Brazilian Journal of Anesthesiology 2023;73(5): 641—664

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

SYSTEMATIC REVIEW

Effects of dexmedetomidine in non-operating room anesthesia in adults: a systematic review with meta-analysis

Francisca Jerónimo Fonseca [a], **Leonardo Ferreira** [b,*], **Ana Lídia Rouxinol-Dias** [b,c,d], **Joana Mourão** [a,b]

[a] *Faculty of Medicine of the University of Porto, Porto, Portugal*
[b] *São João University Hospital Center, Department of Anesthesiology, Porto, Portugal*
[c] *Faculty of Medicine of the University of Porto, Department of Community Medicine, Information and Decision in Health, MEDCIDS, Porto, Portugal*
[d] *Faculty of Medicine of the University of Porto, Center for Health Technology and Services Research, CINTESIS, Porto, Portugal*

Received 7 April 2021; accepted 5 December 2021
Available online 20 December 2021

KEYWORDS
Anesthesiology;
Conscious sedation;
Dexmedetomidine;
Hypnotics and sedatives;
Patient safety

Abstract

Background: Dexmedetomidine (DEX) is an α2-adrenergic receptor agonist used for its sedative, analgesic, and anxiolytic effects. Non-Operating Room Anesthesia (NORA) is a modality of anesthesia that can be done under general anesthesia or procedural sedation or/and analgesia. In this particular setting, a level-2 sedation, such as the one provided by DEX, is beneficial. We aimed to study the effects and safety of DEX in the different NORA settings in the adult population.

Methods: A systematic review with meta-analysis of randomized controlled trials was conducted. Interventions using DEX only or DEX associated with other sedative agents, in adults (18 years old or more), were included. Procedures outside the NORA setting and/or without a control group without DEX were excluded. MEDLINE, ClinicalTrials.gov, Scopus, LILACS, and SciELO were searched. The primary outcome was time until full recovery. Secondary outcomes included hemodynamic and respiratory complications and other adverse events, among others.

Results: A total of 97 studies were included with a total of 6,706 participants. The meta-analysis demonstrated that DEX had a higher time until full recovery (95% CI = [0.34, 3.13] minutes, a higher incidence of hypotension (OR = 1.95 [1.25, 3.05], $p = 0.003$, $I^2 = 39\%$) and bradycardia (OR = 3.60 [2.29, 5.67], $p < 0.00001$, $I^2 = 0\%$), and a lower incidence of desaturation (OR = 0.40 [0.25, 0.66], $p = 0.0003$, $I^2 = 60\%$).

* Corresponding author.
E-mail: leomigfer@gmail.com (L. Ferreira).

https://doi.org/10.1016/j.bjane.2021.12.002

Conclusion: DEX in NORA procedures in adults was associated with a lower incidence of amnesia and respiratory effects but had a long time to recovery and more hemodynamic complications.

Introduction

Dexmedetomidine (DEX) is an α2-Adrenergic Receptor (α2-AR) agonist used for its sedative, analgesic, and anxiolytic effects.[1] It is a relatively new drug, having been approved by the Food and Drug Administration (FDA) in 1999 for use in short-term sedation and analgesia (< 24 hours) in the Intensive Care Unit (ICU).[1] It provides a unique type of sedation, "arousable sedation", in which patients appear to be sleepy but are easily aroused, cooperative, and communicative when stimulated, resembling natural sleep.[1] Furthermore, in the ICU setting, it is associated with reduced anesthetic requirements and preservation of respiratory function, offering hemodynamic stability with a reduced dose of vasopressor in septic shock patients,[2] hence facilitating early weaning from the ventilator and thereby reducing overall ICU stay costs.[1,3]

Non-Operating Room Anesthesia (NORA) is an upcoming and challenging modality of anesthesia in remote locations within the hospital that requires expertise and skill.[4] In this particular backdrop, level 2 sedation is beneficial because it allows the patient to follow commands during the procedure while maintaining airway function and reflexes.[4] The particular goals of sedation are patient safety and welfare, minimizing discomfort and pain, controlling anxiety, minimizing psychological trauma, maximizing the potential of anterograde amnesia, controlling movement for safer completion of the procedure, and rapid recovery of the patient to a state of safe discharge from medical supervision.[4]

In NORA sedation, there is a paucity of literature describing the efficacy and safety of DEX, alone and in combination, both in children and in adults.[5] A recent review reported DEX as a promising alternative to midazolam for use in procedural sedation in adults, providing more comfort during the procedure for the patient and clinician.[6] Therefore, further embracing investigation is warranted to better understand the effects and safety of DEX, alone or in combination, in the different NORA settings, especially in the adult population.[7] For children, there is already a recent systematic review reporting significant benefits of DEX in NORA sedation. But for the adult population, a preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews, and the JBI Database of Systematic Reviews and Implementation Reports was conducted and no current or underway systematic reviews on the topic were identified. Therefore, we developed a systematic review to evaluate and report time until recovery and side effects of DEX only or DEX associated with other sedative agents in NORA settings for adults' procedures in comparison to other sedatives.

Methods

The protocol of this systematic review and meta-analysis was written following the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidance.[8] Under the guidelines, our systematic review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) on the 22nd of October 2020 (registration number CRD42020215880). This systematic review was written following the PRISMA Statement.[9]

Eligibility criteria

We included papers that studied patients with 18 years of age or older. Only Randomized Controlled Trials (RCTs), regardless of their population size, were included. Of interest were interventions using DEX only or DEX associated with other sedative agents, comparing with the use of another pharmacological sedative strategy (without DEX).

Search strategy

The full queries applied to the different information sources and results are presented in Appendix I. Search was conducted on MEDLINE (through Pubmed), ClinicalTrials.gov, Scopus, LILACS (through Virtual Health Library Regional Portal), and SciELO for all available literature on the subject until October 12, 2021. The bibliographies of relevant systematic reviews were studied to identify any studies missed by our literature search. Articles written in all languages were searched.

Data collection and assessment

Two reviewers independently read all titles and abstracts and selected the studies to include in the review according to the eligibility criteria. Then, the full article was obtained and read in its integrity by the two authors, and it was decided if it met the inclusion criteria. Uncertainty and disagreement were resolved by discussion between the reviewers. Reviewers were blind to the journal titles and institutions. The data extraction from the selected studies was independent and in duplicate to avoid errors and reduce biases. Any remaining discrepancies were resolved by a third author.

The following outcomes were evaluated in this review: recovery time (primary outcome), sedation level, pain and discomfort, patient and physician satisfaction, hemodynamic complications (hypotension and hypertension, bradycardia, and tachycardia), respiratory depression and other respiratory complications, and nausea or vomiting.

Literature search results were uploaded to EndNote Vx9 (Clarivate Analytics, PA, USA), a reference management software that facilitates the collection, duplicate exclusion, and analysis of research materials and collaboration between researchers during the selection process. For screening, a database was built using Microsoft Excel

V16.42/2020 (Microsoft Corporation, USA). For data collection, synthesis, and analysis, data were extracted to RevMan 5.1 (Review Manager 5.1) V5.4 (Copenhagen: The Nordic Cochrane Centre, Cochrane).

Risk of bias in individual studies

The risk of bias for each study was evaluated by the collection of information, using the Cochrane Risk of Bias Tool,[10] by 2 review authors independently. The inter-rater agreement was measured. All studies were retained independently of their risk of bias.

Certainty assessment

Certainty assessment was performed using GRADEpro GDT software to prepare the "Summary of findings" tables (GRADEpro Guideline Development Tool [Software]. McMaster University, 2020 developed by Evidence Prime, Inc.). All decisions to down- or up-grade the certainty of studies is reported as footnotes.

Statistical analysis

If the studies were sufficiently homogeneous, we conducted a meta-analysis using a random-effects approach, with a 5% significance level. For dichotomous variables, we determined the Odds Ratio (OR) with a 95% Confidence Interval (95% CI). As for continuous variables, we determined the mean with a 95% CI. Heterogeneity was evaluated by using I^2 and Cochran's Q test. Values of I^2 greater than 50% were considered as indicative of substantial heterogeneity,[11] and investigated by subgroup analysis (setting and comparator/control intervention).

Publication bias evaluation

The outcome reporting and small study biases were assessed with the help of Funnel plots and Egger's Test.[12]

Results

Description of studies

After systematically searching five electronic databases, we obtained studies according to the search strategy as follows: MEDLINE (n = 1,874), ClinicalTrials.gov (n = 64), Scopus (n = 205), LILACS (n = 104), and SciELO (n = 103). Among these articles, 232 studies were excluded because they were duplicates. A total of 1,946 studies were excluded because they did not meet the inclusion criteria after reviewing their titles and abstracts. Cohen's kappa of agreement between the two authors was 67%, fair to a good agreement.[13] The remaining 172 studies were considered relevant, and reviewers carefully screened the full articles. The study selection process is outlined through the PRISMA (Preferred Reporting Items for Systematic Reviews) [14] diagram in Appendix II.

Included trials

The 97 RCTs studies included involved a total of 6,706 participants and 6,853 procedures. This difference is due to Nooh et al.,[15] Shetty et al.,[16] and Hiwarkar et al.,[17] where each subject participated in two procedure sessions and received both interventions. We summarized the characteristics of the included studies in Table 1.

The studies included were from 2004 onward, 21 from before 2013 and 75 from 2013 onward. Twenty-three studies were conducted in India, [16,17,86,48,51,20,90,28,61,64–66,30,21,106,107,84,71,108,32,82,78,68] sixteen in China,[41,87,88,59,23–25,89,81,36,109,69,110,111,95,103] thirteen in Turkey,[38,96,98,40,43,44,19,99,52,55,56,104,22] nine in Japan,[49,27,54,63,77,67,33,35,100] seven in the Republic of Korea,[73,42,53,80,57,58,92] five in the USA,[18,74,105,29,34] four in each of the following countries: Iran [72,39,83,101] and Saudi Arabia,[15,97,46,70] and two in each of the following countries: Egypt [85,75] and Singapore. [26,37] For other countries, only one study was reported.

The age of participants ranged from 18 to 99 years. Four studies included patients with an American Society of Anesthesiologists (ASA) physical status of I only,[15–17,33] and sixteen studies did not report the patients' ASA physical status.[90,21,106,88,40,49,27,54,77,67,80,83,76,91]

Most of the studies used standard monitorization with non-invasive Blood Pressure (BP), Electrocardiogram (ECG), pulse oximetry, and capnography.[4] Depth of sedation was evaluated with Bispectral Index (BIS), Ramsay Sedation Score (RSS), or Observer Assessment of Alertness/Sedation Scale (OAA/S) in the majority of the studies, although five used the Richmond Agitation Sedation Scale (RASS),[61,27,54,77,62] and seven used another sedation score.[108,43,19,22,80,91,60]

Risk of Bias and GRADE assessment

Twenty-five trials were judged to be low risk of bias in all domains.[86,90,64,66,107,78,68,41,87,23–25,81,36,69,103,58,92,105,29,85,37,62,47,93] Forty trials had unclear risk of bias,[15,16,51,20,28,30,21,106,84,108,32,82,89,109,110,95,96,40,19,52,56,22,49,27,54,72,39,83,70,60,45,50,79,102,94] The domains judged to have the highest risk of bias were both blinding of participants and personnel (performance bias) as well as incomplete outcome data (attrition bias) (Fig. 1 and Appendix 4). GRADE assessment is described in Table 2.

Outcomes

Time until full recovery

Overall, 41 studies evaluated time until full recovery as outcomes, although there was not a consistent definition of recovery. Of the studies, 46.3% used Aldrete's scoring system (the full description of the outcome's definition can be found in Appendix III). A meta-analysis was computed to evaluate this outcome (just for RCTs considering Aldrete or modified Aldrete > 9) (Fig. 2). Overall, there was a tendency for a mean higher time until full recovery of 1.73 minutes (95% CI [0.34, 3.13] minutes). There was severe heterogeneity (I^2 = 96%), not fully explained by subgroup analysis (test for subgroup differences: Chi^2 = 10.41, df = 3 (p = 0.02), I^2 = 71.2%), nor control group (test for subgroup differences: Chi^2 = 33.11, df = 5 ($p < 0.00001$), I^2 = 84.9%) (Appendix IV).

Table 1 Studies' characteristics.

NORA setting	Study	Country	Age (yr)	Male (%)	Sample size	ASA physical status	Type of procedure	Monitorization	Intervention/comparator	Timing of DEX injection	Main outcome	Other outcomes
Not specified (n = 1)	Candiotti [18]	USA	NR	NR	326	1, 2, 3, 4	Not specified	Vital signs and OAA/S score	1: 0.5 $\mu g.kg^{-1}$ DEX for 10 min + 0.6 $\mu g.kg^{-1}.h^{-1}$ (initial rate) infusion DEX 2: 1 $\mu g.kg^{-1}$ DEX for 10 min + 0.6 $\mu g.kg^{-1}.h^{-1}$ (initial rate) infusion DEX 3: Normal saline	Before and during the procedure	Percentage of patients not requiring MDZ for rescue sedation	Total amount of rescue MDZ, time from onset of study drug infusion to the first dose of rescue MDZ, percentage of patients who converted to alternative sedative and/or anesthetic therapy, recovery time, time until discharge, the total amount of fentanyl, incidence of adverse events and complications, hemodynamic stability, and patient and physician satisfaction.
Burn unit procedure (n = 4)	Gündüz [19]	Turkey	(19-65)	67.8	90	1, 2, 3	Dressing changes	HR, SBP, DBP, MAP, SpO_2 and urine output (bladder catheter)	1: 1 $\mu g.kg^{-1}$ iv DEX for 10 min + 1 $mg.kg^{-1}$ iv ketamine 2: 0.05 $mg.kg^{-1}$ iv MDZ for 10 min + 1 $mg.kg^{-1}$ iv ketamine 3: iv normal saline for 10 min + 1 $mg.kg^{-1}$ iv ketamine	Before the procedure	No clear definition	Hemodynamic effects, analgesic effect, and sedation score.
	Kundra [20]	India	NR	28.3	60	1, 2	Dressing changes	BP, SpO_2, HR and RSS	1: 4 $\mu g.kg^{-1}$ oral DEX 2: 5 $mg.kg^{-1}$ oral ketamine	Before the procedure	No clear definition	Analgesic efficacy, pain, sedation score and adverse events and complications.
	Ravipati [21]	India	(18-60)	23.3	60	NR	Dressing change and debridement	NIBP, ECG, pulse oximeter and RSS	1: 1 $\mu g.kg^{-1}$ IM DEX + 0.5 $mg.kg^{-1}$ iv bolus ketamine + 1 $mg.kg^{-1}$ iv bolus propofol + 1 $mg.kg^{-1}.h^{-1}$ iv infusion ketamine + 100 $\mu g.kg^{-1}.min^{-1}$ iv infusion propofol 2: 0.5 $mg.kg^{-1}$ iv bolus ketamine + 1 $mg.kg^{-1}$ iv bolus propofol + 1 $mg.kg^{-1}.h^{-1}$ iv infusion ketamine + 100 $\mu g.kg^{-1}.min^{-1}$ iv infusion propofol	1h before induction	No clear definition	Total drug consumption and recovery time
	Zor [22]	Turkey	(19-54)	83.3	24	2, 3	Dressing change	HR, non-invasive SBP, SpO_2 and RR	1: 1 $mg.kg^{-1}$ IM tramadol + 1 $mg.kg^{-1}$ IM DEX HCl + 2 $mg.kg^{-1}$ IM ketamine 2: 2 $mg.kg^{-1}$ IM ketamine 3: 1 $mg.kg^{-1}$ IM tramadol + 0.05 $mg.kg^{-1}$ IM MDZ HCl+ 2 $mg.kg^{-1}$ IM ketamine	15 min before the procedure	No clear definition	Pain, sedation score, adverse events and complications and patient satisfaction.
Dental procedure (n = 19)	Cheung [23]	China	(18-50)	30	60	1, 2	Unilateral third molar surgery	HR, BP, RR, SpO_2 and RSS	1: 1 $\mu g.kg^{-1}$ infusion DEX for 10 min 2: 5 mg infusion MDZ for 10 min	Before the procedure	Patient satisfaction	Pain, relaxation during the operation, amnesia, surgical conditions, physician satisfaction and adverse events and complications.
	Cheung [24] (1)	China	(18-50)	41.0	105	1, 2	Bilateral third molar surgery	HR, BP, RR and SpO_2 and RSS	1: 1 $\mu g.kg^{-1}$ iv infusion DEX for 10 min + infiltration normal saline 2: iv infusion normal saline + 1 $\mu g.mL^{-1}$ infiltration DEX 3: iv infusion normal saline + infiltration normal saline	Before and at the end of the procedure	No clear definition	Recovery profile, pain, BP, HR, SpO_2, RSS, postoperative analgesic consumption and adverse events and complications.
	Cheung [25] (2)	China	(18-50)	45	60	1, 2	Unilateral third molar surgery	HR, BP, RR and SpO_2, BIS and OAA/S score	1: 1 $\mu g.kg^{-1}$ intranasal DEX 2: intranasal normal saline	45 min before the procedure	Postoperative pain relief	Sedation score and psychomotor function.
	Fan [26]	Singapore	NR	70	60	1, 2	Not specified	NIBP, ECG, pulse oximeter, BIS and OAA/S score	1: 0.1 $\mu g.kg^{-1}.min^{-1}$ infusion DEX + 0.2 $\mu g.kg^{-1}.h^{-1}$ infusion DEX 2: 0.005 $mg.kg^{-1}.min^{-1}$ infusion MDZ + 0.01 $mg.kg^{-1}.h^{-1}$ infusion MDZ	Before and during the procedure	Efficacy (sedation score, anxiolysis, analgesic effects, operating conditions, and patient satisfaction) and safety.	NR

