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REVIEW ARTICLE

Effectiveness of pharmacological procedural sedation in children with autism spectrum disorder: A systematic review and meta-analysis

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Abstract

Aim: Management of primary healthcare and routine minor procedures for children with autism spectrum disorder (ASD) can be challenging; therefore, when behavioural strategies fail, sedative medications are often employed. We evaluated the effectiveness of the current pharmacological strategies for managing children with ASD.

Methods: We performed a systematic review and meta-analysis of the current approaches for procedural sedation in children with ASD.

Results: Twenty studies met inclusion criteria. Dexmedetomidine, midazolam, propofol and chloral hydrate were the most efficient agents for successful procedures, while propofol had the highest number of adverse events. The most frequently used agents were dexmedetomidine and midazolam or a combination of the two, and the effectiveness of dexmedetomidine plus midazolam was superior to dexmedetomidine alone.

Conclusion: Multiple effective drug regimens exist for procedural sedation in children with ASD. These results could support the development of specific guidelines for procedural sedation in children with ASD.

KEYWORDS
autism spectrum disorders, children, dexmedetomidine, midazolam, procedural sedation

1 | INTRODUCTION

Autism spectrum disorder (ASD) includes neurodevelopmental conditions characterised by impairment of social interaction and communication, often accompanied by restricted-repetitive behaviours. ASD comprises individuals with intellectual disability, deficient language skills and children with average or above-average intellectual function with difficulty in social communication. These children often present with concurrent conditions, such as epilepsy, anxiety, attention deficit disorder, self-harm and depression. The World Health Organization estimates a prevalence of ASD of 1 in 100 children worldwide.[1,2] However, this figure is likely underestimated, as ASD is not always well monitored or recognised in low and middle-income countries.[1]

Managing these patients in the clinical setting raises numerous challenges. A new environment, including new sounds, smells, unfamiliar personnel and medical equipment, can provoke overwhelming

Abbreviations: ASD, autism spectrum disorder; CEM, common effect model; CI, confidence interval; REM, random effect model.

anxiety and distress. Therefore, routine primary care, including physical examinations, venipuncture and immunisation, can be challenging for both provider and patient. Physical restraint is often required to successfully complete minor procedures, resulting in traumatic episodes for these children.[3] Behavioural interventions, where available, often fail to manage the extreme anxiety and distress these children exhibit, especially when they have been previously traumatised.[4] As a result, medical care may be postponed indefinitely or, in many cases, patients undergo general anaesthesia, a limited resource with related risks. With the advent of procedural sedation, many of these procedures can now be done in the outpatient setting (i.e. emergency department, hospital sedation service) and be a resource for medical providers.[5]

Procedural sedation, the use of sedative, analgesic and dissociative agents to relieve anxiety and pain associated with diagnostic and therapeutic procedures outside of the operating theatre, has evolved into a widely practiced discipline by a diverse group of specialists.[5] In a recent survey of current practice at 47 hospitals in the United States caring for children with ASD, less than 30% of existing sedation programs included either an ASD-specific protocol or additional time or staffing for sedation of patients with ASD. Most hospitals use distraction (77%), involvement of parents (94%) or physical restraint (45%) for minor procedures. Hospitals affiliated with an autism centre tend to develop a specific protocol for ASD procedural sedation (71%) compared to unaffiliated hospitals (51%). This recent survey found that sedation program directors were not satisfied with their practice for children with ASD and that more training was needed, and more studies were required to define protocols and international guidelines, as well as more information disseminated at academic conferences.[6]

There are currently no guidelines published by international medical societies for managing procedural anxiety and pain in children with ASD. We performed a systematic review and a meta-analysis to evaluate the effectiveness of the current pharmacological regimens for procedural sedation in children with ASD.

Key Notes

- The study investigated the effectiveness of current pharmacological strategies employed in medical procedures in children with autism spectrum disorder (ASD).
- Procedural sedation was efficacious in the clinical management of children with ASD.
- These results could support the development of specific guidelines for procedural sedation in children with ASD.

2 | MATERIALS AND METHODS

We employed Rstudio[7,8] to perform a systematic review according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement.[9]

We searched PubMed (https://pubmed.ncbi.nlm.nih.gov), employing the following optimised key terms: 'sedation' or 'procedural sedation' or 'conscious sedation' (in 'Title/Abstract') and 'autism' (in 'Title/Abstract') and paediatric or children (in 'all fields'). The search concluded on 30 September 2023, producing 134 results. Keywords were automatically extracted from 92 articles, while in the remaining 42 articles keywords were extracted from the title using the Rapid Automatic Keyword Extraction (RAKE) method of the Litesearch R package.[10]

A literature search was then conducted in PubMed and Web of Science databases, retrieving 134 and 124 items, respectively and then the deduplication resulted in 155 items. The deduplication was performed by importing the references in Zotero citation manager[11] and merging the items in one library.

