



A Comparison of the Sedative Effect of Dexmedetomidine and Midazolam on Patients Undergoing Gastrointestinal Endoscopy Outside the Operating Room

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Abstract

Background: Patients may experience anxiety, discomfort, and pain during endoscopy, which cannot be tolerated without sedative drugs.

Objectives: This study aimed to compare the sedative effects of dexmedetomidine and midazolam on patients undergoing endoscopy outside the operating room.

Methods: This randomized, double-blind clinical trial was conducted on 126 patients aged 18 - 65 years old with American Society of Anesthesiologists (ASA) physical status I - II undergoing elective endoscopy. Patients were randomly divided into 2 groups. The dexmedetomidine group received dexmedetomidine (1 μ g/kg) for 25 minutes with propofol (0.5 mg/kg) and fentanyl (1 μ g/kg) at the start of the procedure. The midazolam group received midazolam (0.03 mg/kg) with propofol (0.5 mg/kg) and fentanyl (1 μ g/kg). Heart rate, mean arterial pressure (MAP), and oxygen saturation (SpO₂) were recorded before and 5, 10, and 15 minutes after starting the procedure. The Ramsay Sedation Scale (RSS) and the need for an additional dose of propofol were recorded during the procedure. The Numeric Pain Rating scale (Ambesh score) scores were recorded at the beginning, immediately after, and 1 hour after the procedure. Nausea and vomiting were assessed using the Visual Analogue Scale in cooperation with the patient.

Results: The dexmedetomidine group had significantly higher SpO₂ and RSS scores during sedation than the midazolam group (P = 0.02). Overall, specialist satisfaction was higher in the dexmedetomidine group than in the midazolam group. There was no clinically significant difference in pain score and nausea and vomiting frequencies between the 2 groups.

Conclusions: Dexmedetomidine is more effective than midazolam for sedation during gastrointestinal endoscopy.

Keywords: Dexmedetomidine, Midazolam, Sedation, Gastrointestinal, Endoscopy

1. Background

The number of therapeutic and diagnostic interventions done outside the operating room has increased in recent years. Issues such as sedation and inertia are especially needed to succeed in these procedures (1). Sedation has always been a critical part of endoscopy. The goal of sedation in endoscopy is to increase patient comfort, improve the procedure, and increase patient satisfaction (2). Many drugs are used alone or in combination to induce sedation during

endoscopic procedures or outpatient interventions, including benzodiazepines with or without opiate and alpha-2 adrenoceptor agonists (such as dexmedetomidine, propofol, and ketamine) (3, 4). Midazolam is a hydrochloric acid benzodiazepine with a central nervous system (CNS) suppressant effect, whose effect is CNS dose-dependent (5). Midazolam is frequently used for sedation. This drug has an immediate effect on onset and recovery (6). Using high doses causes sedation and severe sleepiness (7). Dexmedetomidine is a selective agonist

for alpha-2 adrenoceptors with sedation, anti-anxiety, and analgesic effects (8-10). Therefore, this drug has the least effect on patient's respiration; it has been used as a sedative drug in intensive care units (ICUs) (11-13). The sedation, anti-anxiety, and anti-hypertensive effects of dexmedetomidine are induced by central stimulation of alpha-2 adrenoceptors and type I imidazoline receptors (5, 14). The analgesic effects of dexmedetomidine have been reportedly attributed to the activation of alpha-2B adrenoceptors in the posterior horn of the spinal cord and an inhibitory effect on the release of the P compound (5, 17). In adults, the administration of dexmedetomidine begins with an initial increase in blood pressure and reflex bradycardia and continues with a lower blood pressure and heart rate lower than the initial state (18, 19).

2. Objectives

The present study aimed to compare the sedation, analgesic, and hemodynamic effects of dexmedetomidine and midazolam, as well as the occurrence of nausea and vomiting, between patients undergoing gastrointestinal endoscopy outside the operating room. The main objective was to reach a new combination of these drugs to induce a greater level of relaxation in those patients outside the operating room.