Table 1 (*Continued*)

NORA setting	Study	Country	Age (yr)	Male (%)	Sample size	ASA physical status	Type of procedure	Monitorization	Intervention/comparator	Timing of DEX injection	Main outcome	Other outcomes
	Hiwarkar [17]	India	(18-60)	NR	20	1	Surgical removal of bilaterally impacted mandibular third molars	SpO_2, HR, BP and modified OAA/S	1: 1.5 μg.kg^{-1} intranasal DEX 2: 0.2 mg.kg^{-1} intranasal MDZ	10 min before procedure	No clear definition	Efficacy
	Kawaai [27]	Japan	NR	35	40	NR	Dental implant surgery	BP, HR, ECG, SpO_2 and RASS	1: 0.05 mg.kg^{-1} iv bolus butorphanol + 0.05 mg.kg^{-1} iv bolus MDZ + 0.56 (±0.14) μg.kg^{-1}.h^{-1} infusion DEX 2: 0.05 mg.kg^{-1} iv bolus butorphanol + 0.05 mg.kg^{-1} iv bolus MDZ + 2.3 mg.kg^{-1}.h^{-1} infusion propofol	During the procedure	No clear definition	Amnesic action, recovery profile and sedation comfort.
	Mishra [28]	India	(18-65)	76.7	60	1, 2	Multiple days care oral and maxillofacial surgical procedures	SBP, DBP, HR, RR, SpO_2 and BIS	1: 1 μg.kg^{-1} bolus DEX for 10 min + 0.5 μg.kg^{-1}.h^{-1} DEX 2: 0.08 mg.kg^{-1} bolus MDZ for 10 min + 0.05 mg.kg^{-1}.h^{-1}MDZ	Before and during the procedure	No clear definition	Respiratory and hemodynamic effects, adverse events and complications, amnesia, discharge score, patient relaxation and patient satisfaction.
	Nolan [29]	USA	(18-35)	33.3	144	1,2	Surgical removal of third molar	NIBP, ECG, pulse oximetry and capnography	1: 0.03 mg.kg^{-1} MDZ + 1 μg.kg^{-1} infusion DEX for 10 min + 0.5 μg.kg^{-1}.h^{-1} infusion DEX 2: 0.03 mg.kg^{-1} MDZ + 0.8 μg.kg^{-1} fentanyl + 125 mg.kg^{-1}.min^{-1} infusion propofol ± 0.1 mg.kg^{-1} boluses propofol, as needed	Before and during the procedure	Respiratory events requiring intervention	Pain, cooperation score, time to ambulation, time to discharge, amnesia, patient satisfaction, operating conditions score and hemodynamic stability.
	Nooh [15]	Saudi Arabia	(20-28)	56	18	1	Surgical removal of the third molar	NIBP, ECG, pulse oximeter, modified OAA/S score and BIS	1: 1.5 μg.kg^{-1} intranasal atomized DEX 2: intranasal water	30 min before the procedure	No clear definition	Preoperative anxiety, reaction to the anesthetic injection, pain, sedation score, vital signs, adverse events and complications and total analgesic consumption.
Dental procedure (n = 19)	Rasheed [30]	India	(20-50)	46	50	1, 2	Not specified	NIBP, ECG, pulse oximeter and OAA/S score	1: 1 μg.kg^{-1} iv DEX for 2 min + 0.5 mg.kg^{-1} iv ketamine 2: 0.05 mg.kg^{-1} iv MDZ for 2 min + 0.5 mg.kg^{-1} iv ketamine	NR	No clear definition	Duration of procedure, induction-incision time, hemodynamic effects, duration of analgesia, mean a total extra dose of ketamine and patient and physician satisfaction.
	Salazar [31]	Venezuela	(18-30)	38.6	44	1, 2	Surgical removal of the third molar	RR, SBP, DBP, MAP, SpO_2, ECG, HR and RSS	1: 0.2 μg.kg^{-1}.h^{-1} iv infusion DEX 2: 0.1 mg.kg^{-1}.min^{-1} iv infusion propofol	Before and during the procedure	Patient behavior (pain or discomfort) during the procedure	Sedation score, time until sedation, patient response, hemodynamic and respiratory effects, need for additional anesthetic, recovery time, need for rescue Alfentanil and adverse events and complications.
	Shetty [16]	India	(18-35)	NR	15	1	Surgical removal of the third molar	NIBP, pulse oximeter and modified OAA/S score	1: 1.5 LG kg^{-1} intranasal atomized DEX 2: Intranasal normal saline	30 min before the procedure	No clear definition	Sedation score and pain.
	Sivasubramani [32] (1)	India	(18-40)	NR	30	1, 2	Minor oral surgery	HR, SBP, DBP, ECG, SpO_2 and RR	1: 1 μg.kg^{-1}.h^{-1} infusion DEX for 10 min + 0.5 μg.h^{-1} infusion DEX 2: 0.05 mg.kg^{-1} infusion MDZ + 0.5 μg.h^{-1} infusion MDZ	Before and during the procedure	No clear definition	Vital signs, sedation score, pain, cognitive judgment, amnesia, patient ambulatory status and surgical wound and output.
	Sivasubramani [32] (2)	India	(18-40)	NR	60	1, 2	Minor oral surgery	HR, ECG, pulse oximeter, SpO_2, BP, RR and RSS	1: 1 μg.kg^{-1}.h^{-1} iv infusion DEX for 10 min + 0.5 μg.h^{-1} infusion DEX 2: 0.05 mg.kg^{-1} iv infusion MDZ for 10 min + infusion normal saline	Before and during the procedure	No clear definition	RSS and bite force.
	Taniyama [33]	Japan	NR	21.4	14	1	Minor oral surgery	BP, HR, SpO_2, Mackenzie's sedation assessment score and BIS	1: 6 mg.kg^{-1}.h^{-1} iv DEX hydrochloride for 10 min + 0.4 μg.kg^{-1}.h^{-1} infusion DEX hydrochloride 2: 20 mg iv lidocaine	Before and during the procedure	No clear definition	Amnesia, comfort, sedation score and hemodynamic and respiratory effects.

Table 1 (*Continued*)

NORA setting	Study	Country	Age (yr)	Male (%)	Sample size	ASA physical status	Type of procedure	Monitorization	Intervention/comparator	Timing of DEX injection	Main outcome	Other outcomes
									hydrochloride + 0.5 mg.kg^{-1} bolus propofol + 4 mg.kg^{-1}.h^{-1} infusion propofol			
	Taylor [34]	USA	(32-74)	42	12	1, 2	Maxillary and mandibular arch extractions with associated dentoalveolar preprosthetic surgery	NIBP, ECG, pulse oximetry, capnography, RR	1: 4 mg.kg^{-1}.h^{-1} infusion DEX + 2 mg iv MDZ + 50 mg iv fentanyl 2: 2 mg iv MDZ + 50 mg iv fentanyl + infusion normal saline	Before and during the procedure, until 15 min to the end of the procedure	Anesthesia times, vital signs and the patient subjective experience	NR
	Togawa [35]	Japan	(20-80)	93.2	88	1, 2	Minor oral surgery	NIBP, ECG, HR, SpO_2 and BIS	1: 0.02 mg.kg^{-1} MDZ + 3 μg.kg^{-1}.h^{-1} infusion DEX for 10 min + 0.2-0.7 μg.kg^{-1}.h^{-1} infusion DEX 2: 0.02 mg.kg^{-1} MDZ + 1.0 μg.mL^{-1} target plasma concentration propofol (up titrated until desired sedation level)	Before and during the procedure	Unexpected patient movement	Responsiveness, mouth opening time, cough, snoring, total and rescue dose of MDZ, patient and physician satisfaction, amnesia, recovery profile, hemodynamic and respiratory effects, operating time and sedation time.
	Wang [36]	China	NR	61.7	60	1,2	Dental implant surgery	NIBP, ECG, pulse oximeter and OAA/S score	1: 1.0 μg.kg^{-1} DEX for 10 min + 0.2-0.7 μg.kg^{-1}. h^{-1} infusion DEX 2: 0.05 mg.kg^{-1} MDZ + 0.04-0.2 mg.kg^{-1}.h^{-1} infusion MDZ	Before and during the procedure	Hemodynamic stability	Duration of surgery, the dosage of local anesthesia, vital signs, sedation score, pain, physician and patient satisfaction and recovery time.
Dental procedure (n = 19)	Yu [37]	Singapore	(19-60)	61.7	60	1, 2	Unilateral impacted teeth extraction	SBP, HR, SpO_2 and OAA/S	1: 0.5 μg.kg^{-1} DEX and 1μg.kg^{-1} fentanyl for 10 min + 0.5 μg.kg^{-1}.h^{-1} infusion DEX 2: 0.05 mg.kg^{-1} MDZ and 1 μg.kg^{-1} fentanyl for 10 min + 0.05 mg.kg^{-1}.h^{-1} infusion MDZ	Immediately before and during the procedure	No clear definition	Vital signs, sedation score, pain, preoperative anxiety, patient and physician satisfaction and total time for analgesic effect.
Gastroenterologic procedure (n = 39)	Akarsu [38]	Turkey	(18-80)	NR	121	1, 2	Colonoscopy	NIBP, ECG, pulse oximetry and BIS	1: 0.2 μg kg^{-1} h^{-1} DEX 2: 0.1 μg.kg^{-1} intranasal sufentanil; 3: 0.4 mg.kg^{-1} iv meperidine + 1 mg.kg^{-1} bolus propofol + 0.5-3 mg.kg^{-1}.h^{-1} infusion propofol 4: 0.4 mg.kg^{-1} iv meperidine + 0.03 mg.kg^{-1} iv midazolam + 0.5-3 mg.kg^{-1}.h^{-1} infusion propofol	NR	No clear definition	The total dose of propofol used, total sedation time, patient and physician satisfaction, sedation score, recovery time, total cost and adverse events and complications.
	Amri [39]	Iran	(20-70)	52.5	80	1, 2	Colonoscopy	NIBP, ECG and pulse oximetry	1: 1 μ.kg^{-1} bolus DEX + 0.5 μ kg^{-1} h^{-1} infusion DEX 2: 0.5 μ.kg^{-1} fentanyl + infusion normal saline	Until 10 min before and during the procedure	No clear definition	The analgesic effect, hemodynamic stability, duration of colonoscopy, patient and physician satisfaction and adverse events and complications.
	Bavullu [40]	Turkey	NR	NR	40	NR	Percutaneous treatment of hepatic hydatid cyst	NIBP, ECG, end-tidal CO_2, SpO_2, BIS and modified OAA/S score	1: 1 μg.kg^{-1} bolus DEX for 10 min + 0.2 μg.kg^{-1}.h^{-1} infusion DEX 2: 0.07 mg.kg^{-1} iv bolus MDZ + 0.01 mg.kg^{-1}.h^{-1} infusion MDZ	Before and during the procedure	No clear definition	Need for additional doses of propofol infusion and sedation score.
	Cheung [41]	China	(18-60)	NR	50	1, 2, 3	Upper gastrointestinal endoscopy	HR, BP, SpO_2, RR and OAA/S score	1: 0.015 mL.kg^{-1} intranasal undiluted DEX 2: 0.015 mL.kg^{-1} intranasal placebo	1h before the procedure	Total consumption of PCS propofol	Sedation scores, recovery profile, vital signs, adverse events and complications and patient satisfaction.
	Cho [42]	Republic of Korea	NR	85.9	66	1, 2	Drug-induced sleep endoscopy	NIBP, ECG, pulse oximetry, end-tidal CO_2, BIS and OAA/S score	1: 1.0 μg.kg^{-1} bolus DEX for 10 min + 0.2 μg.kg^{-1}.h^{-1} (initial rate) infusion DEX + 1.5 ng.mL^{-1} Ce infusion remifentanyl 2: 1.0 μg.mL^{-1} propofol + infusion normal saline 3: 1.0 μg.mL^{-1} propofol + 1.5 ng.mL^{-1} Ce remifentanyl	NR	Incidence of oxygen desaturation	Incidence of cough reflex, hemodynamic stability, time until sufficient sedation, sedation score and adverse events and complications.
	Demiraran [43]	Turkey	(18-60)	NR	50	1, 2	Upper gastrointestinal endoscopy	HR, MAP, SpO_2 and RR	1: 1 μg.kg^{-1} iv infusion DEX for 10 min + 0.2 μg.kg^{-1}.h^{-1} infusion DEX 2: 0.07 mg.kg^{-1} (max 5 mg) iv MDZ	Before and during the procedure	No clear definition	Respiratory and hemodynamic effects, patient and physician satisfaction, adverse events and complications, analgesic effect and sedation score.

Table 1 (*Continued*)

