sinomed.ac.cn). All the databases were searched up to November 2014, with no language restriction. The literature search was performed using the relevant keywords of 'dexmedetomidine', 'midazolam',

Table I. Patient characteristics in studies comparing the use of dexmedetomidine with midazolam for sedation during endoscopy.

Authors	Year	Patients, n	Age, years	Male, n	Female, n	Refs.
Wei *et al*	2014	30/30	35.3/36.6	16/17	14/13	(17)
Sethi *et al*	2014	30/30	42/44	13/14	17/16	(18)
Demiraran *et al*	2007	25/25	42.2/43.3	13/9	12/16	(19)
Dere *et al*	2010	30/30	57.9/60.1	22/21	8/9	(20)
Zhang *et al*	2013	30/30	≥65	NR	NR	(21)
Li *et al*	2014	30/30	55.1	38	22	(22)
Arpaci and Bozkirli	2013	20/20	50.4/47.1	6/7	14/13	(23)
Karaaslan *et al*	2007	35/35	32.5/34.4	23/21	12/14	(24)
Liao *et al*	2012	99/98	58.5/60.1	61/62	38/36	(25)

NR, not reported.

Table II. Main results of the meta-analysis.

	Patients included			
Results	Dexmedtomidine	Midazolam	Standard deviation Mean Difference	P-value
SpO_2	224	223	1.25 [-0.31,0.61]	0.12
MAP	175	175	-0.08 [-0.29,0.1]	0.49
RSS	95	95	0.64 [0.35,0.93]	<0.0001
Adverse events				
Hypertension	4	12	-	
Hypotension	11	8	-	
Tachycardia	13	12	-	
Hypoxia	1	11	-	
Nausea	10	2	-	
Other	31	69	-	
Total	70	112	0.40 [0.26,0.61]	<0.0001

MAP, mean arterial pressure; RSS,. Ramsay sedation scale.

'Dormicum', 'endoscopy'. For the Chinese databases, free-text terms were used, including 'mi da zuo lun' or 'mi zuo an ding' (which is the translation of 'midazolam' in Chinese), as well as 'nei jing', 'chang jing' and 'wei jing' (which refer to different types of endoscopy in Chinese). The search strategy was independently performed by two investigators. Any disagreements were resolved by consensus and discussion.

Study selection. The inclusion criteria for the trials included in the present meta-analysis were as follows: i) Randomized controlled trials (RCTs); ii) the study focused on the sedation effects of dexmedetomidine and midazolam; and iii) the study involved patients with an American Society of Anesthesiologists (ASA) (12) grade I to III, and who presented for outpatient endoscopy procedures under conscious sedation. Exclusion criteria were as follows: i) Case reports, letters, reviews, editorial articles, meta-analyses and retrospective studies; ii) duplicates of previous published articles; and iii) studies which included children.

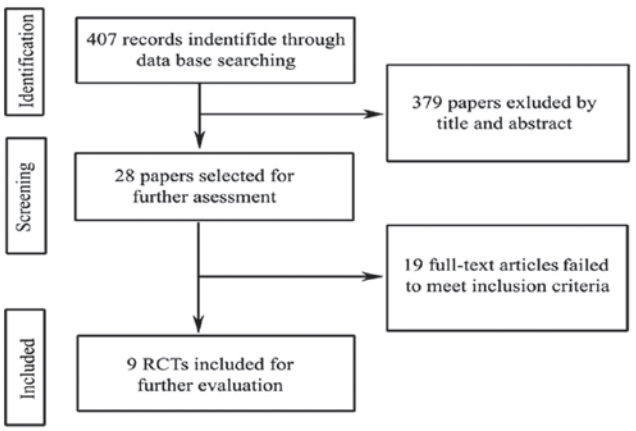

Figure 1. Study selection flow chart. RCT, randomized controlled trial.