3. Methods

After obtaining approval from the Ethics Committee of Jundishapur University of Medical Sciences, Ahvaz (code: [IR.AJUMS.REC.1398.002](#)), 126 patients (age range, 18 - 65 years old) admitted to the Endoscopy Ward of Imam Khomeini Hospital, Ahvaz, Iran, from April 2015 to March 2016 as candidates of gastrointestinal endoscopy process were selected according to the classification of American Society of Anesthesiologists (ASA) physical status I - II as the inclusion criteria. This study was also registered on the Iranian Registry of Clinical Trials website (code: [IRCT20190417043295N1](#)). In this randomized, double-blind clinical trial, a total of 126 patients were randomly divided into 2 groups (n = 63 in each group) using odd and even numbers according to the number of the medical record.

At the beginning of the patients' admission, written informed consent was obtained prior to their participation in the study, and data were collected from patients' medical records. The exclusion criteria were patients with drug allergy, age less than 18 or over 65 years old, renal or hepatic failure, chronic pain syndromes, unwillingness to participate in the study, cardiovascular diseases, respiratory, metabolic, and neurological

disorders, difficulties in the airway, ASA physical status III or IV, and contraindication of dexmedetomidine, midazolam, propofol, or fentanyl. After connecting the monitoring facilities to the patients in both groups, vital signs, including systolic and diastolic blood pressure, heart rate, and oxygen saturation (SpO₂), were measured and recorded in the form of information. Then, systolic and diastolic blood pressure, heart rate, apnea, and arterial oxygen saturation (SaO₂) were measured from this time to the end of the procedure every 5 minutes.

In the dexmedetomidine group, 1 µg/kg infusion of dexmedetomidine (Hospira Co, America) for 20 minutes and 0.5 mg/kg of propofol (Dongkook Co, South Korea) in a single dose with fentanyl (Caspian Co, Iran) at a dose of 1 µg/kg were administered before starting the procedure. In the midazolam group, 0.33 mg/kg of midazolam (Exir Co, Iran) and 0.5 mg/kg of propofol (Dongkook Co, South Korea) in a single dose with fentanyl (Caspian Co, Iran) at a dose of 1 µg/kg were injected before starting the procedure.

To make the study double-blind, the patient's degree of relaxation according to the Ramsay Sedation Scale (RSS) was recorded during the procedure by another trained person who did not know the prescribing drugs. Regarding the RSS scores, 4 or 5 was the desirable tranquilizer, and a score below 4 was considered inadequate sedation (necessary to administer additional doses of propofol). If inadequate patient sedation was seen, a dose of 0.5 mg/kg of bolus propofol was prescribed, and, if necessary, this dose was repeated every 60 seconds.

3.1. Ramsay Sedation Scale

- (1) Completely awake and anxious.
- (2) Quiet and calm with enough cooperation.
- (3) Sleeps and wakes up with a language command.
- (4) Sleeping and waking up with mild excitement but heavily responds to painful stimuli.
- (5) Slow reaction to painful stimuli.
- (6) No response to painful stimuli (20).

Four ranking scores evaluated patients' pain during the procedure based on the patient's response to the (Ambesh score) questions:

- (1) Painless: Negative answer to questions about pain.
- (2) Mild: A positive response to questions about pain, but without any apparent symptoms.
- (3) Moderate: Positive answer to questions about pain and the appearance of symptoms or complaints of pain.

Severe: The patient complains of pain with frown or discomfort or by hand or fear. A score of more than 1 was considered pain, and a score of 1 was considered a lack of pain (21). Nausea and vomiting were recorded from the end of the procedure until the patient was discharged from the recovery room. As nausea is a symptom expressed by the

person himself, the Visual Analogue Scale (VAS) was used to measure and evaluate nausea. The scale is scored from 0 (no nausea) to 10 (severe nausea). The patient was asked to show the severity of her nausea between 0 and 10 (0, no nausea; 1 to 3, mild nausea; 4 to 7, moderate nausea; 8 to 10, severe nausea) (22).

Given the ethical considerations, if a patient complained of moderate or severe nausea and vomiting due to 0.1 to 0.15 mg per kg of body weight of ondansetron, it was reduced to a maximum of 4 mg (23).