NORA setting	Study	Country	Age (yr)	Male (%)	Sample size	ASA physical status	Type of procedure	Monitorization	Intervention/comparator	Timing of DEX injection	Main outcome	Other outcomes
	Dere [44]	Turkey	(20-80)	NR	60	1, 2	Colonoscopy	NIBP, ECG, pulse oximetry and RSS	1: 1 mg.kg^{-1} iv infusion DEX for 10 min + 1 mg.kg^{-1} iv fentanyl + 0.5 mg.kg^{-1}.h^{-1} infusion DEX 2: 0.05 mg.kg^{-1} iv MDZ + 1 mg.kg^{-1} iv fentanyl + 0.1 mL.kg^{-1}.h^{-1} infusion normal saline	Before and during the procedure	No clear definition	Hemodynamic effects, sedation score, pain, satisfaction score and recovery score.
	Eberl [45]	The Netherlands	NR	80.6	63	1, 2, 3	Endoscopic esophageal procedures	NIBP, ECG, SpO_2, HR, end-tidal CO_2, NICO, stroke volume, systemic vascular resistance and OAA/S score	1: 1 mg.kg^{-1} (if > 65yr, 0.5 mg kg^{-1}) iv bolus DEX for 10 min + 0.7^{-1} mg.kg^{-1} h^{-1} infusion DEX 2: 2.0 mg mL^{-1} (targeted plasma concentration) propofol	Before and during the procedure	Patient and physician satisfaction	Safety of sedation (hemodynamic and respiratory effects).
Gastroenterologic procedure (n = 39)	Eldesuky [46]	Saudi Arabia	(18-60)	58	50	1, 2	ERCP	HR, MAP and SpO_2	1: 1 µg.kg^{-1} iv DEX for 10 min + 0.5 µg.kg^{-1}.h^{-1} infusion DEX 2: 1 mg.kg^{-1} ketofol for 10 min + 50 µg.kg^{-1}.min^{-1} ketofol	Before and during the procedure	No clear definition	Respiratory and hemodynamic effects, sedation score, pain, recovery time, patient and physician satisfaction and adverse events and complications.
	Elkalla [47]	Egypt	(18-50)	61.7	60	1, 2, 3	Drug-induced sleep endoscopy	NIBP, ECG, pulse oximeter and RSS	1: 1 µg.kg^{-1} iv DEX for 10 min + 0.3 µg.kg^{-1}.h^{-1} infusion DEX 2: 0.7 mg.kg^{-1} iv propofol for 10 min + 0.5 mg.kg^{-1}.h^{-1} infusion propofol 3: 1 mg.kg^{-1} ketofol (2 mg.mL^{-1} propofol + 2 mg mL^{-1} ketamine) for 10 min + 50 µg.kg^{-1}.h^{-1} infusion ketofol	Before and during the procedure	Incidence of oxygen desaturation	Hemodynamic effects, time to achieve sufficient sedation level, recovery time, patient and physician satisfaction and adverse events and complications.
	Goyal [48]	India	(18-75)	71.1	90	1, 2, 3	ERCP	Noninvasive MAP, ECG, SpO_2, HR and impedance pneumography	1: 0.5 µg.kg^{-1} DEX and 1 mg.kg^{-1} ketamine in 2 divided boluses of each drug, alternately, for 30 seconds + 0.5 mg.kg^{-1}.h^{-1} infusion DEX + 1-2 mg.kg^{-1}.h^{-1} ketamine 2: 1 µg.kg^{-1} fentanyl + 1 mg.kg^{-1} bolus propofol + 2-4 mg.kg^{-1}.h^{-1} infusion propofol	Before and during the procedure	Efficacy and safety.	NR
	Hashiguchi [49]	Japan	(38-54)	100	100	NR	Upper gastrointestinal endoscopy	NIBP, HR, SpO_2, RSS, mSAS and GRS	1: 6.0 µg.kg^{-1}.h^{-1} infusion DEX for 10 min + 0.6 µg.kg^{-1}.h^{-1} infusion DEX 2: 0.05 iv infusion MDZ for 1 min 3: Not sedated	Before and during the procedure	No clear definition	Sedative properties, safety profile, respiratory and hemodynamic effects, characteristics of scope insertion and patient perception of the procedure.
	Jalowiecki [50]	Poland	(18-60)	42.2	64	1, 2	Colonoscopy	HR, MAP, SpO_2, RR and OAA/S score	1: 1 µg.kg^{-1} iv infusion DEX for 15 min + 0.2 µg.kg^{-1}.h^{-1} infusion DEX 2: 1 mg.kg^{-1} iv meperidine + 0.05 mg.kg^{-1} iv MDZ 3: Not sedated, but were given 0.1-0.2 mg iv fentanyl in response to pain	Before and during the procedure	No clear definition	Respiratory and hemodynamic effects, analgesia/sedation score, adverse events and complications and patient readiness for home discharge.
Gastroenterologic procedure (n = 39)	Karanth [51]	India	(25-60)	66.7	60	1, 2	Colonoscopy	NIBP, ECG, pulse oximeter and modified OAA/S score	1: 1 µg.kg^{-1} iv DEX for 10 min + 0.2-0.8 µg.kg^{-1}.h^{-1} infusion DEX 2: 2-3 mg.kg^{-1} iv propofol for 10 min iv + 25-100 µ.kg^{-1}.min^{-1} infusion propofol	Before and during the procedure	No clear definition	Efficacy
	Kilic [52]	Turkey	(18-80)	62	50	1, 2	ERCP	Noninvasive SBP, DBP and MAP, HR, SpO_2, RR and RSS	1: 1 µg.kg^{-1}.h^{-1} bolus DEX + 0.2-0.7 µg.kg^{-1}.h^{-1} infusion DEX 2: 0.04 mg.kg^{-1} iv bolus MDZ +	Before and during the procedure	Respiratory, hemodynamic, sedative and	Patient degree of comfort and usefulness of the drug to surgeons.

Table 1 (*Continued*)

NORA setting	Study	Country	Age (yr)	Male (%)	Sample size	ASA physical status	Type of procedure	Monitorization	Intervention/comparator	Timing of DEX injection	Main outcome	Other outcomes
									0.5 mg bolus MDZ until RSS score 3-4		cognitive effects	
	Kim [53]	Republic of Korea	NR	69.5	60	1, 2, 3	Endoscopic submucosal dissection	SpO_2, SBP and DBP, ECG, HR and modified OAA/S score	1: 0.5 $\mu g.kg^{-1}$ iv bolus DEX for 5 min + 0.3-0.7 $\mu g.kg^{-1}.h^{-1}$ infusion DEX 2: 0.5 $mg.kg^{-1}$ bolus propofol + 30 $\mu g.kg^{-1}.min^{-1}$ infusion propofol	5 min before the procedure	No clear definition	Efficacy (ease of advancing the scope, gastric motility and patient and physician satisfaction) and patient safety (respiratory and hemodynamic effects, adverse events and complications and the total amount of sedative drug and remifentanil used).
	Kinugasa [54]	Japan	(18-90)	51.3	80	NR	Endoscopic submucosal dissection	BP, SpO_2, HR, BIS and RASS	1: 6.0 $\mu g.kg^{-1}.h^{-1}$ infusion DEX for 5 min + 0.4 $\mu g.kg^{-1}.h^{-1}$ infusion DEX 2: 6.0 $\mu g.kg^{-1}.h^{-1}$ infusion placebo for 5 min + 0.4 $\mu g.kg^{-1}.h^{-1}$ infusion placebo	Before and during the procedure	Patient satisfaction	Patient pain level, physician satisfaction, objective patient pain level viewed from the physician's perspective, patient movement, the difficulty of the procedure, rate of patient response, rate of *en bloc*, rate of R0 resection, resection time, resected tumor size, the total amount of analgesic used, rate of adverse events and complications.
	Koruk [55]	Turkey	(20-78)	45	40	1, 2, 3	ERCP	MAP, SpO_2, HR, RR and BIS	1: 1 $\mu g.kg^{-1}$ iv DEX for 10 min + 1-1.5 $mg.kg^{-1}$ bolus propofol + 20 mg intermittent bolus propofol until desired sedation level 2: 0.05 $mg.kg^{-1}$ iv MDZ for 10 min + 1-1.5 $mg.kg^{-1}$ bolus propofol + 20 mg intermittent bolus propofol until desired sedation level	Before the procedure	Recovery time	Respiratory and hemodynamic effects.
	Kuyrukluyıldız [56]	Turkey	(18-50)	NR	40	1, 2	Drug-induced sleep endoscopy	MAP, RR, SpO_2, HR, RSS and BIS	1: 1 $\mu g.kg^{-1}$ iv DEX for 10 min + 0.3 $\mu g.kg^{-1}.h^{-1}$ infusion DEX (up titrated by 0.1 $\mu g.kg^{-1}.h^{-1}$ every 5 min until desired sedation level - max 0.6 $\mu g.kg^{-1}.h^{-1}$) 2: 0.7 $mg.kg^{-1}$ iv propofol for 10 min + 0.5 $mg.kg^{-1}.h^{-1}$ infusion propofol (up titrated by 0.1 $mg.kg^{-1}.h^{-1}$ every 5 min until desired sedation level)	Before and during the procedure	No clear definition	The sedative effect, hemodynamic and respiratory effects and patient and physician satisfaction.
	Lee [57]	Republic of Korea	(20-80)	58.2	116	1, 2, 3	ERCP	MAP, RR, SpO_2, RSS and BIS	1: 1 $\mu g.kg^{-1}.h^{-1}$ iv infusion DEX 2: normal saline	15 min before insertion of the scope	Sedation score and requirement for additional sedative (MDZ) or analgesic (meperidine)	Total procedure time, time until discharge, pain, patient satisfaction, BIS score and adverse events and complications.
Gastroenterologic procedure (n = 39)	Lee [58]	Republic of Korea	(20-80)	85	80	1, 2	Endoscopic submucosal dissection	BP, ECG, pulse oximetry, HR, RR and modified OAA/S score	1: 1 $\mu g.kg^{-1}$ iv bolus DEX for 10 min + 0.4 $\mu g.kg^{-1}.h^{-1}$ infusion DEX 2: 0.1 $mL.kg^{-1}.h^{-1}$ normal saline for 10 min + 0.05 $mg.kg^{-1}$ (max 5 mg) iv MDZ	Before and during the procedure	Suitability of drugs for sedation	Safety, patient and physician satisfaction, total procedure time, complete resection rate, additional MDZ used, frequency of body movements, rapidity of recovery and adverse events and complications.
	Lu [59]	China	(18-85)	52.6	208	1, 2, 3	ERCP					

Table 1 (*Continued*)

NORA setting	Study	Country	Age (yr)	Male (%)	Sample size	ASA physical status	Type of procedure	Monitorization	Intervention/comparator	Timing of DEX injection	Main outcome	Other outcomes
								Noninvasive SBP, DBP and MAP, HR, RR, SpO_2 and RSS	1: 1 μg.kg^{-1} bolus (if > 65 yr, 0.5 μg.kg^{-1}) DEX for 10 min + 0.05-0.2 μg.kg^{-1}.min^{-1} infusion remifentanyl 2: 0.05 mg.kg^{-1} MDZ (titrated slowly with 1 mg.mL^{-1} diluted formula) + 0.05-0.2 μg.kg^{-1}.min^{-1} infusion remifentanyl	Before the procedure	Efficacy and safety	Respiratory and hemodynamic effects, sedation score, recovery score and adverse events and complications.
	Mazanikov [60]	Finland	(34-65)	84	50	1, 2, 3	ERCP	HR, ECG, RR, end-tidal CO_2, SpO_2, modified OAA/S score and Gillham score	1: 1 μg.kg^{-1} infusion DEX for 10 min + 0.7 μg.kg^{-1}.h^{-1} iv infusion DEX 2: Normal saline + 300 mL h^{-1} Ringer acetate	Before and during the procedure	Propofol consumption	Sedation score, sedation success rate, adverse events and complications, vital signs, pain, recovery time and patient and physician satisfaction.
	Mukhopadhyay [61]	India	NR	44	45	1, 2, 3	ERCP	BP, HR, ECG, RR, SpO_2, RSS and RASS	1: 1 μg.kg^{-1} infusion DEX for 7-10 min + 0.2-0.5 μg.kg^{-1}.h^{-1} infusion DEX for ≥ 30 min + 0.5 mg iv MDZ + 6 mg iv pentazocine + 25 mg iv ketamine + 0.75^{-1} mg.kg^{-1} iv propofol + 10-20 mg iv propofol as top up 2: 1 mg iv MDZ + 0.75^{-1} mg.kg^{-1} iv propofol + 10-20 mg iv propofol as top up 3: 0.5 mg iv MDZ + 6 mg iv pentazocine + 25 mg iv ketamine + 0.75-1 mg.kg^{-1} iv propofol + 10-20 mg iv propofol as top up	Before and during the procedure, but an attempt was made to stop the infusion 15-20 min before the end of the procedure	No clear definition	Sedation score, efficacy and adverse events and complications.
	Muller [62]	Brazil	(20-78)	26.9	26	1,2,3	ERCP	BP, HR, RR, end-tidal CO_2, SpO_2 and RASS	1: 1.0 μg.kg^{-1} bolus DEX for 10 min + 0.7 μg.kg^{-1}.h^{-1} iv DEX until desired sedation level 2: 1.5 μg.mL^{-1} Ce infusion propofol (titrated by 0.2 μg.mL^{-1} until desired sedation level)	Before and during the procedure	Sedation score and requirement of additional sedative or analgesic	Vital signs.
Gastroenterologic procedure (n = 39)	Nonaka [63]	Japan	(52-86)	81.03	58	1, 2	Gastric endoscopic submucosal dissection	ECG, BP, pulse oximetry, capnography and modified OAA/S scale	1: 6 μg.kg^{-1}.h^{-1} infusion DEX for 10 min + 20 mg iv bolus propofol repeated until desired sedation level + 0.5 μg.kg^{-1}.h^{-1} infusion DEX + 2 mg.kg^{-1}.h^{-1} infusion propofol 2: 20 mg iv bolus propofol repeated until desired sedation level + 2 mg.kg^{-1}.h^{-1} infusion propofol	Before and during the procedure	Physician satisfaction	Effectiveness and safety.
	Padiyara [64]	India	(18-65)	87	60	1, 2	Drug-induced sleep endoscopy	NIBP, ECG, pulse oximetry and BIS	1: 1 μg.kg^{-1} bolus DEX for 10 min + 0.5-1.0 μg.kg^{-1}.h^{-1} infusion DEX titrated until desired sedation level 2: 50-150 μg.kg^{-1}.min^{-1} infusion propofol titrated until desired sedation level	NR	Airway obstruction pattern at tongue base level	Airway obstruction (at velum, oropharyngeal lateral wall, and epiglottis), hemodynamic and respiratory effects, time until sufficient sedation, recovery time and adverse events and complications.
	Pushkarna [65]	India	(40-80)	53.3	60	2, 3	ERCP	HR, MAP and SpO_2	1: 1 μg.kg^{-1} iv DEX for 10 min + 0.5 μg.kg^{-1}.h^{-1} infusion DEX 2: 0.05 mg.kg^{-1} iv bolus MDZ for 10 min + infusion normal saline	NR	Requirement of propofol and patient and physician comfort.	Recovery characteristics and patient and physician satisfaction.
	Ramkiran [66]	India	(18-75)	57.3	75	1, 2,3	ERCP	NIBP, ECG, pulse oximeter and BIS	1: 1 μg.kg^{-1} bolus DEX + 0.5 μg.kg^{-1}.h^{-1} infusion DEX 2: 0.25 mg.kg^{-1} bolus ketamine +	After patient positioning and	Total propofol consumption	Recovery profile and hemodynamic profile.

Table 1 (*Continued*)

NORA setting	Study	Country	Age (yr)	Male (%)	Sample size	ASA physical status	Type of procedure	Monitorization	Intervention/comparator	Timing of DEX injection	Main outcome	Other outcomes
									infusion 5 μg. kg^{-1} min^{-1} infusion ketamine 3: Bolus normal saline + infusion normal saline	during the procedure		
	Takimoto [67]	Japan	(47-80)	47	90	NR	Endoscopic submucosal dissection	BP, HR, SpO_2, ECG and RSS	1: 3 μg kg^{-1} h^{-1} iv DEX for 5 min + 0.4 μg kg^{-1} h^{-1} iv DEX 2: 5 mg iv propofol + 3 mg. kg^{-1}. h^{-1} iv propofol 3: 0.1 mg.kg^{-1} MDZ	Before and during the procedure	No clear definition	BP, HR, SpO_2, ECG, body movement, additional doses of midazolam and sedation score.
	Trivedi [68]	India	(18-40)	35.6	90	1, 2	Short surgical procedures	NIBP, ECG and HR	1: 0.5 μg.kg^{-1} DEX in 10 mL normal saline for 10 min + 2 mg.kg^{-1} ketamine 2: 0.05 mg.kg^{-1} MDZ in 10 mL normal saline for 10 min + 2 mg. kg^{-1} ketamine 3: 10 mL normal saline for 10 min + 2 mg.kg^{-1} ketamine	Before the procedure	No clear definition	Delirium, hemodynamic stability and pain.
	Wu (2014)	China	(20-60)	55	60	1, 2	Upper gastrointestinal endoscopy	NIBP, ECG, pulse oximetry and RSS	1: 0.3 mg.kg^{-1} bolus DEX and 1 mg.kg^{-1} iv infusion fentanyl citrate for 10 min + 0.2-0.3 mg. kg^{-1}.h^{-1} infusion DEX until desired sedation level 2: 0.05 mg.kg^{-1} iv bolus MDZ and 1 mg.kg^{-1} iv infusion fentanyl citrate for 10 min + 0.01 mg.kg^{-1} bolus MDZ every 2-5 min until desired sedation level	10 min before procedure	No clear definition	Time to full sedation, recovery time, adverse events and complications, patient satisfaction, sedation score and pain.
Gastroenterologic procedure (n = 39)	Wu [69]	China	(18-65)	40	70	1, 2	Esophago-gastroduodenoscopy	NIBP, ECG, pulse oximetry, RR	1: 1 μg.kg^{-1} DEX + 0.5 μg.kg^{-1}. h^{-1} infusion DEX until desired sedation level 2: 0.6 mg.kg^{-1} bolus propofol + 10-20 mg doses propofol until desired sedation level	Immediately before the procedure	No clear definition	Hemodynamics and respiratory effects, sedation score, recovery profile, adverse events and complications and patient and physician satisfaction.
	Yin (2019)	China	(60-80)	44.2	120	1, 2, 3	Gastrointestinal endoscopy	NIBP, ECG, pulse oximetry, end-tidal CO_2 and RSS	1: 0.4 μg.kg^{-1} infusion DEX for 5 min + 1 mg.kg^{-1} infusion propofol for 30s + 3-5 mg.kg^{-1}.h^{-1} infusion propofol 2: 0.1 μg.kg^{-1} infusion sufentanil for 5 min + 1 mg.kg^{-1} infusion propofol for 30s + 3-5 mg.kg^{-1}. h^{-1} infusion propofol 3: 0.4 mg.mL^{-1} infusion ketamine for 5 min + 1 mg.kg^{-1} infusion propofol for 30s + 3-5 mg. kg^{-1}.h^{-1} infusion propofol 4: Normal saline + 1 mg.kg^{-1} infusion propofol for 30s + 3-5 mg.kg^{-1}.h^{-1} infusion propofol	Before the procedure	Hemodynamic and respiratory stability	Sedation score, total propofol consumption, recovery time, adverse events and complications and the use of additional medications.
Gynecology procedure (n = 2)	Elnabtity [70]	Saudi Arabia	(25-38)	0	52	1, 2	In vitro fertilization	BP monitor, ECG, pulse oximeter and RSS	1: 1 μg.kg^{-1} iv DEX for 10 min + 0.5 μg.kg^{-1}.h^{-1} infusion DEX 2: 0.06 mg.kg^{-1} iv MDZ for 10 min + 0.5 mg incremental doses MDZ	Before and during the procedure	Pain relief and patient satisfaction	NR
	Sethi [71]	India	(18-60)	NR	50	1, 2	Dilatation and curettage	HR, SBP, DBP, MAP, RR, SpO_2 and RSS	1: 1 μg.kg^{-1} iv DEX for 10 min + 0.5 μg.kg^{-1}.h^{-1} infusion DEX 2: 1.5 mg.kg^{-1} iv bolus propofol for 10-15 min	NR	Hemodynamic and respiratory effects	Recovery profile and patient and physician satisfaction and adverse events and complications.
		Iran	(18-70)	NR	68	2, 3, 4						