The articles (title/abstract) were manually screened by three authors independently, and if discordant, the selection was further discussed with two other authors. Moreover, we employed the 'revtool' package for R studio to test if the articles could cluster around topics,[12] but they did not, as shown in Figure 1.[12] We initially performed the manual screening of the title and abstract, then we retrieved and evaluated articles according to the following inclusion/exclusion criteria.

Inclusion criteria were:

- clinical studies on human subjects with autistic spectrum disorder (ASD)
- paediatric subjects (ages 0–20 years)
- use of pharmacological agents
- use of sedation to perform medical procedures
- English language
- Peer-reviewed paper

Exclusion criteria:

- ASD patients over 20 years of age
- in vitro and in vivo pre-clinical studies
- Other no-English Language

Twenty papers fulfilled the inclusion criteria and were selected for the meta-analysis (Figure 2).[13]

Three authors independently performed data extraction. The number of successful procedures performed during sedation was selected as the primary outcome, the number of adverse effects was also registered, and other relevant information regarding the results achieved.

2.1 | Meta-analysis

We performed the meta-analysis with the 'meta'[14] packages in Rstudio,[7] comparing two sedative agents with the 'metabin' function of binary outcome data using odds ratio—OR for the measurement of treatment. When we did not proceed with a comparison, as for single-arm studies or when a single study compared two

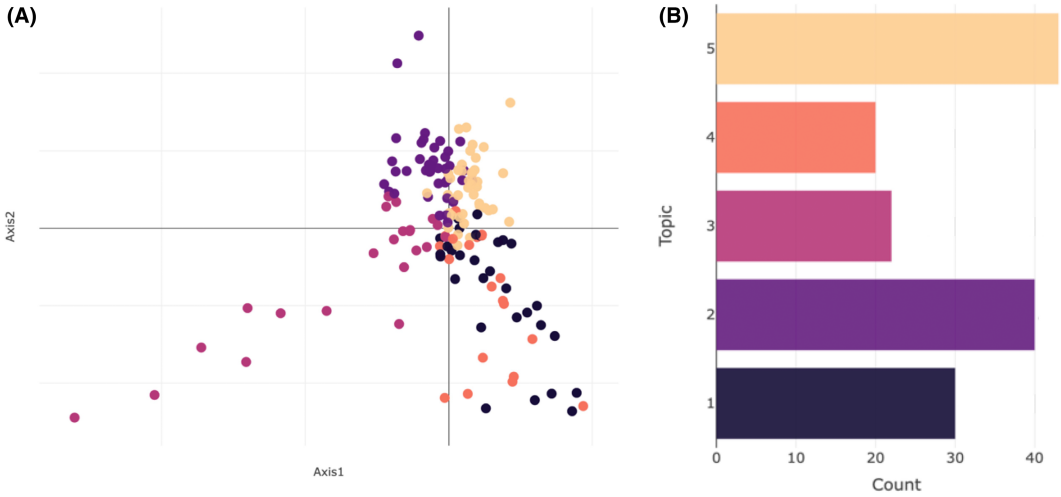

FIGURE 1 Analysis of clustering performed with Revtool R package. (A) Topic clustering visualisation. (B) Topic frequencies. (C) List of the topic terms.