From the time the procedure was completed until the patient's alertness and appropriate response to the questions, recovery was considered (every 30 seconds of recovery was investigated). A duration of less than 5 minutes was a fast recovery, between 5 - 10 minutes was an average recovery, and more than 10 minutes was a slow recovery (24).

SPSS version 20 (SPSS Inc, Chicago, IL, USA) was used to analyze the data. Mean and SD were used in quantitative variables to describe the data, and frequency and percentage were used for qualitative variables. The Mann-Whitney U test, *t*-test, or repeated measures test were used to compare the quantitative data between the 2 groups. The chi-square test was used to analyze the qualitative data.

4. Results

In the dexmedetomidine group, 46% were men and 54% were women. In the midazolam group, 47.6% were men and 52.4% were women. The chi-square test was used to compare the 2 groups, and the level of significance was 0.85, indicating no significant difference between the groups. In addition, age, weight, height, duration of anesthesia, and procedure time were compared between the 2 groups using the *t*-test; there was no significant difference between the 2 groups ($P > 0.05$; Table 1). The chi-square test was used to compare the recovery time. A significant level of 0.26 was obtained that showed no significant difference between all groups according to the duration of recovery, and they were fully alert. The 2 groups were statistically similar. In addition, the number of patients requiring propofol injection during the procedure to maintain calmness was statistically significant between the 2 groups, and 8 patients in the dexmedetomidine group and 34 in the midazolam group received propofol (Table 1).

The studied hemodynamic variables were arterial pressure, heart rate, and SaO₂. Mean arterial pressure (MAP) changes in the 2 groups were examined at 4 different times (Table 2). The *t*-test was used to compare the mean arterial blood pressure between the 2 groups

at different times. Mean arterial pressure at all times was similar between the groups, and there were no statistically significant differences between the 2 groups ($P > 0.05$). A comparison of heart rate values showed no significant differences between the 2 groups at different times, and heart rate changes were similar in the 2 groups ($P > 0.05$). The *t* test was used to compare SaO₂ between the 2 groups at different times. The 2 groups showed no significant difference in the levels of SaO₂ before starting the procedure and 10 and 15 minutes after the start of the procedure ($P > 0.05$). Arterial oxygen saturation was only significantly different 5 minutes after the start of the procedure between the 2 groups; thus, the dexmedetomidine group showed a significantly higher value than the midazolam group ($P < 0.05$).

The pain scores reported by the patients during the procedure were compared between the 2 groups (Table 3). None of the patients had moderate to severe levels of pain. In the dexmedetomidine group, 62 patients had no pain at all, and only 1 patient had mild pain. In the midazolam group, 61 patients had no pain at all, and only 2 patients had mild pain. No significant differences were found in pain between the 2 groups ($P > 0.05$).

The complications examined in the study were nausea, vomiting, and apnea during the procedure. Our results showed that 30% of patients in the dexmedetomidine group and 36.5% of patients in the midazolam group experienced nausea during the study; these were statistically significant between the groups, with no significant differences ($P = 0.58$). In both groups, there were only 2 cases with dyspnea (1 case in each group), and we had no apnea cases in both groups. Regarding the occurrence of these complications, there was no difference between the 2 groups ($P > 0.05$). Patients' and endoscopy specialists' satisfaction levels were compared; in the dexmedetomidine group, patients had more satisfaction with the endoscopic procedure ($P = 0.04$; Table 2).

Furthermore, 87.3% of the patients in the dexmedetomidine group had a sedation level of 5 and 6 (which is a desirable sedation rate), but in the midazolam group, 46% of the patients had proper sedation, and the difference between the 2 groups was statistically significant. The dexmedetomidine group had better sedation during the procedure than the midazolam group ($P < 0.05$).