Table 1 (*Continued*)

NORA setting	Study	Country	Age (yr)	Male (%)	Sample size	ASA physical status	Type of procedure	Monitorization	Intervention/comparator	Timing of DEX injection	Main outcome	Other outcomes
Hemodynamic lab procedure (n = 13)	Alizadehasl [72]						Transoesophageal echocardiography	NIBP, ECG, pulse oximetry, BIS and RSS	1: 1 $\mu g.kg^{-1}$ infusion DEX for 10 min + 0.1-0.5 $\mu g.kg^{-1}.h^{-1}$ DEX 2: 0.1 $mg.kg^{-1}$ propofol + 25-75 $\mu g.kg^{-1}.min^{-1}$ propofol	Before and during the procedure	No clear definition	Sedation scores, hemodynamic stability, recovery time and total procedure time.
Hemodynamic lab procedure (n = 13)	Cho [73]	Republic of Korea	(20-70)	NR	90	1, 2	AF catheter ablation	NIBP, ECG, SpO_2 and RR	1: 1.0 $mg.kg^{-1}$ bolus DEX for 10 min + 0.2-0.7 $mg.kg^{-1}.h^{-1}$ infusion DEX + 1.2-2.4 $mg.kg^{-1}.h^{-1}$ infusion remifentanyl 2: 0.02-0.05 $mg.kg^{-1}$ bolus MDZ + 3.6-7.2 $mg.kg^{-1}.h^{-1}$ infusion remifentanyl	Before and during the procedure	Sedation score	Incidence of adverse events and complications, pain score and patient and physician satisfaction.
	Cooper [74]	USA	(18-65)	NR	22	1, 2, 3, 4	Transoesophageal echocardiography	NIBP, ECG, pulse oximetry, HR, RR and RSS	1: 1 $\mu g.kg^{-1}$ DEX for 15 min + 0.2 $\mu g.kg^{-1}.h^{-1}$ infusion DEX 2: Normal saline for 15 min + infusion normal saline	Before and during the procedure	Adequacy of sedation and patient satisfaction	NR
	Khalil [75]	Egypt	NR	66	50	3, 4	Transcatheter aortic valve implantation	Invasive BP, ECG, pulse oximetry, capnography, RRS and BIS	1: 1 $\mu g.kg^{-1}$ DEX + 0.5 $\mu g.kg^{-1}.h^{-1}$ iv infusion DEX 2: 0.5 $mg.kg^{-1}$ bolus propofol + 30-50 $\mu g.kg^{-1}.min^{-1}$ infusion propofol	NR	No clear definition	Pain, patient and physician satisfaction, sedation score and adverse events and complications.
	Prachanpanich [76]	Thailand	NR	29.4	34	NR	Electrophysiology study	HR, BP, SpO_2 and modified OAA/S score	1: 0.5 $\mu g.kg^{-1}$ infusion DEX for 10 min + 0.4 $\mu g.kg^{-1}.h^{-1}$ infusion DEX 2: 1 $mg.kg^{-1}$ propofol for 10 min + 3 $mg.kg^{-1}.h^{-1}$ propofol	NR	RR	Sedation score and hemodynamic and respiratory effects.
	Sairaku [77]	Japan	(18-75)	80	88	NR	Atrial fibrillation ablation	NIBP, SpO_2, HR and RASS	1: 1.0 $\mu g.kg^{-1}$ DEX for 10 min + 0.2 $\mu g.kg^{-1}.h^{-1}$ infusion DEX 2: 1.25 $mg.kg^{-1}$ bólus iv thiamylal every 15 min	At the time of the venipuncture	Respiratory disturbance index	Movement index, adverse events and complications and sedation score.
	Sruthi [78]	India	(18-60)	44	50	NR	Transesophageal echocardiography	NIBP, ECG, HR, pulse oximetry, end-tidal CO_2 and RSS	1: 10 $\mu g.mL^{-1}$ infusion DEX 2: 3.2 mg ketamine and 9.5 $mg.mL^{-1}$ propofol infusion	Before and during the procedure	Time until desired sedation	Hemodynamic effects need for rescue sedation, adverse events and complications, patient and physician satisfaction, analgesic effect, total drug dose, total procedure time, and total recovery time.
	Loh [79]	Malaysia	(18-70)	53.3	30	1, 2	MRI	NIBP, ECG, pulse oximetry, HR and RSS	1: 1 $\mu g.kg^{-1}$ bolus DEX for 10 min + 0.2 $\mu g.kg^{-1}1.h^{-1}$ infusion DEX (up titrated by 0.1 $\mu g.kg^{-1}.h^{-1}$) until desired sedation level 2: 1.5 $\mu g.kg^{-1}$ propofol (up titrated by 0.1 $\mu g.kg^{-1}$) until desired sedation level	Before and during the procedure	Efficacy of sedation	Patient satisfaction, image quality and safety profile.
Invasive radiology procedure (n = 1)	Kim [80]	Republic of Korea	(30-50)	0	56	NR	Uterine artery embolization	NIBP, SpO_2 and HR	1: 0.2 $\mu g.kg^{-1}.h^{-1}$ infusion DEX for 30 min + 0.4 $\mu g.kg^{-1}.h^{-1}$ infusion DEX for 6h 2: Infusion normal saline	30 min before and during the procedure	Efficacy of dexmedetomidine in reduction of fentanyl consumption and adverse events and complications.	Pain and sedation score.
Neuroradiologic procedure (n = 3)	Ren [81]	China	(40-75)	52.3	109	1, 2, 3	Aneurysm embolization	NIBP, ECG, pulse SpO_2, temperature and BIS	1: 0.5 $\mu g.kg^{-1}$ infusion DEX for 10 min + 0.2 $\mu g.kg^{-1}.h^{-1}$ infusion DEX 2: 0.5 $\mu g.kg^{-1}$ infusion DEX for 10 min + 0.4 $\mu g.kg^{-1}.h^{-1}$ infusion DEX 3: Infusion normal saline	NR	Total consumption of nimodipine during the first 48 h after the procedure	Recovery time, pain, consumption of dexmedetomidine and sufentanil, patient and physician satisfaction, neurological examination, comfort, adverse events and complications, sedation score, the incidence of

Table 1 (*Continued*)

NORA setting	Study	Country	Age (yr)	Male (%)	Sample size	ASA physical status	Type of procedure	Monitorization	Intervention/comparator	Timing of DEX injection	Main outcome	Other outcomes
												symptomatic cerebral vasospasm during 7 days after the procedure, Glasgow Outcome Score at 3 months and incidence of cerebral infarction 30 days after the procedure.
	Sriganesh [82]	India	NR	45	60	NR	Cerebral angiography	NIBP, ECG, pulse oximetry, capnography and RSS	1: 1 $\mu g.kg^{-1}$ DEX for 10 min + 0.5 $\mu g.kg^{-1}.h^{-1}$ infusion DEX 2: 1.5 $mg.kg^{-1}$ bolus propofol + 1.5 $mg.kg^{-1}.h^{-1}$ infusion propofol	Before and during the procedure	Incidence of adverse respiratory events	Onset and recovery times, movement during the procedure and additional sedative needed to complete the procedure.
Orthopedic procedure (n = 1)	Masoumi [83]	Iran	(18-70)	86.7	60	NR	Reduction of anterior dislocation of the glenohumeral joint	NR	1: 1 $\mu g.kg^{-1}$ iv bolus DEX + 0.2 $\mu g.kg^{-1}.h^{-1}$ DEX for 10 min 2: 0.05 $mg.kg^{-1}$ iv MDZ and 1 $\mu g.kg^{-1}$ MDZ-fentanyl for 10 minutes	NR	No clear definition	Pain and onset time of sedation.
Psychiatric unit procedure (n = 1)	Sannakki [84]	India	(18-50)	63	30	1, 2	Electroconvulsive therapy	NIBP, ECG, pulse oximetry, RR, pneumatic tourniquet to assess motor seizures and RASS	1: 1 $\mu g.kg^{-1}$ DEX for 10 min 2: Normal saline	NR	No clear definition	Vital signs, duration of the motor seizure and recovery profile.
Upper airway procedure (n = 11)	El Mourad [85]	Egypt	(18-60)	70	80	1, 2, 3	Laryngeal mass biopsy	NIBP, ECG, pulse oximetry and RSS	1: 4 $\mu g.mL^{-1}$ iv bolus DEX for 10 min + 0.5 $\mu g.kg^{-1}.h^{-1}$ infusion DEX + 4 $mg.mL^{-1}$ infusion propofol (same rate as DEX) 2: 0.125 $mL.kg^{-1}$ Ketofol (4 $mg.mL^{-1}$ propofol + 2 $mg.mL^{-1}$ ketamine) for 10 min + 0.125 $mL.kg^{-1}.h^{-1}$ infusion Ketofol (4 mg mL^{-1} propofol and 2 $mg.mL^{-1}$ ketamine) + infusion normal saline (same rate as ketofol)	NR	Time to reach sufficient sedation level	Intubation time and the number of intubation trials, the number of patients in need of rescue propofol, patient discomfort, patient tolerance to the procedure, cough score, vital signs, adverse events and complications and patient and physician satisfaction.
	Gonepapana-var [86]	India	(18-70)	77.2	57	1, 2, 3	Flexible bronchoscopy	NIBP, ECG, pulse oximeter, HR, RR and RSS	1: 1 $\mu g.kg^{-1}$ infusion DEX + bolus normal saline 2: 0.02 $mg.kg^{-1}$ bolus MDZ + infusion normal saline	10 min before and during the procedure	A composite score for best patient tolerance and improved fiberscopist comfort without compromising patient safety	NR
	Gu [87]	China	NR	58.3	63	1, 2	Flexible bronchoscopy	NIBP, ECG, SpO_2 and BIS	1: 0.6 $\mu g.kg^{-1}$ nebulized DEX + 10 mL nebulized 2% lidocaine 2: 0.6 $\mu g.kg^{-1}$ iv DEX + 10 mL nebulized 2% lidocaine 3: 10 mL nebulized 2% lidocaine	During the procedure	Incidence of moderate to severe coughing	Rate of glottis closure, complete jaw relaxation and limb movement, recovery time and dosages of vasoconstrictors and atropine.
	Liao [88]	China	NR	62.2	226	NR	Flexible bronchoscopy	NIBP, ECG, SpO_2 and RSS	1: 1 $\mu g.kg^{-1}$ infusion DEX for 10 min + 0.5 $\mu g.kg^{-1}.h^{-1}$ infusion DEX 2: 2 mg MDZ ± 1 mg iv boluses MDZ (as needed)	Before and during the procedure	Mean lowest SpO_2	Respiratory and hemodynamic effects, patient tolerance of procedure and cough scores.
	Ma [89]	China	NR	NR	60	1, 2	Radiofrequency volume tissue reduction	Noninvasive MAP, HR, ECG, pulse oximeter, end-tidal CO_2, RSS and BIS	1: 1.0 $\mu g.kg^{-1}$ infusion DEX for 10 min + 0.7 $\mu g.kg^{-1}.h^{-1}$ iv DEX until desired sedation level 2: 1.5 $\mu g.mL^{-1}$ Ce infusion propofol (titrated by 0.2 $\mu g.ml^{-1}$) until desired sedation level	Before and during the procedure	No clear definition	Sedation score, analgesic effects, pain, patient tolerability and satisfaction, airway obstruction score, consumption of study drugs, final propofol Ce, adverse events and

Table 1 (*Continued*)

NORA setting	Study	Country	Age (yr)	Male (%)	Sample size	ASA physical status	Type of procedure	Monitorization	Intervention/comparator	Timing of DEX injection	Main outcome	Other outcomes
												complications and need for atropine, esmolol, adrenaline or requirement for supplemental analgesia.
Upper airway procedure (n = 11)	Magazine [90]	India	(18-65)	61.1	54	NR	Flexible bronchoscopy	NIBP, HR, RR, SpO_2 and RSS	1: 0.5 $\mu g.kg^{-1}$ infusion DEX for 10 min + normal saline 2: Normal saline + 0.035 mg kg^{-1} MDZ	Before the procedure	Composite score (sedation, respiratory response, calmness, facial tension and physical movement)	Pain, respiratory and hemodynamic effects, number of doses of rescue MDZ, duration of the procedure, total lignocaine used, cough, ease of the procedure and postprocedural patient response.
	Riachy [91]	Lebanon	(18-70)	52.5	162	NR	Flexible bronchoscopy	BP, HR, RR, SpO_2, ECG and end-tidal CO_2	1: 0.5 $\mu g.kg^{-1}$ iv infusion DEX + 2 mL iv infusion normal saline 2: iv infusion normal saline + 10 $\mu g.kg^{-1}$ iv infusion alfentanil 3: iv infusion normal saline + 2 mL iv infusion normal saline	5 min before procedure	No clear definition	Bronchoscopy feasibility, sedation score, tolerance to the procedure and adverse events and complications.
	Ryu [92]	Republic of Korea	(18-70)	66.7	72	1, 2, 3	Flexible bronchoscopy	NIBP, ECG, pulse oximetry and modified OAA/S score	1: 0.5 $mg.kg^{-1}$ infusion propofol + 0.05 $mL.kg^{-1}$ bolus DEX (4 $\mu g.mL^{-1}$) + 0.1-0.5 $mL.kg^{-1}.h^{-1}$ infusion DEX (4 $\mu g.mL^{-1}$) 2: 0.5 $mg.kg^{-1}$ infusion propofol + 0.05 $mL.kg^{-1}$ bolus remifentanyl (10 $\mu g.ml^{-1}$) + 0.1-0.5 $ml.kg^{-1}.h^{-1}$ infusion remifentanyl (10 $\mu g.ml^{-1}$)	NR	Incidence of oxygen desaturation and oxygen saturation trend	Hemodynamic effects, cough score, patient and physician satisfaction, requirements for oral cavity suction and instillation of topical anesthesia, adverse events and complications, sedation score, recovery time, the experience of the physician, bronchoscope diameters and procedure type.
	St-Pierre [93]	Canada	(18-75)	NR	60	1, 2, 3	Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration	NIBP, ECG, pulse oximetry, RR and OAA/S	1: 0.4 $\mu g.kg^{-1}$ iv bolus DEX for 10 min + 0.5-1.0 $\mu g.kg^{-1}.h^{-1}$ infusion DEX 2: 0.5 $\mu g.kg^{-1}$ iv bolus remifentanyl for 10 min + 0.05-0.25 $\mu g.kg^{-1}$ min^{-1} infusion remifentanyl	During the procedure	Number of major respiratory adverse events per patient	Vocal cords movement, the total dose of endotracheal lidocaine, sedation score, pain, amnesia, patient and physician satisfaction, discharge conditions, cumulative doses of vasopressors administered and adverse events and complications.
	Wu [94] (1)	Taiwan	NR	38.8	80	1, 2, 3	Flexible bronchoscopy	NIBP, ECG, HR, SpO_2, capnography and abdominal wall and chest excursions	1: 0.7 $\mu g.kg^{-1}$ bolus DEX for 10 min + 0.07 $\mu g.kg^{-1}.h^{-1}$ infusion DEX 2: 1 mg bolus MDZ ± 1 mg bolus MDZ repeated until desired sedation level	Before and during the procedure	Safety profile	Recovery profile, physician and patient satisfaction and postprocedural events.
	Yuan [95]	China	(20-75)	49	100	1, 2, 3	Flexible Bronchoscopy	NIBP, ECG and SpO_2 and modified OAA/S score	1: 1 $\mu g.kg^{-1}$ bolus DEX for 12 min + 0.5 $\mu g.kg^{-1}.h^{-1}$ infusion DEX 2: 2-4 $\mu g.mL^{-1}$ Ce infusion propofol	NR	Mean SpO_2 and hemodynamic effects	Cough, discomfort, willingness to repeat procedure, sedation score, duration of procedure and recovery time.
Urologic procedure (n = 9)	Akça [96]	Turkey	(18-75)	NR	75	1, 2	Cystoscopy	NIBP, ECG, pulse oximetry and RSS	1: 1 $\mu g.kg^{-1}$ DEX 2: 250 $\mu g.kg^{-1}$ iv ketamine 3: normal saline	5 min before the end of the procedure	No clear definition	CRBD, patient satisfaction and postoperative pain, sedation score and adverse events and complications.
	Alhashemi [97]	Saudi Arabia	(18-60)	NR	60	1, 2	ESWL	NIBP, ECG, pulse oximetry, AAI and OAA/S score	1: 1 $\mu g.kg^{-1}$ iv DEX for 10 min + 0.5 $\mu g.kg^{-1}.h^{-1}$ infusion DEX + 2 $mg.hr^{-1}$ infusion morphine + 2 mg PCA morphine (1 every 5 min) 2: 1.5 $mg.kg^{-1}$ iv tramadol premixed with 30 $\mu g.kg^{-1}$ MDZ for 10 min + infusion normal saline +	Before and during the procedure	Patient's pain (VAS scale)	Vital parameters, sedation scores, recovery score (TDT), patient and physician satisfaction, the total dose of analgesic used, number of PCA demand, number of shockwaves delivered, shockwave intensity and recovery time.