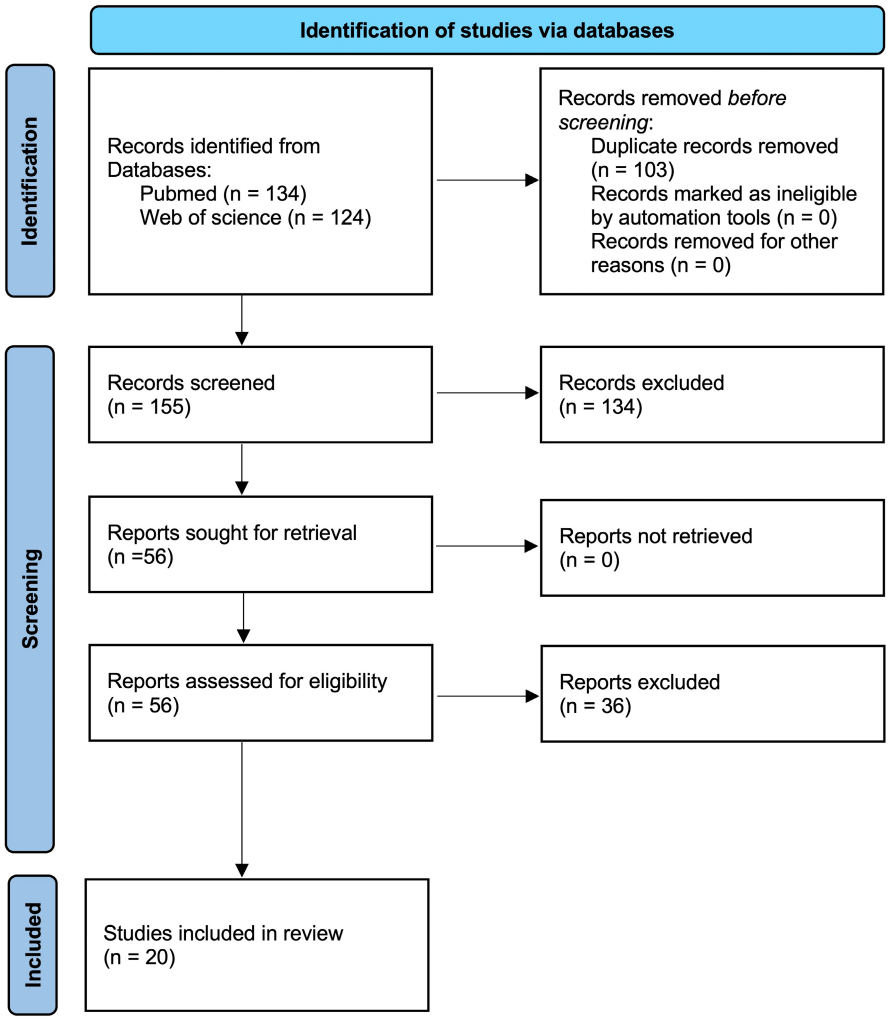

FIGURE 2 PRISMA flow diagram for the selection of the articles.

specific drugs, we utilised the 'metaprop' function for proportion data, estimating the overall effect size across the selected investigations. We used standard and random effect models to synthesise the results and check heterogenicity. In the case of high variability, we used the 'find.outliers' function and recalculated the models excluding outliers. The 'InfluenceAnalysis' function in the 'dmetar'[15] package allowed examination of the impact of each study's heterogeneity.

Since the 20 studies were heterogeneous regarding procedures and type of sedation agent, we grouped the studies based on the drug(s) employed. Moreover, we considered only the groups where the number of studies was equal or greater than two, while when a single drug was employed in only one study no comparison was possible so we excluded it form the meta-analysis; therefore, four studies were excluded (Kaplan et al.,[16] Mehta et al.,[17] Pisalchaiyong et al.,[18] Ross et al.[19]).

The primary outcome was the incidence of successful procedures; the only outcome reported across all the studies. The secondary outcome was the incidence and type of adverse events. The common effect model (CEM) and the random effect model (REM) were employed to estimate the overall effect size of the analysis.

2.2 | Risk of bias and certainty assessment

The risk of bias was assessed by using the NHLBI (National Heart, Lung and Blood Institute) Study Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies available at https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools,[20] composed of 14 items (Table S1). Five authors independently evaluated the selected articles and classified risk of bias of each item as low, moderate, high or critical. We achieved an overall classification, considering the scale with the following numerical values: low = 0, moderate = 1, high = 2 and critical = 3. The numerical sum of each item was provided for the 'overall' classification in the 4 areas: low = 0–10 (0%–25%), moderate = 11–21 (25%–50%), high = 21–31 (50%–75%) and critical = 32–42 (75%–100%).

We produced a median of all numerical evaluations for each item, and the results were visualised with the 'robvis' online tool[21] (available at https://mcguinlu.shinyapps.io/robvis/).

Certainty was assessed in compliance with the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework.[22]

3 | RESULTS

3.1 | Meta-analysis

Data from the 20 included studies are presented in Table 1. Six (30%) were single-arm studies of children treated with a sedation agent. In 4 (20%), the same sedative was administered to the children with ASD and in a control population. In 9 (45%) studies, children with ASD were divided into two arms and different drugs were administered. In 1 (5%) study, the same cohort with ASD underwent procedural sedation with two different pharmacological agents at different times.