5. Discussion

Endoscopic techniques have a critical and significant role in the diagnosis and treatment of diseases. As this procedure is done orally using an endoscope, it can be very painful and, to some extent, impossible in

Table 1. Comparison of Demographic and Clinical Information of Patients During the Operation

Variables	Dexmedetomidine (N = 63) (%)	Midazolam (N = 63) (%)	P-Value
Age (y)	52.46 ± 62.16	51.76 ± 12.05	0.29
Gender			0.85
Female	34 (54)	33 (52.4)	
Male	29 (46)	30 (47.6)	
Weight (kg)	68.81 ± 11.78	70.13 ± 9.01	0.48
Height (cm)	169.23 ± 16.42	173.31 ± 17.54	0.59
Duration of anesthesia	24.83 ± 5.87	25.62 ± 5.20	0.42
Duration of procedure	20.94 ± 5.29	21.67 ± 5.10	0.43
Duration of recovery (min)			0.26
< 5	26 (41.3)	34 (54)	
5 - 10	34 (54)	28 (44.4)	
> 10	3 (4.7)	1 (1.6)	
Received propofol	8 (12.70)	34 (54)	0.002

Table 2. Comparison of the Hemodynamic Status Before and During the Procedure Between the 2 Groups

Variables	Dexmedetomidine (N = 63)	Midazolam (N = 63)	P-Value
MAP			
Before the procedure	106.56 ± 15.55	108.43 ± 13.70	0.47
5 min	103.03 ± 14.14	97.10 ± 10.22	0.80
10 min	101.14 ± 13.13	93.43 ± 9.26	0.14
15 min	99.71 ± 12.70	91.76 ± 8.49	0.31
Heart rate			
Before the procedure	89.75 ± 14.35	92.90 ± 15.56	0.12
5 min	83.97 ± 15.41	83.21 ± 15.42	0.78
10 min	83.46 ± 13.25	80.08 ± 13.65	0.16
15 min	82.83 ± 13.37	78.73 ± 12.19	0.07
SpO₂			
Before the procedure	98.60 ± 0.66	98.65 ± 0.70	0.69
5 min	98.24 ± 1.38	97.08 ± 2.74	0.02
10 min	98.17 ± 1.41	98.95 ± 1.64	0.41
15 min	98.27 ± 1.36	98.17 ± 1.35	0.69

Abbreviations: MAP, mean arterial pressure; SpO₂, oxygen saturation.

many patients without the use of sedative and analgesic drugs. To prevent coughing, gag reflex, nausea, and vomiting, sedative medications are recommended for the patient (6, 25). Accordingly, we tried to compare the effects of dexmedetomidine and midazolam on patients undergoing gastrointestinal endosurgery to find a more appropriate drug combination for the relaxation of patients outside the operating room.

The results showed that the dexmedetomidine group

had a better degree of relaxation during the procedure than the midazolam group, and SpO₂ was higher in arterial blood 5 minutes after the start of the procedure. Wu et al. obtained a similar result in patients undergoing endoscopy of the upper gastrointestinal tract, showing better sedation and higher blood saturation. It seems that higher levels of blood saturation in these studies can be related to the difference in the effect of these 2 drugs on the respiratory system of patients (20). Moreover,

Table 3. Comparison of Complications During and After the Procedure between the 2 Groups and Satisfaction of Patients and Endoscopic Specialist

Variables	Dexmedetomidine (N = 63)(%)	Midazolam (N = 63)(%)	P-Value
Pain			0.79
Painless	62 (98.4)	61 (96.8)	
Mild	1 (1.6)	2 (3.2)	
Moderate	0	0	
Severe	0	0	
Nausea			0.58
No	44 (70)	40 (63.5)	
Mild	12 (19)	15 (23.8)	
Moderate	4 (6.3)	6 (9.5)	
Severe	3 (4.7)	2 (3.2)	
Vomit	2 (3.2)	1 (1.6)	0.55
Apnea	0	0	-
Patient satisfaction	8.05 ± 1.26	7.89 ± 1.39	0.74
Endoscopic specialist satisfaction	8.11 ± 1.42	7.03 ± 1.18	0.04