Table 1 (*Continued*)

NORA setting	Study	Country	Age (yr)	Male (%)	Sample size	ASA physical status	Type of procedure	Monitorization	Intervention/comparator	Timing of DEX injection	Main outcome	Other outcomes
									20 mg.h^{-1} infusion tramadol + 20 mg PCA tramadol (1 every 5 min)			
Urologic procedure (n = 9)	Arpaci [98]	Turkey	(20-70)	NR	40	1, 2	Cystoscopy	NIBP, ECG, pulse oximetry, VNS, OAA/S score, and BIS	1: 0.2-0.7 μg.kg^{-1}.h^{-1} infusion DEX 2: 0.05-0.15 μg.kg^{-1}.h^{-1} infusion MDZ	During the procedure	No clear definition	Total procedure time, adverse events and complications and type of treatment.
	Kaygusuz [99]	Turkey	(18-60)	47.5	46	1, 2	ESWL	RR, HR, noninvasive MAP, SpO_2 and modified OAA/S score	1: 6 μg.kg^{-1}.h^{-1} iv infusion DEX for 10 min + 0.2 μg.kg^{-1}.h^{-1} infusion DEX 2: 6 mg.kg^{-1}.h^{-1} iv infusion propofol for 10 min + 2.4 mg.kg^{-1}.h^{-1} infusion propofol	Before and during the procedure	Improved analgesia	Respiratory and hemodynamic effects, pain, patient satisfaction and adverse events and complications.
	Kumakura [100]	Japan	NR	80.6	36	1, 2, 3	TUR of Bladder	NIBP, ECG, pulse oximeter, temperature, regional cerebral tissue oxygen saturation and BIS.	1: 4 μg.kg^{-1}.h^{-1} iv DEX for 10 min + 0.4 μg.kg^{-1}.h^{-1} infusion DEX 2: 2 μg.mL^{-1} target-controlled infusion propofol	20 min after spinal anesthesia	Regional cerebral tissue oxygen saturation	SpO_2, MAP and HR.
	Modir [101]	Iran	(18-65)	51.7	60	1, 2	Cystoscopy	MAP, HR, RR, SpO_2 and RSS	1: 0.5 mg.kg^{-1} ketamine + 1 μg.kg^{-1} DEX 2: 0.5 mg.kg^{-1} ketamine +2 μg.kg^{-1} fentanyl	Before the procedure	Efficacy of sedation and analgesia	Sedation score, recovery score, physician satisfaction and adverse events and complications.
	Shariffuddin [102]	Malaysia	(18-65)	78.3	60	1, 2	Ureteroscopy and ureteric stenting	NIBP, ECG, pulse oximetry, HR and BIS	1: 0.5 μg.kg^{-1} iv DEX 2: Normal saline	Before general anesthesia	Minimum alveolar concentration	Postoperative pain, perioperative analgesia requirements, adverse events and complications and recovery profile.
	Tan [103]	China	(60-85)	100	96	1, 2, 3	TUR of Prostate	MAP, ECG, HR, pulse oximeter and BIS	1: 6 μg.kg^{-1}.h^{-1} iv DEX for 10 min + 1.2 μg kg^{-1} h^{-1} iv infusion DEX 2: 0.225 mg.kg^{-1}.h^{-1} iv MDZ for 10 min + 0.045 mg.kg^{-1}.h^{-1} iv infusion MDZ 3: Normal saline	10 min after spinal injection	Postoperative sleep quality	NR
	Zeyneloglu [104]	Turkey	(18-80)	52	50	1, 2	ESWL	NIBP, HR, RR, SpO_2 and OAA/S	1: 1.0 μg.kg^{-1} bolus DEX for 10 min + 0.2 μg.kg^{-1}.h^{-1} infusion DEX 2: 0.05 mg.kg^{-1} iv MDZ and 1 mg.kg^{-1} iv fentanyl for 10 min + infusion normal saline	5 min before and during the procedure	Recovery time	Pain, sedation score, procedure characteristics, number of shocks delivered and maximal voltage, patient satisfaction and effectiveness and safety.
	Huncke [105]	USA	NR	NR	55	1, 2, 3, 4	Not specified	BP, HR, RR, SpO_2 and OAA/S score	1: 1 μg.kg^{-1} DEX + 0.6 mg.kg^{-1}.h^{-1} infusion DEX 2: 0.5 μg.kg^{-1} DEX + 0.6 mg.kg^{-1}.h^{-1} infusion DEX 3: Normal saline + infusion normal saline	10 min before and during the procedure	Efficacy (percentage of patients not requiring MDZ)	Total doses of MDZ required for rescue sedation and the total dose of fentanyl required to treat pain.
	Samantaray [106]	India	(18-65)	77.8	54	NR	Central venous catheter insertion	SpO_2, RR, SBP, HR and modified OAA/S score	1: 1 μg.kg^{-1} infusion DEX for 10 min 2: Infusion normal saline	Before the procedure	Discomfort and pain	Sedation score, SpO_2 and hemodynamic and respiratory effects.
Vascular procedure (n = 5)	Samantaray [107]	India	(18-65)	56.7	60	1, 2	Central venous catheter insertion	HR, SBP, RR, SpO_2 and modified OAA/S score	1: 1 μg kg^{-1} infusion DEX for 10 min 2: 1 μg.kg^{-1} infusion fentanyl for 10 min 3: Infusion normal saline	Before the procedure	No clear definition	Discomfort, pain, sedation score and adverse events and complications.
	Wu [94] (2)	China	(40-75)	52.5	80	2, 3	Carotid artery stenting	BP, HR, RR and SpO_2 and RSS	1: 1 μg.kg^{-1} DEX + 0.5 μg.kg^{-1} bolus infusion DEX for 15 min + 0.6 μg.kg^{-1}.h^{-1} infusion DEX 2: 0.6 μg.kg^{-1}.h^{-1} normal saline	15 minutes before and during the procedure	No clear definition	Cognitive function, vital signs, sedation score and anxiety score.

Table 2 DEX compared to comparator in NORA.

Outcomes	N° of paripants (studies) follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with comparator	Risk difference with DEX
Time until full recovery	2052 (32 RCTs)	⊕⊕x̂x̂ Low[a]	—	MD 1.73 minutes higher (0.34 higher to 3.13 higher)	
Hypotension	2274 (33 RCTs)	⊕⊕⊕⊕ High[d]	OR 1.89 (1.43 to 2.48)	78 per 1000	60 more per 1000 (30 more to 95 more)
Bradycardia	1521 (21 RCTs)	⊕⊕⊕⊕ High[d]	OR 3.60 (2.29 to 5.67)	128 per 1000	218 more per 1000 (124 more to 327 more)
Desaturation	1394 (16 RCTs)	⊕⊕⊕x̂ Moderate[d]	OR 0.44 (0.21 to 0.91)	87 per 1000	47 fewer per 1000 (67 fewer to 7 fewer)
Nausea	1643 (25 RCTs)	⊕⊕⊕x̂ Moderate[c]	OR 1.06 (0.72 to 1.56)	84 per 1000	5 more per 1000 (22 fewer to 41 more)
Pain/Discomfort	(52 RCTs)	⊕x̂x̂x̂ Very low[b,c]	42.6% studies reported better control 42.6% studies reported similar control 7.7% reported insufficient control of pain/discomfort with DEX		
Amnesia and awareness of the procedure	(9 RCTs)	⊕x̂x̂x̂ Very low[b,c]	55.6% found no difference 44.4% studies reported inferior amnesic effects		
Physician satisfaction	(35 RCTs)	⊕x̂x̂x̂ Very low[b,c]	42.8% studies reported higher physician satisfaction 42.8% studies reported no differences 10.9% studies reported lower satisfaction		
Patient satisfaction	(48 RCTs)	⊕x̂x̂x̂ Very low[b,c]	33.3% studies reported higher patient satisfaction 58.3% studies reported similar patient satisfaction 8.3% studies reported lower patient satisfaction		
Grade of conscious sedation	(75 RCTs)	⊕⊕x̂x̂ Low[b]	34.7% studies reported better sedation profile 28.0% studies reported similar sedation profile 24.0% studies reported lower sedation profile		

*The risk in the intervention group (and its 95% Confidence Interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI, Confidence Interval; MD, Mean difference; OR, Odds Ratio; GRADE Working Group grades of evidence; High certainty, We are very confident that the true effect lies close to that of the estimate of the effect; Moderate certainty, We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect; Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Explanations:

[a] There was severe heterogeneity (I_2 = 96%), not fully explained by subgroup analysis.

[b] Heterogeneity in the reporting style.

[c] Some imprecision exists: Few events and wide confidence intervals.

[d] Some heterogeneity in the reporting style.

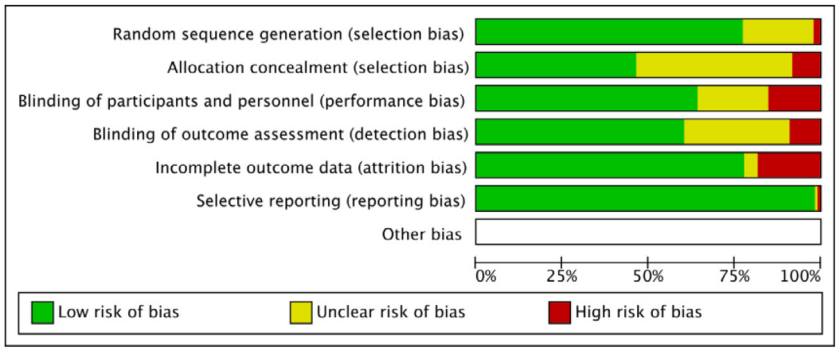

Figure 1 Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

Pain/Discomfort

Overall, 52 studies evaluated pain or discomfort as outcomes: 27 studies evaluated pain or discomfort during the procedure, 9 during recovery time, and 16 during both periods. The full description of pain definition and measurement can be found in Appendix III. The pain outcome measure most frequently used in the 52 eligible studies was the VAS score (0 no pain — 10 worst pain).

Regarding the analgesic properties of DEX, 42.6% studies reported better pain/discomfort control with DEX.[16,51,106,107,68,24,89,36,43,44,99,22,54,73,80,57,105,39,83,101,97,70,102] 42.6% studies reported similar analgesic effects with DEX, when compared with other drugs [15,90,108,78,23,25,81,109,95,96,19,52,27,33,35,92,46,85,75,37,93,31,50]; and 7.7% reported insufficient analgesia with DEX.[20,65,104,60]

Reporting of pain outcomes were mostly presented as repeated measures during procedure time, either presented as graphic evolution of pain score or in tables for different time sets. Due to this heterogeneity in the reporting style, no metanalysis was performed for this outcome [112].

Amnesia and awareness of the procedure

The ability to produce amnesia of the procedure was evaluated in 9 studies, using different methods of measurement and different reporting styles, therefore, no metanalysis was performed for this outcome (Appendix III).

Amnesic effects were inferior in DEX groups in 44.4% of studies.[28,108,23,35] However, in Togawa et al. [35], this difference was not statistically significant. The other studies (55.6%) found no difference in amnesic effects. It is important to note that midazolam was used in both the DEX group and the control group in 2 of these studies, [27,29] while St-Pierre et al. [93] compared DEX to remifentanil. Taniyama et al. [33] did not evaluate intraoperative recalling, and Hiwarkar et al. [17] did not perform statistical analyses.

Physician satisfaction

Overall, 35 studies evaluated physician satisfaction as an outcome. Every study used a different method to evaluate this outcome, for example, a VAS scale (0 being most unsatisfactory and 100 being most satisfactory),[61,63] NRS scale score (0 being least satisfied and 10 being most satisfied) [23,36] or a satisfaction score (4 = excellent, 3 = good, 2 = fair, and 1 = bad), [65,71,46,47,94] among others. Akarsu et al.,[38] Candiotti et al. [18] Mazanikov et al.,[60] Ren et al. [81] and Ryu et al. [92] did not report the scale applied. Due to this heterogeneity in the reporting style, no metanalysis was performed for this outcome.

Most of the studies reported a statistically significant higher physician satisfaction with DEX (n = 15; 42.8%), when compared to the control group, [61,65,30,71,36,98,43,52,63,73,58,18,97,37,94] or did not report any statistically significant difference between both groups (n = 15; 42.8%).[23,81,69,38,44,56,104,54,35,53,29,72,39,75,47] A few studies (n = 6; 10.9%) reported a statistically significant higher physician satisfaction in favor of the control group.[30,78,92,46,85,45]

Patient satisfaction

In total, 48 studies evaluated patient satisfaction as an outcome. The scales used were very different and included, for example, VAS score 10 cm,[61,89,69,54,35,57,58,29,75,26] a questionnaire,[109,74,34,45] a 7-point Likert scale [30,56,97,70,60] or a satisfaction score (4 = excellent, 3 = good, 2 = fair, and 1 = bad),[65,71,46,47,94] among others. Candiotti et al. [18] applied the Iowa Satisfaction with Anesthesia Scale. Akarsu et al.,[38] Amri et al. [39] Mishra et al. [28] and Ren et al. [81] did not report the scale applied. Due to this heterogeneity in the reporting style, no metanalysis was performed for this outcome.

Most of the studies did not report any statistically significant difference in patient satisfaction between the groups studied (n = 28; 58.3%).[61,78,41,23,25,81,36,38,96,43,56,35,73,53,58,92,74,29,39,85,75,26,37,60,47,93,79,94] However, 33.3% (n = 16) reported a statistically significant higher patient satisfaction with DEX, when compared with the control group,[28,65,30,71,89,109,98,44,52,22,54,57,18,34,97,70] and 8.3% (n = 4) studies reported a statistically significant higher patient satisfaction in favor of the control group.[69,104,46,45]

Grade of conscious sedation

Of the included studies, 75 evaluated the grade of sedation acquired during the procedure. The method used for accessing adequate sedation was not consistent and the different methods used can be found in summary in Appendix III.