The drugs most frequently used were dexmedetomidine ($n = 12$), midazolam ($n = 6$), chloral hydrate ($n = 2$), dexmedetomidine + midazolam ($n = 3$), propofol ($n = 2$), clonidine ($n = 1$), Trichlofos sodium (TFS) ($n = 1$), diazepam ($n = 1$), fentanyl + pentobarbital ($n = 1$), ketamine ($n = 1$), midazolam + ketamine ($n = 1$). The procedures executed were electroencephalogram (EEG, $n = 6$), magnetic resonance imaging (MRI, $n = 6$), auditory brainstem response (ABR, $n = 2$), dental procedures ($n = 2$), emergency department procedures ($n = 2$), computerised tomography (CT, $n = 1$), ophthalmology exams ($n = 1$), intravenous access ($n = 1$) and immunisation ($n = 1$).

Considering the sedative agents singularly, we found that dexmedetomidine was administered in 12 studies in a total of 815 patients. The meta-analysis showed a medium efficacy of the treatment with CEM (0.52, 95% CI = 0.49–0.55), and a medium-high effectiveness was determined when the REM was applied (0.85, 95% CI = 0.61–0.96) with high heterogeneity in CEM ($I^2 = 95.30\%$) and in REM ($\tau^2 = 4.49$). There were overall 44 minor adverse events.

Midazolam was used in six studies of 166 patients. A medium proficiency of midazolam was displayed when CEM was utilised (0.72; 95% CI = 0.64–0.78), and a medium-high when REM was applied (0.84; 95% CI = 0.31–0.98). High heterogeneity was detected with both models ($I^2 = 87.50\%$; $\tau^2 = 7.52$). The studies reported five adverse events.

Dexmedetomidine plus midazolam was employed in three studies in 432 patients. The meta-analysis indicated a high efficacy by combining the two drugs with both models (CEM = 0.94; 95% CI = 0.91–0.96; REM = 0.96; 95% CI = 0.80–0.99). The heterogeneity was high in the CEM ($I^2 = 91.10\%$) but low in REM ($\tau^2 = 1.75$). Eleven adverse events were documented.

Chloral hydrate was used in two studies of 145 children. Medium-high efficacy was identified with both models (CEM = 0.86; 95% CI = 0.79–0.90; REM = 0.83; 95% CI = 0.61–0.94), showing a high heterogeneity with CEM ($I^2 = 91.20\%$) and low with REM ($\tau^2 = 0.59$). Eleven adverse events were registered.

Propofol was used in two studies on a total of 159 patients. The meta-analysis showed high usefulness of propofol (CEM = 0.99; 95% CI = 0.96–1.00; REM = 0.99; 95% CI = 0.96–1.00) with null heterogeneity ($I^2 = 0.00\%$; $\tau^2 = 0.00$). Thirty adverse events were reported.

Considering all the drugs together, procedural sedation was an efficacious form of intervention in patients with ASD with an overall REM of 0.90 (95% CI = 0.77–0.96) and CEM of 0.72 (95% CI = 0.69–0.74) with few side effects (CEM = 0.08; 95% CI = 0.06–0.09; REM = 0.04; 95% CI = 0.02–0.09). Summary results are presented in Figures 3 and 4, the forest plot and Table 2.

Since the heterogeneity of study design was high, we conducted an influence analysis (Figures S1 and S2), but no precise results emerged. Therefore, the analysis of the outliers was performed automatically by the 'meta' package function. The only group with outliers was the first one, using dexmedetomidine as the only drug. Kaku et al.[23] and Lubisch et al.[24] were removed according to the analysis and the new forest plot was presented in Figure 5. The CEM and REM resulted increased

TABLE 1 Data extracted from the 20 articles selected for the meta-analysis.