previous studies have shown that dexmedetomidine is highly reluctant to bind to alpha-2 adrenoceptors and is very close to γ -aminobutyric acid (GABA) receptors. Dexmedetomidine is more protective in avoiding decreased blood saturation compared to benzodiazepines (such as midazolam), but midazolam is more protective in respiratory depression compared to dexmedetomidine (26, 27). Contrary to the results of the study, Kilic et al. showed that dexmedetomidine and midazolam provide a similar relaxation effect during endoscopic retrograde cholangiopancreatography (ERCP), showing no difference between the groups. In their study, they used dexmedetomidine and midazolam to reach proper maintenance and sedation levels, but in our study, we used dexmedetomidine and midazolam only at the onset of ossification. In addition, if needed, we used propofol very short duration of action; thus, we were able to prevent prolonged recovery time in the midazolam group; however, in the study by Kilic et al., patients in the midazolam group experienced a significantly longer recovery time. Furthermore, they observed a significant decrease in heart rate in the dexmedetomidine group. Nevertheless, in the study, it seems that the long-term use of dexmedetomidine led to a significant reduction in heart rate (28). In a long-term study of ICU patients, Riker et al. indicated that bradycardia was more frequent in the dexmedetomidine group (42.2%) than in the midazolam group (18%) (29).

Delmade and Parikh conducted a prospective study on patients referred to the ear, nose, and throat (ENT) service. They used anxiolytic anesthetic monitoring of

dexmedetomidine and midazolam alone, showing no difference in the degree of relaxation between the groups in contrast to our study (30). Upper gastrointestinal endoscopy is a common procedure, which may have an unpleasant and painful experience for patients. In some previous studies, only local anesthesia was used to reduce the cost and risk of sedation, which was not likely to be tolerated by patients and caused dissatisfaction among patients and endoscopic specialists (31, 32). In new methods, sedative drugs (such as propofol, midazolam, and dexmedetomidine) are used to calm down during different procedures, and it is recommended to use medications with fewer side effects for sedation in the endoscopy producer. Our results showed no differences between the 2 groups in terms of pain. Peng et al. (33) found no significant differences in pain during and after surgery in a similar study in patients undergoing lumbar disc surgery using sedation. In the present study, we used the same amount of fentanyl for the 2 groups at the beginning of the study because of the short duration of the procedure. We used propofol during the procedure to maintain sedation, and the amount of propofol needed was significantly lower in the dexmedetomidine group than in the midazolam group. However, if there was a need for long surgery, fentanyl was used to control pain during and after surgery.

The non-significance of the pain score can be justified due to receiving fentanyl in both groups. Receiving dexmedetomidine even intradermally reduces anxiety by affecting the locus coeruleus region of the CNS (12, 33).

In conclusion, in the studies with no differences

in pain, different methods (such as the administration of narcotic drugs [such as fentanyl and meperidine], administration of topical anesthetic with epinephrine, etc.) have been commonly used (30, 33). In our study, because of the short duration of the procedure and the administration of fentanyl intravenously, there was no need for re-administration of analgesic drugs during the procedure, and patients in both groups experienced similar experiences.

In the present study, at the end of the procedure, the level of satisfaction of the endoscopic expert and patients was evaluated. The level of satisfaction of the endoscopic specialist significantly decreased in the dexmedetomidine group due to less reflux stimulation and abrupt movements of the patients during the procedure due to proper relaxation. However, the satisfaction of patients in the 2 groups did not differ significantly in our study, which may be due to the anti-anxiety effects of both drugs and the lack of pain during the procedure in most patients. In a similar study, Kilic et al. reported that the use of dexmedetomidine to induce and maintain the erection of patients who were ERCP candidates favored endoscopic specialists (28). Demiraran et al. and Sethi et al. reported similar results with expert satisfaction (6, 34). In line with our study, Peng et al. reported that the satisfaction of patients with sedation was similar to that of dexmedetomidine or midazolam. Moreover, it seems that the use of fentanyl with sedation drugs (such as this study) and especially the administration of lidocaine topically in all the studied patients resulted in relative satisfaction of patients in the 2 groups, and no difference was observed between the 2 groups (33). In our study, no complications (such as apnea) were observed during and after the procedure. None of the patients experienced nausea in the 2 groups, and few patients in both groups experienced vomiting, seen between the 2 groups in terms of occurrence. There were no significant differences in any of the complications. Peng et al. witnessed the incidence of complications during and after induction of sedation. According to the results of our study, respiratory depression was not seen in any of the patients; among 120 patients studied, only 5 patients in the dexmedetomidine group and 8 patients in the midazolam group experienced nausea and vomiting; the difference was not significant (33). Kilic et al. also did not observe the incidence of vomiting and hemodynamic complications (such as bradycardia and hypotension) between the groups receiving midazolam and dexmedetomidine (28) in the treatment of patients receiving sedation for the reverse endoscopic procedure of biliary and pancreatic ducts.