Overall, the majority of the studies (62.6%) reported either a better sedation profile with DEX groups, with higher achievement of the desired level of sedation for the procedure (n = 26) [15,86,107,32,82,41,23,36,109,38,96,19,99,54,77,67,35,73,80,57,58,92,101,70,37,60]; or no difference at all when compared to the control groups (n = 21).[48,51,28,61,24,69,111,95,43,

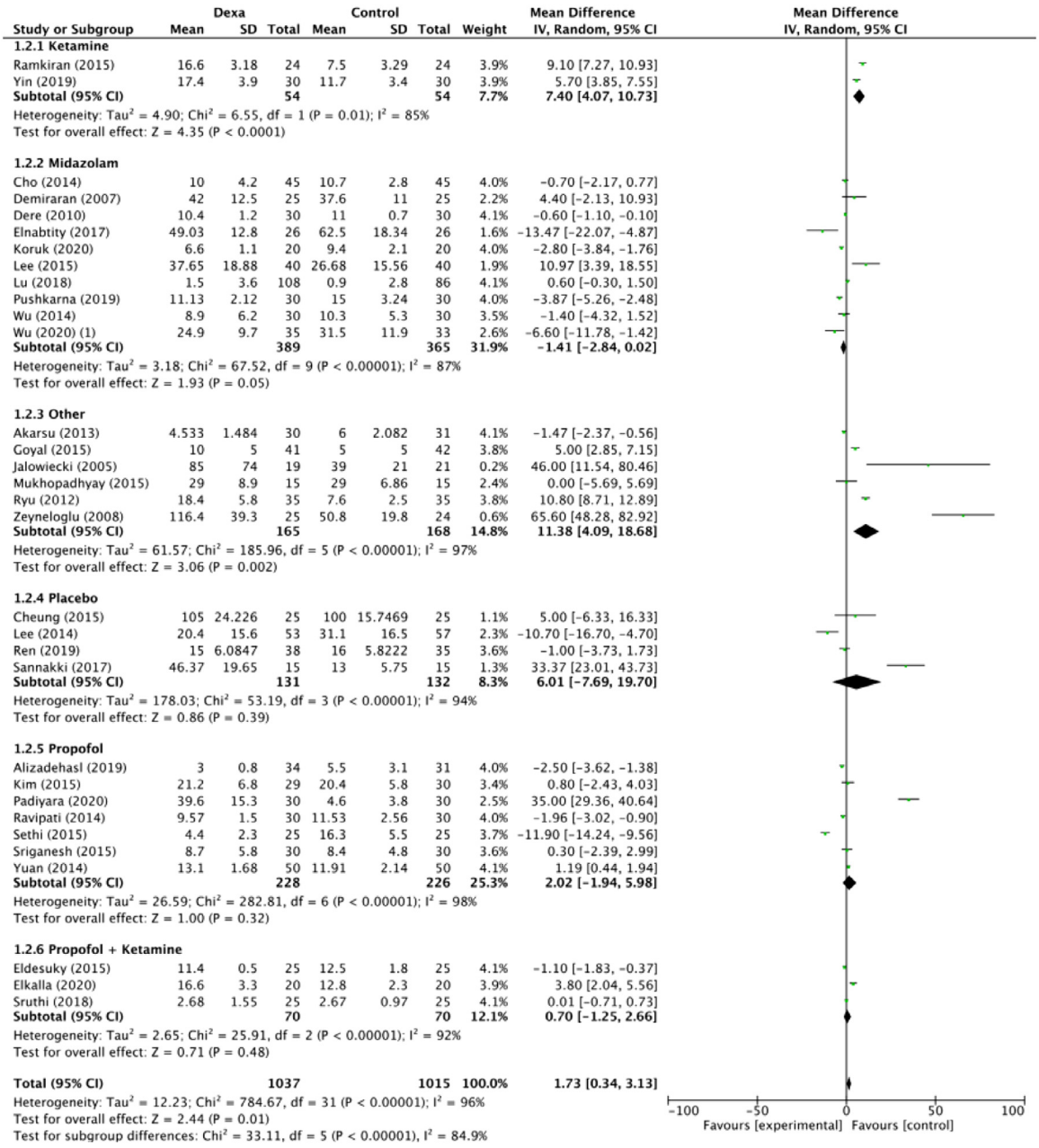

Figure 2 Forest plot of comparison: Time until recovery by control.

[52,55,53,74,105,72,97,46,26,76,93,102] Twenty four percent of studies reported DEX regimens as either insufficient for adequate sedation during the procedure or as having a higher demand for rescue medication [16,20,64,106,59,89,110,40,44,56,104,22,42,18,85,91,31,45]; 13.3% studies did not compare the grade of sedation between different regimens.[17,90,108,88,27,33,62,50,79]

Reporting of the grade of conscious sedation is generally presented as repeated measures during procedure time, with different methods of evaluation, leading to heterogeneity in the evaluation method and the characteristics of the outcome (repeated measures). As such, no metanalysis was performed for this outcome.

Hemodynamic complications and adverse events

The hemodynamic stability of the patient during the NORA procedure was one of the most reported outcomes, especially in terms of Blood Pressure (BP) and Heart Rate (HR) alterations. However, the definitions of hypotension (n = 53 studies), hypertension (n = 8 studies), bradycardia (n = 47 studies) and tachycardia (n = 8 studies) varied among studies.

Regarding hypotension, definitions used varied from alterations in the Mean Arterial Pressure (MAP) or Systolic BP (SBP) to define this outcome, although the cut-off varied. A meta-analysis was computed for RCT with comparable definitions (including subgroup analysis for different settings), shown in

Fig. 3 (see also Appendix V). Dexmedetomidine sedation was associated with a significantly higher incidence of hypotension than the other sedatives (OR = 1.95 [1.25, 3.05], $p = 0.003$, $I^2 = 39\%$), and there were significant differences in the effect of DEX between subgroups ($p = 0.02$).

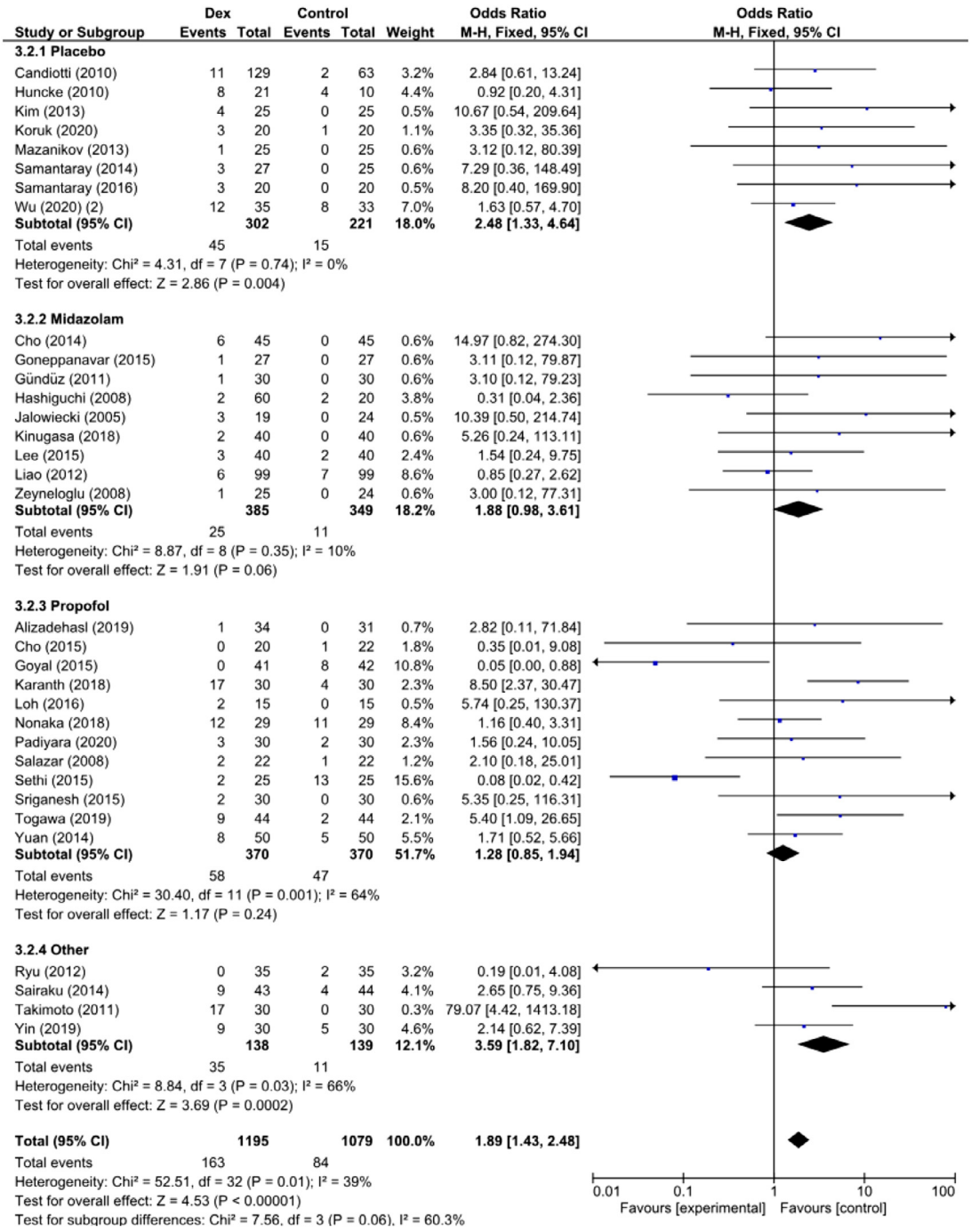

Figure 3 Forest plot of RCTs reporting hypotension with subgroup analysis by setting.

Concerning changes in HR, bradycardia was generally defined by HR cut-offs, differing from absolute changes to relative ones in relation to baseline (further details in Appendix III), except for Khalil et al., that defined bradycardia as the need for synchronized cardioversion or defibrillation, use of cardiopulmonary resuscitation and emergency extracorporeal circulation.

A meta-analysis was computed for RCTs considering bradycardia from HR < 40 to HR < 60 bpm, or < 20%–25% from baseline, shown in Figure 4 (see also Appendix V). Dexmedetomidine sedation was associated with a significantly higher incidence of bradycardia than in control groups (OR = 3.60 [2.29, 5.67], $p < 0.00001$, $I^2 = 0\%$), independently of the definition used for bradycardia.

Overall, tachycardia and hypertension did not occur during the procedure. When they did, the difference between the study groups was not statistically significant.[111,95,2,92]

Respiratory complications and adverse events

Reporting the involvement of the respiratory system was one of the major outcomes studied, however, there was not a consistent definition for respiratory depression. A total of 13.4% of studies did not define respiratory depression but

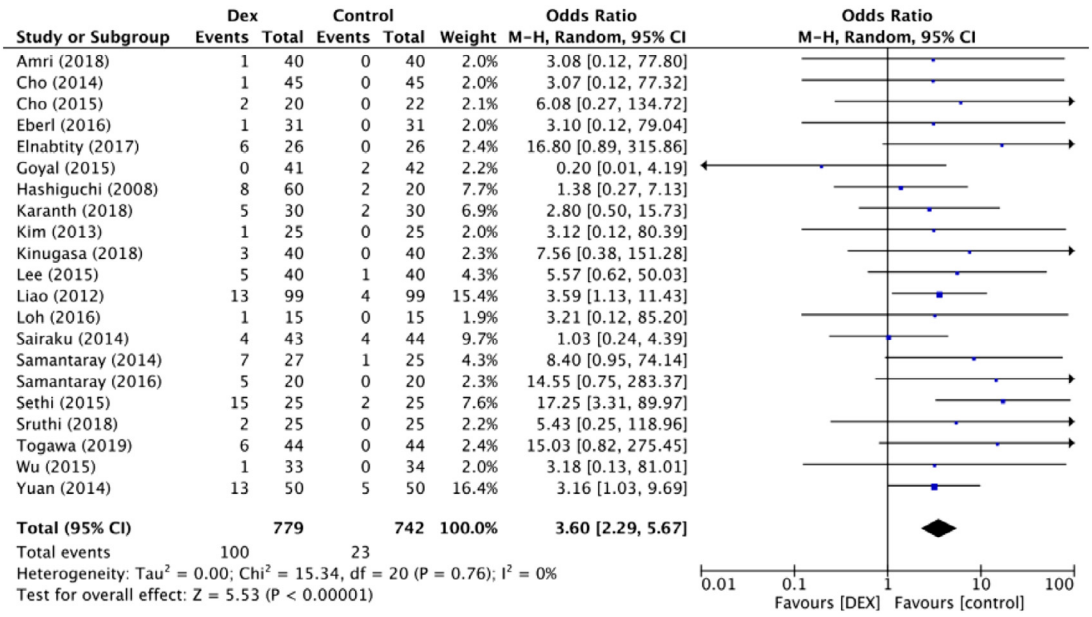

Figure 4 Forest plot of comparison of RCT reporting bradycardia incidences (defining bradycardia as HR < 40 to HR < 60 bpm, or < 20%−25% from baseline).

reported major respiratory events, such as desaturation, coughing, bradypnea, apnea, and aspiration pneumonia.

A meta-analysis of the studies that reported desaturation < 90% or < 92% (either as an outcome itself or as an indicator of respiratory depression with respective data exclusive to desaturation incidence) was computed. Significant lower incidence of desaturation was found (OR = 0.40 [0.25, 0.66], p = 0.0003), but with heterogeneity between studies (I^2 = 60%), not completely explained by setting (p-value for subgroup differences = 0.26, I^2 = 23.4%), nor comparator (p-value for subgroup differences = 0.65, I^2 = 0%; with only the placebo and propofol control group achieving I^2 < 50%) (Fig. 5 and Appendix V). Five studies reported incidence and severity of coughing, using different tools for measurement.[90,109,111,95,85]

Nausea

A post hoc analysis of 26 RCT reporting the incidence of nausea, as an adverse outcome, was performed. Overall, no differences were found in the incidence of nausea with DEX, compared to control groups (OR = 1.06 [0.72, 1.56], I^2 = 3%).

Discussion

Our results support the evidence that DEX produces effective sedative, analgesic, and hypnotic effects, without respiratory depression.[6,7] These characteristics enhance patient's and physician's satisfaction with DEX.[6] Kinugasa et al. [54] reported also an interaction of the use of DEX with the difficulty of the procedure in the correlation between physicians, especially when considering gastroenterology endoscopic procedures, with increased endoscopist satisfaction with DEX in higher difficulty cases compared to the placebo group, but with similar endoscopist satisfaction between groups in lower difficulty procedures.

There are insufficient data to determine a conclusion on DEX dose and method of administration for NORA. Most of the studies used a strategy of an intravenous (IV) bolus of 0.4 to 1 $\mu g.kg^{-1}$ followed by continuous perfusion of 0.1 −0.5 $\mu g.kg^{-1}.h^{-1}$. As reported in this review, DEX is often associated with bradycardia, as a consequence of its central sympathetic blockage, an effect that is more evident with continuous infusions (compared to single boluses).[7] There is also a concern about the higher risk of hypotension with DEX. However, this can be suppressed by a slower rate of intravenous infusion or intranasal administration of DEX, achieving the same adequate plasma levels without the prejudicial high peak plasma level.[6,15−17,41,24] More studies are needed comparing the type of DEX administration (IV boluses alone or followed by infusion vs. intranasal) and additive effect with ketamine (considering the merge of sedative and analgesic effects and the different directions in hemodynamic effects, keeping the beneficial respiratory safety profile).

In this review, we intended to carry out an extended analysis and description of the existing evidence on the effects of DEX on sedation in NORA for adults, therefore, many different settings of NORA were considered: burn unit, dental, gastrointestinal, gynecological, hemodynamic lab, invasive radiology, neuroradiology, orthopedical, psychiatric unit, urological, vascular, and upper airway procedure setting. This scope allowed for a transversal perspective to different configurations and different sedation protocols (comparative drugs) that can be communicated in NORA.