Data extraction. The following variables were recorded for each of the studies: First author, journal, publication date,

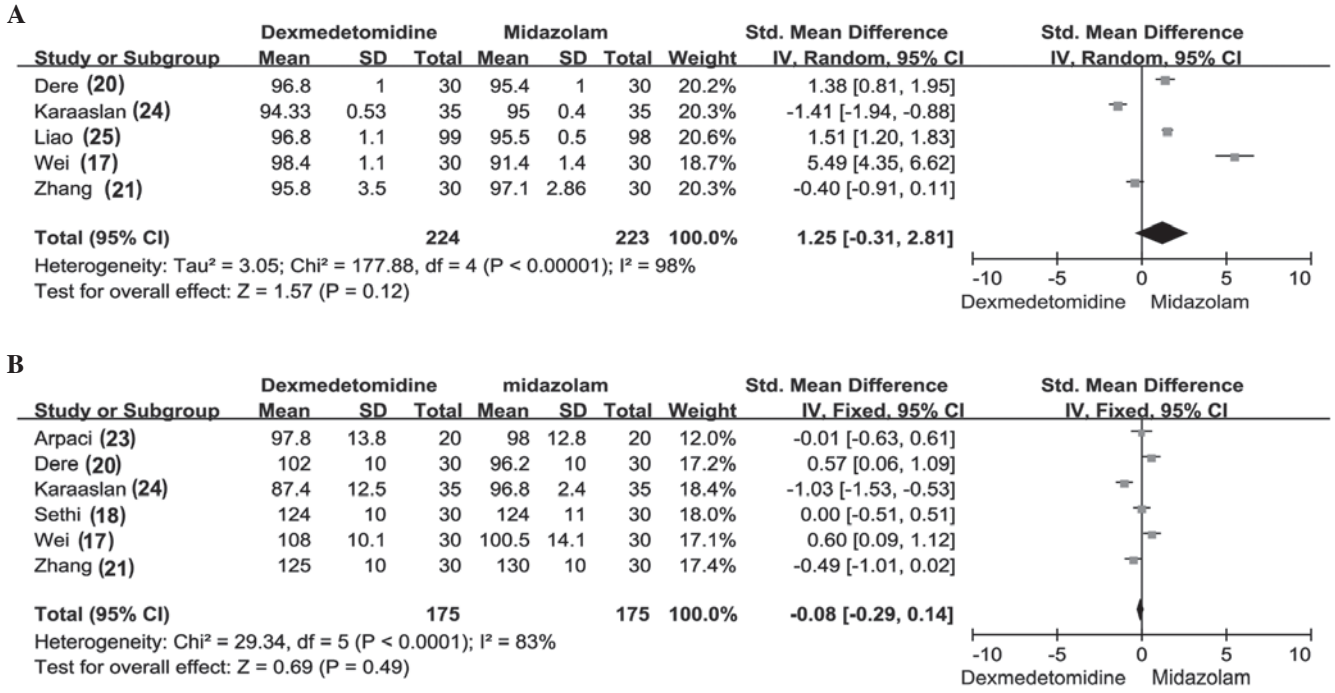

Figure 2. Forest plots of the dexmedetomidine sedation compared with midazolam in terms of (A) peripheral oxygen saturation, and (B) mean arterial pressure. SD, standard deviation; Std, standard; CI, confidence interval.