5.1. Conclusions

The use of dexmedetomidine instead of midazolam is better for the patients undergoing endoscopy in the gastrointestinal tract, whereas the level and occurrence of pain during the procedure and the occurrence of endoscopic complications are similar between the 2 groups.

Footnotes

Authors' Contribution: Study concept and design: R. A. and R. B.; analysis and interpretation of data: K. M., N. B., and S. M. R. G.; drafting of the manuscript: K. M., N. B., and R. B.; statistical analysis: N. B.

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References

1. Akin A, Esmoğlu A, Tosun Z, Gulcu N, Aydoğan H, Boyacı A. Comparison of propofol with propofol-ketamine combination in pediatric patients undergoing auditory brainstem response testing. *Int J Pediatr Otorhinolaryngol.* 2005;69(11):1541-5. [PubMed ID: 15936092]. <https://doi.org/10.1016/j.ijporl.2005.04.011>.
2. Amornyotin S. Sedation and monitoring for gastrointestinal endoscopy. *World J Gastrointest Endosc.* 2013;5(2):47-55. [PubMed ID: 23424050]. [PubMed Central ID: PMC3574612]. <https://doi.org/10.4253/wjge.v5.i2.47>.
3. Durmus M, But AK, Dogan Z, Yucel A, Miman MC, Ersoy MO. Effect of dexmedetomidine on bleeding during tympanoplasty or septorhinoplasty. *Eur J Anaesthesiol.* 2007;24(5):447-53. [PubMed ID: 17241505]. <https://doi.org/10.1017/S0265021506002122>.
4. Lichtenstein DR, Jagannath S, Baron TH, Anderson MA, Banerjee S, Dominitz JA, Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy, et al. Sedation and anesthesia in GI endoscopy. *Gastrointest Endosc.* 2008;68(5):815-26. [PubMed ID: 18984096]. <https://doi.org/10.1016/j.gie.2008.09.029>.
5. Khan ZP, Ferguson CN, Jones RM. alpha-2 and imidazoline receptor agonists. Their pharmacology and therapeutic role. *Anaesthesia.* 1999;54(2):146-65. [PubMed ID: 10215710]. <https://doi.org/10.1046/j.1365-2044.1999.00659.x>.
6. Demiraran Y, Korkut E, Tamer A, Yorulmaz I, Kocaman B, Sezen G, et al. The comparison of dexmedetomidine and midazolam used for sedation of patients during upper endoscopy: A prospective, randomized study. *Can J Gastroenterol.* 2007;21(1):25-9. [PubMed ID: 17225879]. [PubMed Central ID: PMC2656627]. <https://doi.org/10.1155/2007/350279>.