Despite bringing a holistic and global view, it also involved greater complexity in the analysis and review of results, considering that different configurations mean different stimuli and different levels of desirable sedation. Added to this complexity, considerable heterogeneity was noted, with at least 15 different domains being used as primary and secondary outcome measures in the included studies. The most frequent efficacy outcomes reported were

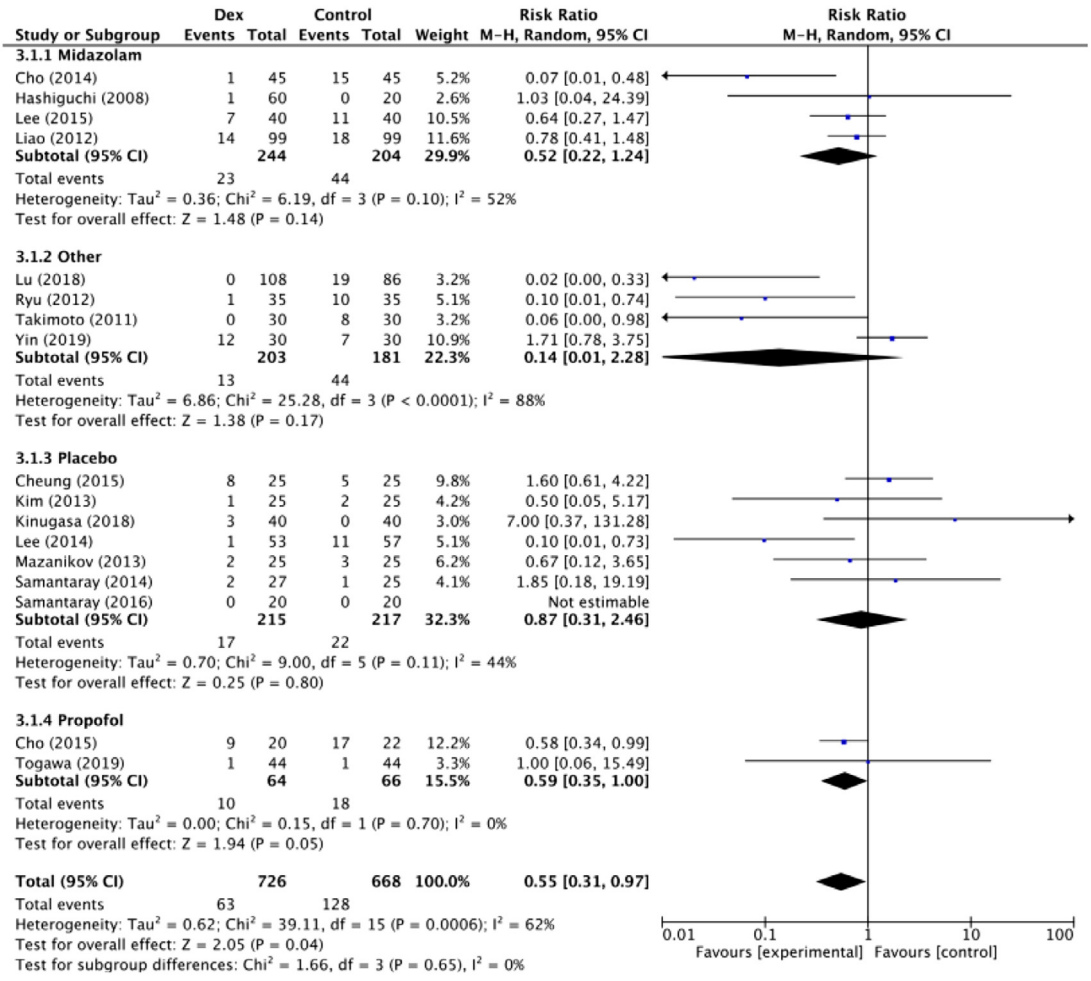

Figure 5 Forest plot of comparison: Desaturation by the comparator.

sedation level (evaluated in 82 studies) and the most frequent adverse outcomes reported were hemodynamic adverse reactions — hypotension (evaluated in 61 studies) and bradycardia (evaluated in 53 studies). There was also variation in outcome definition and measurement as reported in III. Heterogeneity was explored with subgroup analysis for setting and comparator/control intervention. A significant difference was found for control intervention subgroup analysis in time to recovery (although all subgroups presented significant heterogeneity) and a tendency was found for the same analysis in hypotension incidence (comparison with placebo and midazolam had low heterogeneity, with the first presenting significant lower incidence of hypotension). We also found significant differences among settings for the same outcomes. In time to recovery, all settings presented significant heterogeneity, but no heterogeneity was found in hypotension incidence for airway procedure, dental procedures, hemodynamic lab, invasive radiology, and vascular procedures settings, with a significant increase of hypotension incidence found in dental procedures and hemodynamic lab settings.

Overall, the included studies were at low risk of bias. The highest risk bias was found for participant and staff blinding (performance bias) as well as incomplete outcome data. Considering the high heterogeneity found from the outcomes reviewed, only hypotension, bradycardia, desaturation, nausea, and time until full recovery could be considered for meta-analysis. Of these outcomes, high certainty of the evidence was found for a higher incidence of hypotension (OR = 1.89) and bradycardia (OR = 3.60) with DEX, moderate certainty of the evidence for lower desaturation incidence and nausea and, time until full recovery was found to be 1.73 minutes longer with DEX but with low certainty due to severe inconsistency and suspected publication bias. Newman et al. [113] reported a safe discharge time after procedural sedation of 30 minutes. An increase of time-to-discharge of 1.73 would only increase discharge time by about 6%.

Almost 10 years ago, the World SIVA International Sedation Task Force proposed standardized definitions and terminology for adverse events during procedural sedation, to increase comparability of outcomes not only in monitoring clinical practice but also as a research tool. Although the world SIVA adverse sedation event-reporting tool is being applied in clinical practice across the globe,[114] none of the included studies used this tool. New standards for definitions and use of outcome measures for clinical effectiveness research in procedural sedation are therefore needed.

Exploring specific efficacy and safety in different procedures might be of interest in the future, allowing for targeted procedure recommendations. Further research is warranted to include the use of DEX in the following

procedures not evaluated in this review: labor, intubation and awake fibroscopy, endoscopic sinus surgery, chronic and postoperative pain, orthopedic surgery (especially in the elderly), and awake neurosurgery.

This was an extensive systematic review exploring time until recovery and side effects of DEX only or DEX associated with other sedatives, in several different NORA settings for adults' procedures, in comparison to other sedative pharmacological strategies, intending to summarize existing evidence generalizable to different usual procedural sedation and analgesia practices. Although it is advantageous to have such a comprehensive summary of the existing evidence of the use of DEX in NORA, this diversity of contexts and comparators is a synthesis challenge. In addition to this diversity, the heterogeneity in the definition and reporting of outcomes limited the meta-analysis for many of the considered outcomes. Furthermore, most of the studies included were classified as having an unclear or high risk of bias. As such, the effects measured may be affected by this bias.

Conclusion

This systematic review and meta-analysis demonstrated that the use of DEX in NORA procedures in the adult population was associated with similar or better pain and discomfort control, similar or higher physician and patient satisfaction in the majority of the included studies, similar or better sedation profile, with lower incidence of amnesia in 40% of the included studies and 55% lower risk of desaturation < 90%—92%, with a tendency for a longer time to recovery of about 2 minutes (but not exceeding 4 minutes), but with a higher incidence of hypotension and bradycardia. Considering the hemodynamic effects associated with DEX, its administration must be monitored and managed by a trained professional in cardiac life support [4,115] and this physician should only be responsible for the sedation.[4]

Authors' contributions

These authors contributed equally to this work and should both be considered first authors.

Francisca Jerónimo Fonseca is the guarantor. Francisca Jerónimo Fonseca, Leonardo Ferreira and Ana Lídia Rouxinol-Dias drafted the manuscript and all authors contributed to the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria. The search and statistical strategies were defined and conducted by Ana Lídia Rouxinol-Dias. All authors read, provided feedback and approved the final manuscript.

FJF is the guarantor. FJF, LF, and ALRD drafted the manuscript and all authors contributed to the development of the selection criteria, the risk of bias assessment strategy, and data extraction criteria. The search and statistical strategies were defined and conducted by ALRD. All authors read, provided feedback, and approved the final manuscript.

Funding

No funding has been received for this study.

Conflicts of interest

The authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.bjane.2021.12.002.

References

1. Kaur M, Singh PM. Current role of dexmedetomidine in clinical anesthesia and intensive care. Anesth Essays Res. 2011;5:128—33.
2. Morelli A, Sanfilippo F, Arnemann P, et al. The effect of propofol and dexmedetomidine sedation on norepinephrine requirements in septic shock patients: a crossover trial. Crit Care Med. 2019;47:e89—95.
3. Chrysostomou C, Schmitt CG. Dexmedetomidine: sedation, analgesia and beyond. Expert Opin Drug Metab Toxicol. 2008;4:619—27.
4. Hinkelbein J, Lamperti M, Akeson J, et al. European Society of Anaesthesiology and European Board of Anaesthesiology guidelines for procedural sedation and analgesia in adults. Eur J Anaesthesiol. 2018;35:6—24.
5. Mahmoud M, Mason KP. Dexmedetomidine: review, update, and future considerations of paediatric perioperative and periprocedural applications and limitations. Br J Anaesth. 2015;115:171—82.
6. Barends CR, Absalom A, van Minnen B, Vissink A, Visser A. Dexmedetomidine versus midazolam in procedural sedation. A systematic review of efficacy and safety. PLoS One. 2017;12:e0169525.
7. Lin Y, Zhang R, Shen W, et al. Dexmedetomidine versus other sedatives for non-painful pediatric examinations: A systematic review and meta-analysis of randomized controlled trials. J Clin Anesth. 2020;62:109736.
8. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. Bmj. 2015;350:g7647.
9. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6:e1000100.
10. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. Bmj. 2019;366:l4898.
11. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557—60.
12. Higgins JP, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions. John Wiley & Sons; 2019.
13. McHugh ML. Interrater reliability: the kappa statistic. Biochem Med (Zagreb). 2012;22:276—82.
14. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c332.
15. Nooh N, Sheta SA, Abdullah WA, Abdelhalim AA. Intranasal atomized dexmedetomidine for sedation during third molar extraction. Int J Oral Maxillofac Surg. 2013;42:857—62.
16. Shetty SK, Aggarwal G. Efficacy of intranasal dexmedetomidine for conscious sedation in patients undergoing surgical

removal of impacted third molar: a double-blind split mouth study. J Maxillofac Oral Surg. 2016;15:512—6.
17. Hiwarkar S, Kshirsagar R, Singh V, et al. Comparative evaluation of the intranasal spray formulation of midazolam and dexmedetomidine in patients undergoing surgical removal of impacted mandibular third molars: a split mouth prospective study. J Maxillofac Oral Surg. 2018;17:44—51.
18. Candiotti KA, Bergese SD, Bokesch PM, et al. Monitored anesthesia care with dexmedetomidine: a prospective, randomized, double-blind, multicenter trial. Anesth Analg. 2010;110:47—56.
19. Gunduz M, Sakalli S, Gunes Y, Kesiktas E, Ozcengiz D, Isik G. Comparison of effects of ketamine, ketamine-dexmedetomidine and ketamine-midazolam on dressing changes of burn patients. J Anaesthesiol Clin Pharmacol. 2011;27:220—4.
20. Kundra P, Velayudhan S, Krishnamachari S, Gupta SL. Oral ketamine and dexmedetomidine in adults' burns wound dressing - A randomized double blind cross over study. Burns. 2013;39:1150—6.
21. Ravipati P, Reddy PN, Kumar C, Pradeep P, Pathapati RM, Rajashekar ST. Dexmedetomidine decreases the requirement of ketamine and propofol during burns debridement and dressings. Indian J Anaesth. 2014;58:138—42.
22. Zor F, Ozturk S, Bilgin F, Isik S, Cosar A. Pain relief during dressing changes of major adult burns: ideal analgesic combination with ketamine. Burns. 2010;36:501—5.
23. Cheung CW, Ying CL, Chiu WK, Wong GT, Ng KF, Irwin MG. A comparison of dexmedetomidine and midazolam for sedation in third molar surgery. Anaesthesia. 2007;62:1132—8.
24. Cheung CW, Ng KFK, Liu J, Yuen MYV, Ho MHA, Irwin MG. Analgesic and sedative effects of intranasal dexmedetomidine in third molar surgery under local anaesthesia. Br J Anaesth. 2011;107:430—7.
25. Cheung CW, Ng KFJ, Choi WS, et al. Evaluation of the analgesic efficacy of local dexmedetomidine application. Clin J Pain. 2011;27:377—82.
26. Fan TW, Ti LK, Islam I. Comparison of dexmedetomidine and midazolam for conscious sedation in dental surgery monitored by bispectral index. Br J Oral Maxillofac Surg. 2013;51:428—33.
27. Kawaai H, Tomita S, Nakaike Y, Ganzberg S, Yamazaki S. Intravenous sedation for implant surgery: midazolam, butorphanol, and dexmedetomidine versus midazolam, butorphanol, and propofol. J Oral Implantol. 2014;40:94—102.
28. Mishra N, Birmiwal KG, Pani N, Raut S, Sharma G, Rath KC. Sedation in oral and maxillofacial day care surgery: a comparative study between intravenous dexmedetomidine and midazolam. Natl J Maxillofac Surg. 2016;7:178—85.
29. Nolan PJ, Delgadillo JA, Youssef JM, Freeman K, Jones JL, Chehrehsa A. Dexmedetomidine provides fewer respiratory events compared with propofol and fentanyl during third molar surgery: a randomized clinical trial. J Oral Maxillofac Surg. 2020;78:1704—16.
30. Rasheed MA, Punera DC, Bano M, Palaria U, Tyagi A, Sharma S. A study to compare the overall effectiveness between midazolam and dexmedetomidine during monitored anesthesia care: a randomized prospective study. Anesth Essays Res. 2015;9:167—72.
31. Salazar Merchán A. Sedación analgesia con dexmedetomidina comparada con propofol en Procedimientos de cirugía bucal. Acta Odontológica Venezolana. 2008;46:487—94.
32. Sivasubramani SM, Pandyan DA, Chinnasamy R, Kuppusamy SK. Comparison of bite force after administration of midazolam and dexmedetomidine for conscious sedation in minor oral surgery. J Pharm Bioallied Sci. 2019;11:S446—s9.
33. Taniyama K, Oda H, Okawa K, Himeno K, Shikanai K, Shibutani T. Psychosedation with dexmedetomidine hydrochloride during minor oral surgery. Anesth Prog. 2009;56:75—80.
34. Taylor DC, Ferguson HW, Stevens M, Kao S, Yang FM, Looney S. Does including dexmedetomidine improve outcomes after intravenous sedation for outpatient dentoalveolar surgery? J Oral Maxillofac Surg. 2020;78:203—13.
35. Togawa E, Hanamoto H, Maegawa H, Yokoe C, Niwa H. Dexmedetomidine and midazolam sedation reduces unexpected patient movement during dental surgery compared with propofol and midazolam sedation. J Oral Maxillofac Surg. 2019;77:29—41.
36. Wang LZ Y, Zhang T, Huang L, Peng W. Comparison in sedative effects between dexmedetomidine and midazolam in dental implantation: a randomized clinical trial. Biomed Res Int. 2020;2020:6130162.
37. Yu C, Li S, Deng F, Yao Y, Qian L. Comparison of dexmedetomidine/fentanyl with midazolam/fentanyl combination for sedation and analgesia during tooth extraction. Int J Oral Maxillofac Surg. 2014;43:1148—53.
38. Akarsu Ayazoğlu T, Polat E, Bolat C, et al. Comparison of propofol-based sedation regimens administered during colonoscopy. Rev Med Chil. 2013;141:477—85.
39. Amri P, Nahrini S, Hajian-Tilaki K, et al. Analgesic effect and hemodynamic changes due to dexmedetomidine versus fentanyl during elective colonoscopy: a double-blind randomized clinical trial. Anesth Pain Med. 2018;8:e81077.
40. Bavullu EN, Aksoy E, Abdullayev R, Göğüş N, Dede D. Comparison of dexmedetomidine and midazolam in sedation for percutaneous drainage of hepatic hydatid cysts. Turk J Anaesthesiol Reanim. 2013;41:195—9.
41. Cheung CW, Qiu Q, Liu J, Chu KM, Irwin MG. Intranasal dexmedetomidine in combination with patient-controlled sedation during upper gastrointestinal endoscopy: a randomised trial. Acta Anaesthesiol Scand. 2015;59:215—23.
42. Cho JS, Soh S, Kim EJ, et al. Comparison of three sedation regimens for drug-induced sleep endoscopy. Sleep Breath. 2015;19:711—7.
43. Demiraran Y, Korkut E, Tamer A, et al. The comparison of dexmedetomidine and midazolam used for sedation of patients during upper endoscopy: a prospective, randomized study. Can J Gastroenterol. 2007;21:25—9.
44. Dere K, Sucullu I, Budak ET, et al. A comparison of dexmedetomidine versus midazolam for sedation, pain and hemodynamic control, during colonoscopy under conscious sedation. Eur J Anaesthesiol. 2010;27:648—52.
45. Eberl S, Preckel B, Bergman JJ, van Dieren S, Hollmann MW. Satisfaction and safety using dexmedetomidine or propofol sedation during endoscopic oesophageal procedures: a randomised controlled trial. Eur J Anaesthesiol. 2016;33:631—7.
46. Eldesuky Ali Hassan HI. Dexmedetomidine versus ketofol for moderate sedation in endoscopic retrograde cholangiopancreatography (ERCP) comparative study. Egypt J Anaesth. 2015;31:15—21.
47. Elkalla RS, El Mourad MB. Respiratory and hemodynamic effects of three different sedative regimens for drug induced sleep endoscopy in sleep apnea patients. A prospective randomized study. Minerva Anestesiol. 2020;86:132—40.
48. Goyal R, Hasnain S, Mittal S, Shreevastava S. A randomized, controlled trial to compare the efficacy and safety profile of a dexmedetomidine-ketamine combination with a propofol-fentanyl combination for ERCP. Gastrointest Endosc. 2016;83:928—33.
49. Hashiguchi K, Matsunaga H, Higuchi H, Miura S. Dexmedetomidine for sedation during upper gastrointestinal endoscopy. Dig Endosc. 2008;20:178—83.
50. Jalowiecki P, Rudner R, Gonciarz M, Kawecki P, Petelenz M, Dziurdzik P. Sole use of dexmedetomidine has limited utility for conscious sedation during outpatient colonoscopy. Anesthesiology. 2005;103:269—73.