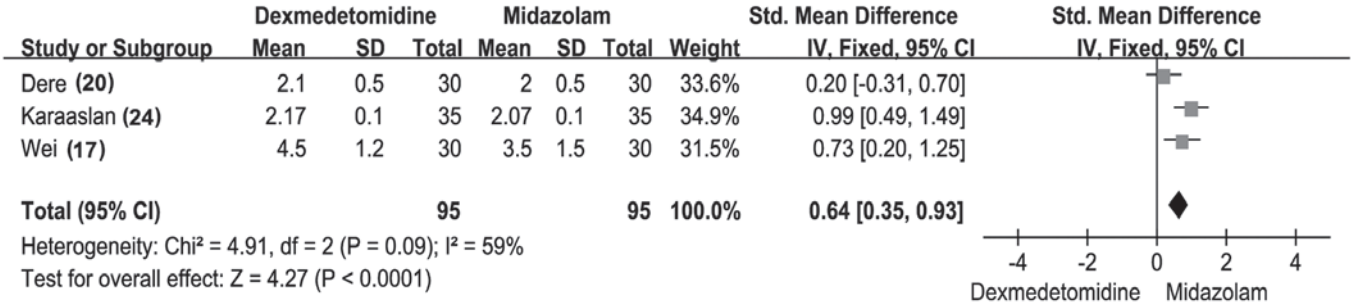

Figure 3. Forest plot comparing dexmedetomidine with midazolam in endoscopy based on the recorded Ramsay sedation scale scores of patients. SD, standard deviation; Std, standard; 95% CI, 95% confidence interval.

country, baseline difference, method of randomization, degree of blinding, dropouts and withdrawals. By baseline difference we mean the basic health condition of the patients. The degree of blinding means the degree of blinding method, i.e. double or single-blinding used. Finally the withdrawals indicate the patients who did not finish the study. The primary outcome of interest were changes in vital signs, including the continuous peripheral oxygen saturation (SpO_2), heart rate, respiration rate, mean arterial pressure (MAP) of the patients, Ramsay sedation scale (RSS) (13) and Alertness/Sedation scale (OOA/S) (14). Secondary outcomes included numeric rating scale pain scores, post-procedure satisfaction questionnaire and adverse events.

Statistical analysis. All statistical analyses were performed using Review Manager version 5.2 statistical software (Cochrane Collaboration, Copenhagen, Denmark). Dichotomous data are expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Continuous variables are presented as the standard mean difference (SMD). The statistical significance of the pooled value was evaluated using the Z test, while heterogeneity was analyzed via the I^2 test. Where the heterogeneity test showed no heterogeneity, the data were processed via a fixed effects model; otherwise, a random effects model was conducted for the analysis. Begg's funnel plots were used to detect publication biases. $P<0.05$ was considered to indicate a statistically significant difference in all the analyses. To ensure the accuracy of the outcomes, two researchers assessed the data independently and obtained the same results.

Assessment of study quality. The included studies were reviewed and assessed for methodological quality using the Jadad composite scale (15). High-quality trials scored >3 out of a maximum score of 5 (16).

Results

Study characteristics. The process of study selection is shown in Fig. 1. According to the inclusion criteria, 9 studies

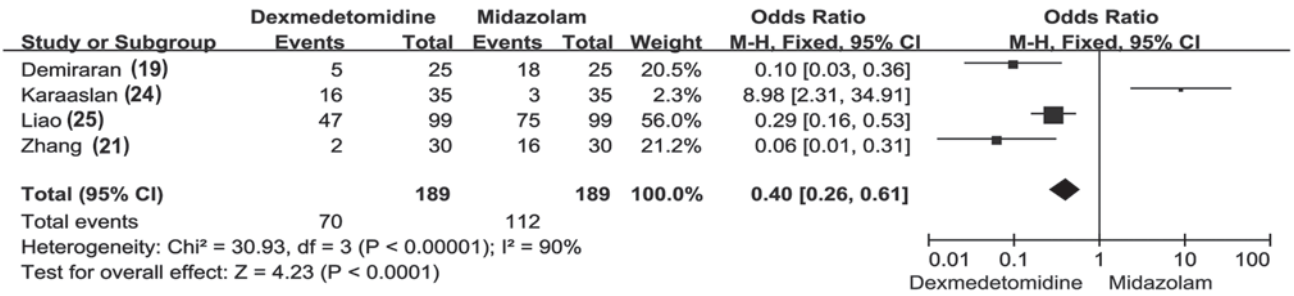

Figure 4. Forest plot comparing dexmedetomidine with midazolam in endoscopy based on the number of adverse events reported. CI, confidence interval.