7. Dere K, Sucullu I, Budak ET, Yeyen S, Filiz AI, Ozkan S, et al. A comparison of dexmedetomidine versus midazolam for sedation, pain and hemodynamic control, during colonoscopy under conscious sedation. *Eur J Anaesthesiol*. 2010;**27**(7):648–52. [PubMed ID: 20531094]. <https://doi.org/10.1097/EJA.0b013e3283347bfe>.
8. McDonald T, Hoffman WE, Berkowitz R, Cunningham F, Cooke B. Heart rate variability and plasma catecholamines in patients during opioid detoxification. *J Neurosurg Anesthesiol*. 1999;**11**(3):195–9. [PubMed ID: 10414675]. <https://doi.org/10.1046/j.1365-2044.1999.01114.x>.
9. Venn RM, Bradshaw CJ, Spencer R, Brealey D, Caudwell E, Naughton C, et al. Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. *Anaesthesia*. 1999;**54**(12):1136–42. [PubMed ID: 10594409]. <https://doi.org/10.1046/j.1365-2044.1999.01114.x>.
10. Virtanen R, Savola JM, Saano V, Nyman L. Characterization of the selectivity, specificity and potency of medetomidine as an alpha 2-adrenoceptor agonist. *Eur J Pharmacol*. 1988;**150**(1-2):9–14. [PubMed ID: 2900154]. [https://doi.org/10.1016/0014-2999\(88\)90744-3](https://doi.org/10.1016/0014-2999(88)90744-3).
11. Carroll CL, Krieger D, Campbell M, Fisher DG, Comeau LL, Zucker AR. Use of dexmedetomidine for sedation of children hospitalized in the intensive care unit. *J Hosp Med*. 2008;**3**(2):142–7. [PubMed ID: 18438790]. <https://doi.org/10.1002/jhm.282>.
12. Dyck JB, Maze M, Haack C, Vuorilehto L, Shafer SL. The pharmacokinetics and hemodynamic effects of intravenous and intramuscular dexmedetomidine hydrochloride in adult human volunteers. *Anesthesiology*. 1993;**78**(5):813–20. [PubMed ID: 8098190]. <https://doi.org/10.1097/0000542-199305000-00002>.
13. Triltsch AE, Welte M, von Homeyer P, Grosse J, Genahr A, Moshirzadeh M, et al. Bispectral index-guided sedation with dexmedetomidine in intensive care: A prospective, randomized, double blind, placebo-controlled phase II study. *Crit Care Med*. 2002;**30**(5):1007–14. [PubMed ID: 12006795]. <https://doi.org/10.1097/00003246-200205000-00009>.
14. Correa-Sales C, Rabin BC, Maze M. A hypnotic response to dexmedetomidine, an alpha 2 agonist, is mediated in the locus coeruleus in rats. *Anesthesiology*. 1992;**76**(6):948–52. [PubMed ID: 1350889]. <https://doi.org/10.1097/0000542-199206000-00013>.
15. Kamisaki Y, Ishikawa T, Takao Y, Omodani H, Kuno N, Itoh T. Binding of [³H]p-aminoclonidine to two sites, alpha 2-adrenoceptors and imidazoline binding sites: Distribution of imidazoline binding sites in rat brain. *Brain Res*. 1990;**514**(1):15–21. [PubMed ID: 2162708]. [https://doi.org/10.1016/0006-8993\(90\)90430-j](https://doi.org/10.1016/0006-8993(90)90430-j).
16. Nelson LE, Lu J, Guo T, Saper CB, Franks NP, Maze M. The alpha2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. *Anesthesiology*. 2003;**98**(2):428–36. [PubMed ID: 12552203]. <https://doi.org/10.1097/0000542-200302000-00024>.
17. Philipp M, Brede M, Hein L. Physiological significance of alpha(2)-adrenergic receptor subtype diversity: One receptor is not enough. *Am J Physiol Regul Integr Comp Physiol*. 2002;**283**(2):R287–95. [PubMed ID: 12121839]. <https://doi.org/10.1152/ajpregu.00123.2002>.
18. Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. *Anesthesiology*. 1992;**77**(6):1134–42. [PubMed ID: 1361311]. <https://doi.org/10.1097/0000542-199212000-00014>.
19. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. *Anesthesiology*. 2000;**93**(2):382–94. [PubMed ID: 10910487]. <https://doi.org/10.1097/0000542-200008000-00016>.
20. Wu W, Chen Q, Zhang LC, Chen WH. Dexmedetomidine versus midazolam for sedation in upper gastrointestinal endoscopy. *J Int Med Res*. 2014;**42**(2):516–22. [PubMed ID: 24514431]. <https://doi.org/10.1177/0300060513515437>.