51. Karanth H, Murali S, Koteshwar R, Shetty V, Adappa K. Comparative study between propofol and dexmedetomidine for conscious sedation in patients undergoing outpatient colonoscopy. Anesth Essays Res. 2018;12:98—102.
52. Kilic N, Sahin S, Aksu H, et al. Conscious sedation for endoscopic retrograde cholangiopancreatography: dexmedetomidine versus midazolam. Eurasian J Med. 2011;43:13—7.
53. Kim N, Yoo YC, et al. Comparison of the efficacy and safety of sedation between dexmedetomidine-remifentanil and propofol-remifentanil during endoscopic submucosal dissection. World J Gastroenterol. 2015;21:3671—8.
54. Kinugasa H, Higashi R, Miyahara K, et al. Dexmedetomidine for conscious sedation with colorectal endoscopic submucosal dissection: a prospective double-blind randomized controlled study. Clin Transl Gastroenterol. 2018;9:167.
55. Koruk S, Koruk I, Arslan AM, Bilgi M, Gul R, Bozgeyik S. Dexmedetomidine or midazolam in combination with propofol for sedation in endoscopic retrograde cholangiopancreatography: a randomized double blind prospective study. Wideochir Inne Tech Maloinwazyjne. 2020;15:526—32.
56. Kuyrukluyıldız U, Binici O, Onk D, et al. Comparison of dexmedetomidine and propofol used for drug-induced sleep endoscopy in patients with obstructive sleep apnea syndrome. Int J Clin Exp Med. 2015;8:5691—8.
57. Lee BS, Ryu J, Lee SH, et al. Midazolam with meperidine and dexmedetomidine vs. midazolam with meperidine for sedation during ERCP: prospective, randomized, double-blinded trial. Endoscopy. 2014;46:291—8.
58. Lee SP, Sung IK, Kim JH, et al. Comparison of dexmedetomidine with on-demand midazolam versus midazolam alone for procedural sedation during endoscopic submucosal dissection of gastric tumor. J Dig Dis. 2015;16:377—84.
59. Lu Z, Li W, Chen H, Qian Y. 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. Dig Dis Sciences. 2018;63:1633—40.
60. Mazanikov M, Udd M, Kylänpää L, et al. Dexmedetomidine impairs success of patient-controlled sedation in alcoholics during ERCP: a randomized, double-blind, placebo-controlled study. Surg Endosc Interv Tech. 2013;27:2163—8.
61. Mukhopadhyay S, Niyogi M, Sarkar J, Mukhopadhyay BS, Halder SK. The dexmedetomidine "augmented" sedato analgesic cocktail: an effective approach for sedation in prolonged endoscopic retrograde cholangio-pancreatography. J Anaesthesiol Clin Pharmacol. 2015;31:201—6.
62. Muller S, Borowics SM, Fortis EA, et al. Clinical efficacy of dexmedetomidine alone is less than propofol for conscious sedation during ERCP. Gastrointest Endosc. 2008;67:651—9.
63. Nonaka T, Inamori M, Miyashita T, et al. Can sedation using a combination of propofol and dexmedetomidine enhance the satisfaction of the endoscopist in endoscopic submucosal dissection? Endosc Int Open. 2018;6:E3—e10.
64. Padiyara TV, Bansal S, Jain D, Arora S, Gandhi K. Dexmedetomidine versus propofol at different sedation depths during drug-induced sleep endoscopy: a randomized trial. Laryngoscope. 2020;130:257—62.
65. Pushkarna G, Sarangal P, Pushkarna V, Gupta R. Comparative evaluation of dexmedetomidine versus midazolam as premedication to propofol anesthesia in endoscopic retrograde cholangiopancreatography. Anesth Essays Res. 2019;13:297—302.
66. Ramkiran S, Iyer SS, Dharmavaram S, Mohan CV, Balekudru A, Kunnavil R. BIS targeted propofol sparing effects of dexmedetomidine versus ketamine in outpatient ERCP: a prospective randomised controlled trial. J Clin Diagn Res. 2015;9: Uc07—12.
67. Takimoto K, Ueda T, Shimamoto F, et al. Sedation with dexmedetomidine hydrochloride during endoscopic submucosal dissection of gastric cancer. Dig Endosc. 2011;23:176—81.
68. Trivedi SK R, Tripathi AK, Mehta RK. A comparative study of dexmedetomidine and midazolam in reducing delirium caused by ketamine. J Clin Diagn Res. 2016;10:Uc01—4.
69. Wu Y, Zhang Y, Hu X, Qian C, Zhou Y, Xie J. A comparison of propofol vs. dexmedetomidine for sedation, haemodynamic control and satisfaction, during esophagogastroduodenoscopy under conscious sedation. J Clin Pharm Ther. 2015;40:419—25.
70. Elnabtity AM, Selim MF. A prospective randomized trial comparing dexmedetomidine and midazolam for conscious sedation during oocyte retrieval in an in vitro fertilization program. Anesth Essays Res. 2017;11:34—9.
71. Sethi P, Sindhi S, Verma A, Tulsiani KL. Dexmedetomidine versus propofol in dilatation and curettage: an open-label pilot randomized controlled trial. Saudi J Anaesth. 2015;9:258—62.
72. Alizadehasl A, Sadeghpour A, Totonchi Z, Azarfarin R, Rahimi S, Hendiani A. Comparison of sedation between dexmedetomidine and propofol during transesophageal echocardiography: a randomized controlled trial. Ann Card Anaesth. 2019;22:285—90.
73. Cho JS, Shim JK, Na S, Park I, Kwak YL. Improved sedation with dexmedetomidine-remifentanil compared with midazolam-remifentanil during catheter ablation of atrial fibrillation: a randomized, controlled trial. Europace. 2014;16:1000—6.
74. Cooper L, Candiotti K, Gallagher C, Grenier E, Arheart KL, Barron ME. A randomized, controlled trial on dexmedetomidine for providing adequate sedation and hemodynamic control for awake, diagnostic transesophageal echocardiography. J Cardiothorac Vasc Anesth. 2011;25:233—7.
75. Khalil M, Al-Agaty A, Asaad O, et al. A comparative study between propofol and dexmedetomidine as sedative agents during performing transcatheter aortic valve implantation. J Clin Anesth. 2016;32:242—7.
76. Prachanpanich N, Apinyachon W, Ittichaikulthol W, Moontripakdi O, Jitaree A. A comparison of dexmedetomidine and propofol in Patients undergoing electrophysiology study. J Med Assoc Thai. 2013;96:307—11.
77. Sairaku A, Yoshida Y, Hirayama H, Nakano Y, Ando M, Kihara Y. Procedural sedation with dexmedetomidine during ablation of atrial fibrillation: a randomized controlled trial. Europace. 2014;16:994—9.
78. Sruthi S, Mandal B, Rohit MK, Puri GD. Dexmedetomidine versus ketofol sedation for outpatient diagnostic transesophageal echocardiography: a randomized controlled study. Ann Card Anaesth. 2018;21:143—50.
79. Loh P-S, Ariffin MA, Rai V, Lai L-L, Chan L, Ramli N. Comparing the efficacy and safety between propofol and dexmedetomidine for sedation in claustrophobic adults undergoing magnetic resonance imaging (PADAM trial). J Clin Anesth. 2016;34: 216—22.
80. Kim SY, Chang CH, Lee JS, et al. Comparison of the efficacy of dexmedetomidine plus fentanyl patient-controlled analgesia with fentanyl patient-controlled analgesia for pain control in uterine artery embolization for symptomatic fibroid tumors or adenomyosis: a prospective, randomized study. J Vasc Interv Radiol. 2013;24:779—86.
81. Ren C, Gao J, Xu GJ, et al. The nimodipine-sparing effect of perioperative dexmedetomidine infusion during aneurysmal subarachnoid hemorrhage: a prospective, randomized, controlled trial. Front Pharmacol. 2019;10:858.
82. Sriganesh K, Reddy M, Jena S, Mittal M, Umamaheswara Rao GS. A comparative study of dexmedetomidine and propofol as sole sedative agents for patients with aneurysmal subarachnoid hemorrhage undergoing diagnostic cerebral angiography. J Anesth. 2015;29:409—15.

83. Masoumi K, Maleki SJ, Forouzan A, Delirrooyfard A, Hesam S. Dexmedetomidine versus midazolam-fentanyl in procedural analgesia sedation for reduction of anterior shoulder dislocation: a randomized clinical trial. Rev Recent Clin Trials. 2019;14:269—74.
84. Sannakki D, Dalvi NP, Sannakki S, Parikh DP, Garg SK, Tendolkar B. Effectiveness of dexmedetomidine as premedication prior to electroconvulsive therapy, a Randomized controlled cross over study. Indian J Psychiatry. 2017;59:370—4.
85. El Mourad MB, Elghamry MR, Mansour RF, Afandy ME. Comparison of intravenous dexmedetomidine-propofol versus ketofol for sedation during awake fiberoptic intubation: a prospective, randomized study. Anesth Pain Med. 2019;9: e86442.
86. Goneppanavar U, Magazine R, Periyadka Janardhana B, Krishna Achar S. Intravenous dexmedetomidine provides superior patient comfort and tolerance compared to intravenous midazolam in patients undergoing flexible bronchoscopy. Pulm Med. 2015;2015:727530.
87. Gu W, Xu M, Lu H, Huang Q, Wu J. Nebulized dexmedetomidine-lidocaine inhalation as a premedication for flexible bronchoscopy: a randomized trial. J Thorac Dis. 2019;11:4663—70.
88. Liao W, Ma G, Su QG, Fang Y, Gu BC, Zou XM. Dexmedetomidine versus midazolam for conscious sedation in postoperative patients undergoing flexible bronchoscopy: a randomized study. J Int Med Res. 2012;40:1371—80.
89. Ma XX, Fang XM, Hou TN. Comparison of the effectiveness of dexmedetomidine versus propofol target-controlled infusion for sedation during coblation-assisted upper airway procedure. Chin Med J (Engl). 2012;125:869—73.
90. Magazine R, Venkatachala SK, Goneppanavar U, Surendra VU, Guddattu V, Chogtu B. Comparison of midazolam and low-dose dexmedetomidine in flexible bronchoscopy: a prospective, randomized, double-blinded study. Indian J Pharmacol. 2020;52:23—30.
91. Riachy M, Khayat G, Ibrahim I, et al. A randomized double-blind controlled trial comparing three sedation regimens during flexible bronchoscopy: dexmedetomidine, alfentanil and lidocaine. Clin Respir J. 2018;12:1407—15.
92. Ryu JH, Lee SW, Lee JH, Lee EH, Do SH, Kim CS. Randomized double-blind study of remifentanil and dexmedetomidine for flexible bronchoscopy. Br J Anaesth. 2012;108:503—11.
93. St-Pierre P, Tanoubi I, Verdonck O, et al. Dexmedetomidine versus remifentanil for monitored anesthesia care during endobronchial ultrasound-guided transbronchial needle aspiration: a randomized controlled trial. Anesth Analg. 2019;128:98—106.
94. Wu SH, Lu DV, Hsu CD, Lu IC. The effectiveness of low-dose dexmedetomidine infusion in sedative flexible bronchoscopy: a retrospective analysis. Medicina (Kaunas). 2020;56:193.
95. Yuan F, Fu H, Yang P, et al. Dexmedetomidine-fentanyl versus propofol-fentanyl in flexible bronchoscopy: a randomized study. Exp Ther Med. 2016;12:506—12.
96. Akça B, Aydoğan-Eren E, Canbay Ö, et al. Comparison of efficacy of prophylactic ketamine and dexmedetomidine on postoperative bladder catheter-related discomfort. Saudi Med J. 2016;37:55—9.
97. Alhashemi JA, Kaki AM. Dexmedetomidine in combination with morphine PCA provides superior analgesia for shockwave lithotripsy. Can J Anaesth. 2004;51:342—7.
98. Arpaci AH, Bozkirli F. Comparison of sedation effectiveness of remifentanil-dexmedetomidine and remifentanil-midazolam combinations and their effects on postoperative cognitive functions in cystoscopies: a randomized clinical trial. J Res Med Sci. 2013;18:107—14.
99. Kaygusuz K, Gokce G, Gursoy S, Ayan S, Mimaroglu C, Gultekin Y. A comparison of sedation with dexmedetomidine or propofol during shockwave lithotripsy: a randomized controlled trial. Anesth Analg. 2008;106:114—9.
100. Kumakura Y, Ishiyama T, Matsuoka T, Iijima T, Matsukawa T. Effects of spinal anesthesia and sedation with dexmedetomidine or propofol on cerebral regional oxygen saturation and systemic oxygenation a period after spinal injection. J Anesth. 2020;34:806—13.
101. Modir H, Moshiri E, Yazdi B, Kamalpour T, Goodarzi D, Mohammadbeigi A. Efficacy of dexmedetomidine-ketamine vs. fentanylketamine on saturated oxygen, hemodynamic responses and sedation in cystoscopy: a doubleblinded randomized controlled clinical trial. Med Gas Res. 2020;10:91—5.
102. Shariffuddin II, Teoh WH, Wahab S, Wang CY. Effect of single-dose dexmedetomidine on postoperative recovery after ambulatory ureteroscopy and ureteric stenting: a double blind randomized controlled study. BMC Anesthesiol. 2018;18:3.
103. Tan WF, Miao EY, Jin F, Ma H, Lu HW. Changes in first postoperative night bispectral index after daytime sedation induced by dexmedetomidine or midazolam under regional anesthesia: a randomized controlled trial. Reg Anesth Pain Med. 2016;41:380—6.
104. Zeyneloglu P, Pirat A, Candan S, Kuyumcu S, Tekin I, Arslan G. Dexmedetomidine causes prolonged recovery when compared with midazolam/fentanyl combination in outpatient shock wave lithotripsy. Eur J Anaesthesiol. 2008;25:961—7.
105. Huncke TK, Adelman M, Jacobowitz G, Maldonado T, Bekker A. A prospective, randomized, placebo-controlled study evaluating the efficacy of dexmedetomidine for sedation during vascular procedures. Vasc Endovascular Surg. 2010;44:257—61.
106. Samantaray A. Effects of dexmedetomidine on procedural pain and discomfort associated with central venous catheter insertion. Indian J Anaesth. 2014;58:281—6.
107. Samantaray A, Hanumantha Rao M, Sahu CR. Additional analgesia for central venous catheter insertion: a placebo controlled randomized trial of dexmedetomidine and fentanyl. Crit Care Res Pract. 2016;2016:9062658.
108. Sivasubramani S, Pandyan DA, Ravindran C. Comparision of vital surgical parameters, after administration of midazolam and dexmedetomidine for conscious sedation in minor oral surgery. Ann Maxillofac Surg. 2019;9:283—8.
109. Wu W, Chen Q, Zhang LC, Chen WH. Dexmedetomidine versus midazolam for sedation in upper gastrointestinal endoscopy. J Int Med Res. 2014;42:516—22.
110. Wu LP, Kang WQ. Effect of dexmedetomidine for sedation and cognitive function in patients with preoperative anxiety undergoing carotid artery stenting. J Int Med Res. 2020;48:300060520938959.
111. Yin S, Hong J, Sha T, et al. Efficacy and tolerability of sufentanil, dexmedetomidine, or ketamine added to propofol-based sedation for gastrointestinal endoscopy in elderly patients: a prospective, randomized, controlled trial. Clin Ther. 2019;41:1864—77. e0.
112. Barbosa FT, Lira AB, Neto OBdO, et al. Tutorial for performing systematic review and meta-analysis with interventional anesthesia studies. Br J Anaesth. (English Edition). 2019;69:299—306.
113. Newman DH, Azer MM, Pitetti RD, Singh S. When is a patient safe for discharge after procedural sedation? The timing of adverse effect events in 1,367 pediatric procedural sedations. Ann Emerg Med. 2003;42:627—35.
114. Mason KP, Green SM, Piacevoli Q. Adverse event reporting tool to standardize the reporting and tracking of adverse events during procedural sedation: a consensus document from the World SIVA International Sedation Task Force. Br J Anaesth. 2012;108:13—20.
115. Jayaraman L, Sethi N, Sood J. Anaesthesia outside the operating theatre. Update in Anaesth. 2009;25:37—41.