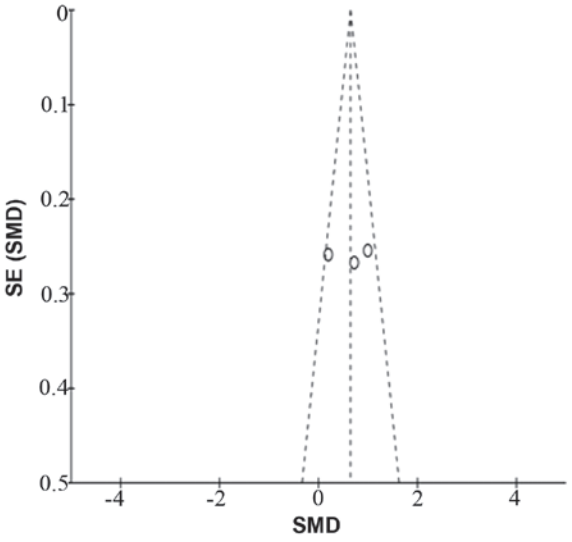

Figure 5. Funnel plot of the Ramsay sedation scale of dexmedetomidine and midazolam. SE, standard error; SMD, standard mean difference.

were included in the present meta-analysis. The included studies were published as full text between January 2007 and December 2014. Of the 657 patients included in the 9 eligible RCTs (17-25), 329 patients were allocated to the dexmedetomidine group, while 328 patients comprised the midazolam group. The sedation effects in the two groups were evaluated. Patient characteristics, including age and gender, are shown in Table I.

Quality of the included studies. The mean Jadad score of the included studies was 3 out of a maximum possible score of 5. This indicated that the majority of the included RCTs were of moderate quality, although 2 Chinese trials (21,22) were of low quality (Jadad score of <3), which was a result of relatively poor study design.

Trial outcomes.

SpO_2. Statistical analysis performed in 5 of the eligible studies (17,20,21,24,25) revealed that the SpO_2 showed no statistically significant difference between the dexmedetomidine and midazolam groups (Fig. 2A). These 5 studies were used for the analysis because of their similar study index which made them comparable for a meta-analysis. In addition, there was no evidence of significant heterogeneity (SMD, 1.25; 95% CI, -0.31 to 2.81; P=0.12; Fig. 2A).

MAP. In total, 6 studies reported the MAP of patients following administration of the two agents (17,18,20,21,23,24). The results demonstrated that there was no significant difference in the MAPs between the dexmedetomidine and midazolam groups [SMD, -0.08; 95% CI, -0.29 to 0.14]. In addition, no significant heterogeneity was detected (Fig. 2B).

RSS. In total, 3 of the 9 included studies reported the RSS of patients (17,20,24). The results revealed that the RSS scores of patients administered dexmedetomidine were significantly higher compared with those in the midazolam group patients (SMD, 0.64; 95% CI, 0.35-0.93; P<0.0001). However, no significant heterogeneity was detected in the results (Fig. 3). With regard to normal adults, 0.05-0.075 mg/kg midazolam intravenous injection produces the effect of sedation. A higher dose of 0.1-0.15 mg/kg is commonly used for anaesthesia induction. For dexmedetomidine, a continuous intravenous infusion of 0.2-0.7 μg/kg/h can achieve a good sedation outcome. General anaesthesia stages may be induced above such a drug dose.

Adverse events. Out of the 9 eligible studies, 4 trials (involving 189 patients) compared the adverse events reported in patients administered with dexmedetomidine and midazolam (19,21,24,25). The main adverse events that were reported were respiratory depression, nausea and vomiting, dysphoria, reflux, dizziness, abdominal distention and pain.

The pooled results displayed a statistically significant difference between the subgroups (Fig. 4). In the dexmedetomidine group, a significantly lower number of adverse events were reported, compared with the midazolam group (OR, 0.40; 95% CI, 0.26-0.61; P<0.0001; Fig. 4). The adverse events and main trail results were shown in Table II.