21. Akhondzadeh R, Ghomeishi A, Nesioonpour S, Nourizade S. A comparison between the effects of propofol-fentanyl with propofol-ketamine for sedation in patients undergoing endoscopic retrograde cholangiopancreatography outside the operating room. *Biomed J*. 2016;**39**(2):145–9. [PubMed ID: 27372170]. [PubMed Central ID: PMC6138805]. <https://doi.org/10.1016/j.bj.2015.11.002>.
22. Smally AJ, Nowicki TA, Simelton BH. Procedural sedation and analgesia in the emergency department. *Curr Opin Crit Care*. 2011;**17**(4):317–22. [PubMed ID: 21677578]. <https://doi.org/10.1097/MCC.0b013e328328348bf43>.
23. Safae M, Safi S. [Evaluation of effect of ondansetron on nausea and vomiting after elective cholecystectomy surgery in women older than 40 years]. *J Isfahan Med Sch*. 2011;**29**(149). Persian.
24. Gharavi MOHAMMAD, Taghai Gilani M, Razavi MAJID. [Comparison of recovery time and complications in general anesthesia with remifentanyl and propofol and topical anesthesia with conscious sedation in non-complicated cataract phaco surgery]. *Med J Mashhad Univ Med Sci*. 2007;**50**(4):433–8. Persian.
25. Riphaut A, Stergiou N, Wehrmann T. Sedation with propofol for routine ERCP in high-risk octogenarians: A randomized, controlled study. *Am J Gastroenterol*. 2005;**100**(9):1957–63. [PubMed ID: 16128939]. <https://doi.org/10.1111/j.1572-0241.2005.41672.x>.
26. Huang Z, Chen YS, Yang ZL, Liu JY. Dexmedetomidine versus midazolam for the sedation of patients with non-invasive ventilation failure. *Intern Med*. 2012;**51**(17):2299–305. [PubMed ID: 22975538]. <https://doi.org/10.2169/internalmedicine.51.7810>.
27. Tellor BR, Arnold HM, Micek ST, Kollef MH. Occurrence and predictors of dexmedetomidine infusion intolerance and failure. *Hosp Pract (1995)*. 2012;**40**(1):186–92. [PubMed ID: 22406894]. <https://doi.org/10.3810/hp.2012.02.959>.
28. Kilic N, Sahin S, Aksu H, Yavascaoglu B, Gurbet A, Turker G, et al. Conscious sedation for endoscopic retrograde cholangiopancreatography: Dexmedetomidine versus midazolam. *Eurasian J Med*. 2011;**43**(1):13–7. [PubMed ID: 25610153]. [PubMed Central ID: PMC4261372]. <https://doi.org/10.5152/eajm.2011.03>.
29. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: A randomized trial. *JAMA*. 2009;**301**(5):489–99. [PubMed ID: 19188334]. <https://doi.org/10.1001/jama.2009.56>.
30. Delmade M, Parikh D. A prospective randomized double blind study to compare dexmedetomidine and midazolam in ear nose and throat surgery for monitored anesthesia care. *J Res Med Sci*. 2016;**3**:159–63. <https://doi.org/10.18203/2320-6012.ijrms.20162228>.
31. Ergul B, Sarikaya M, Dogan Z, Filik L, Biyikoglu I. Is topical pharyngeal anesthesia necessary in esophagogastroduodenoscopy in all unsedated patients? *Dig Endosc*. 2013;**25**(1):90–1. [PubMed ID: 23286268]. <https://doi.org/10.1111/j.1443-1661.2012.01383.x>.
32. Garg PK, Singh AP, Jain BK, Bansal A, Mohanty D, Agrawal V. Safety and acceptance of non-sedated upper gastrointestinal endoscopy: A prospective observational study. *J Laparoendosc Adv Surg Tech A*. 2012;**22**(4):315–8. [PubMed ID: 22489906]. <https://doi.org/10.1089/lap.2011.0463>.
33. Peng K, Liu HY, Liu SL, Ji FH. Dexmedetomidine-fentanyl compared with midazolam-fentanyl for conscious sedation in patients undergoing lumbar disc surgery. *Clin Ther*. 2016;**38**(1):192–201 e2. [PubMed ID: 26699739]. <https://doi.org/10.1016/j.clinthera.2015.11.016>.
34. Sethi P, Mohammed S, Bhatia PK, Gupta N. Dexmedetomidine versus midazolam for conscious sedation in endoscopic retrograde cholangiopancreatography: An open-label randomised controlled trial. *Indian J Anaesth*. 2014;**58**(1):18–24. [PubMed ID: 24700894]. [PubMed Central ID: PMC3968645]. <https://doi.org/10.4103/0019-5049.126782>.