Testing for publication bias. A funnel plot of the outcome of the RSS score following sedation with dexmedetomidine and midazolam in the included studies demonstrated there was no significant publication bias (Fig. 5). However, the number of trials included was <10, thus this conclusion may not be entirely accurate.

Discussion

Endoscopy is an essential procedure for clinical diagnosis and treatment of various diseases such as gastrointestinal neuroendocrine tumours (26-29), gastroesophageal reflux , lung cancer and cervical cancer. Different endosocopes may be used to diagnose different diseases. For example, cystoscopy is used to diagnose diseases in the urinary system. Although conscious

sedation is the most widely used method to relieve sickness and pain during endoscopy, the sedation agents used greatly vary among different regions (30). Midazolam has long been regarded as the golden standard for sedation. However, dexmedetomidine has been increasingly studied in recent years.

To the best of our knowledge, Adams *et al* (31) performed the first meta-analysis concerning the effects of dexmedetomidine and midazolam in adult ICU patients. In addition, Sun *et al* (32) performed a systemic review regarding premedication in children using the two drugs. The present meta-analysis evaluated the sedation effects of dexmedetomidine and midazolam during endoscopy.

The results of the current meta-analysis suggested that dexmedetomidine sedation may achieve a more stable respiratory system. Patients sedated with dexmedetomidine had statistically lower hypoxia rates in the present study. Furthermore, patients administered dexmedetomidine have been previously shown to be easily awaken during endoscopy and experience less respiratory depression compared with those sedated with midazolam (33,34). Therefore, dexmedetomidine may be advantageous compared with midazolam for the sedation of patients with previous history of respiratory diseases.

As reported previously (35), the most significant complications associated with dexmedetomidine are hypotension and bradycardia. However, the results of the present meta-analysis challenge these conclusions, since no significant differences were observed in the arterial pressure or heart rate of the 175 patients investigated. This is in agreement with the results of Yu *et al* (36) reporting that the SBP values did not present any differences after slow infusion of the drug over a 10 min time-frame. Instead, appropriate dose and transfusion velocity of dexmedetomidine may achieve favorable cardiovascular stability (37,38). However, dexmedetomidine should be used with caution in patients diagnosed with severe sinus bradycardia or heart block (39).

Potent sedation effects may be the main advantage of dexmedetomidine for endoscopy. The present study results revealed that the RSS was significantly higher in the dexmedetomidine group, while the OOA/S of patients in the dexmedetomidine was also higher compared with that in the midazolam group. Even a maintenance dose of 0.5 μgkg/h dexmedetomidine was able to provide better sedation compared with 0.05 $mgkg^{-1}$ midazolam. This indicated a superior sedation effect of dexmedetomidine compared with midazolam (40-42). However, despite its outstanding sedation potency, it is also able to maintain awarenesss at the sedative dose (43,44), which may enable the patient to change positions according to orders and make the endoscopy a more smooth procedure (45).

There was also a significant difference between the dexmedetomidine and midazolam groups in terms of the number of adverse events reported. Major complications, including hypertension, requirement for mandible support and intubation, were mainly observed in the midazolam group (46,47). Therefore, dexmedetomidine may be advantageous with regard to the prognosis and outcome of endoscopy patients.

Several limitations exist in the present meta-analysis. First, two of the included trials were published in Chinese (21,22), and these studies were of relatively poor quality due to unclear concealment of research details. In addition, it was difficult to draw a definitive conclusion regarding whether dexmedetomidine was a better sedative compared with midazolam since no uniform criteria exist to assess the effects of sedatives. Furthermore, a greater number of well-designed trials are required to confirm the aforementioned results.

In conclusion, the present meta-analysis included 9 RCTs reporting sedation during endoscopic procedures, and the results indicated that the sedation effects of dexmedetomidine and midazolam were comparable in patients undergoing endoscopy. Therefore, the present study recommends that both of the medications should be considered for patient sedation during endoscopy.

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