Article	Type of study	Population (age mean ± standard deviation)	Intervention	Drug	Route of administration	Sedation treatment	Outcome: the number of successful procedure conducted on the total number of procedure	Adverse effect
Abulebda et al. (2018)[28]	Observational retrospective study Two treatments	ASD Dexmedetomidine $n=56$ (7.3 ± 3.3 years) Propofol $n=46$ (8.0 ± 3.9 years)	MRI	Dexmedetomidine Propofol	IV	Dexmedetomidine: initial 2 μg/kg (10′), then infusion at 1 μg/kg/h Propofol: 1 mg/kg then infusion 83 μg/kg/min	Dexmedetomidine 56 on 56 Propofol 49 on 49	Apnoea: 1 dexmedetomidine 1 propofol
Ahmed et al. (2014)[25]	Observational case–control study Retrospective study	ASD $n=56$ (6.1 ± 0.3 years) Control $n=107$ (5.0 ± 0.2 years)	MRI	Dexmedetomidine Dexmedetomidine + midazolam	IV	Dexmedetomidine: initial 2 μg/kg IV (10′) then infusion at 1 μg/kg/h Midazolam: IV 0.06 ± 0.07 mg/kg, oral 0.37 ± 0.18 mg/kg	ASD Dexmedetomidine 46 on 56 Dexmedetomidine + midazolam 10 on 10	None
Brown et al. (2019)[36]	Observational retrospective study Two treatments	ASD $n=126$ (Median 7 years, IQR 5–11) Ketamine $n=64$ Midazolam $n=64$	Laceration repair (24.6%) Incision & drainage (17.5%) Diagnostic imaging (14.3%) Physical examination (11.9%) Other in emergency department	Ketamine midazolam	IV-ketamine (71.9%) IN—midazolam (71.9%)	Ketamine: IV mg/kg 1.7 ± 0.74; IM mg/kg 3.23 ± 0.92 midazolam: IV mg/kg 0.18 ± 0.15; IN mg/kg 0.34 ± 0.15	Midazolam 59 on 64 Ketamine 64 on 64	Not reported for each drug
Capp et al. (2010)[37]	Case series prospective observational study	ASD $n=7$ (2–54 years)	Dental procedures	Midazolam	IM—IV	IM 0.2–0.3 mg/kg IV 0.1 mg/kg. local anaesthesia lidocaine 2% (0.5–2 mL)	4 on 7	None
Carlone et al. (2019)[33]	Case series observational study	ASD $n=8$ (10.25 ± 3.20 years; 5–14)	Urgent painless diagnostic procedures in the emergency department	Dexmedetomidine	IM	IM 4 μg/kg	8 on 8	None
Kaku et al. (2023)[23]	Observational case–control prospective study	ASD $n=34$ (4.67 ± 2.48 years) Control $n=31$ (5.83 ± 3.09)	MRI	Dexmedetomidine Dexmedetomidine + thiopentone	IV	Initial: 2 μg/kg, then mcg/kg/h	Dexmedetomidine 13 on 34 ASD Dexmedetomidine + thiopentone 21 on 21	None

(Continues)

TABLE 1 (Continued)

Article	Type of study	Population (age mean ± standard deviation)	Intervention	Drug	Route of administration	Sedation treatment	Outcome: the number of successful procedure conducted on the total number of procedure	Adverse effect
Kamat et al. (2018)[41]	Retrospective case–control study	ASD $n=110$ (7.5 years; 5.5–10.3) Control $n=110$ (7.6 years; 5.3–10.3)	MRI	Propofol	IV	98% propofol ASD (9.6 mg/kg) controls (11 mg/kg/h); in 6 patients used methohexital, dexmedetomidine and ketamine.	109 on 110 ASD	Serious adverse events: Airway obstruction 15 and 18 (ASD and NASD), 1 laryngospasm (NASD) Adverse events: (ASD and NASD) Desaturation 5 and 6 Agitation/delirium 3 and 1 Apnoea >15 5 and 3 Unexpected change in HR or BP 1 and 1
Kaplan et al. (2022)[16]	Prospective (dexmedetomidine) retrospective (TFS) case series observational study	ASD $n=82$ (Dexmedetomidine mean 70.4 ± 32.4 months) TSF (69.5 ± 31.6 months)	EEG	Dexmedetomidine Trichlofos sodium (TFS)	Intranasal dexmedetomidine oral TFS	Dexmedetomidine 3 μg/kg optional 1.5 μg/kg TSF initial of 50 mg/kg, and an optional addition of 25 mg/kg of TFS 45 min	Dexmedetomidine: 34 on 41 TFS: 18 on 41	Desaturation: 1 dexmedetomidine 1 TFS, bradycardia dexmedetomidine 8 Vomiting 3 TFS
Keidan et al. (2014)[29]	Retrospective observational study Two treatments	ASD $n=183$ (CH 4.8 ± 2 years, DEX 8.2 ± 4.2 years)	EEG	CH dexmedetomidine	CH oral or rectal Dexmedetomidine IV	Children 1–6 years old 50 mg/kg Children >6 years old were sedated with dexmedetomidine 1 μg/kg over 5 min (a rate of 12 μg/kg/h). Repeat infusion of 1 μg/kg (max 4) was given every 5 min	CH 99 on 108 Dexmedetomidine 73 on 84	CH: 1 oxygen desaturation dexmedetomidine: 7 hypotension and/or bradycardia, 2 oxygen desaturation
Li et al. (2019)[26]	Prospective randomised controlled trial Two treatments	ASD $n=275$ (1–12 years)	CT and/or ABR	Dexmedetomidine Dexmedetomidine + midazolam	IN—dexmedetomidine Oral—midazolam	IN dexmedetomidine 3 μg/kg oral midazolam 0.2 mg/kg	Dexmedetomidine 89 on 136 dexmedetomidine + midazolam 116 on 139	Dexmedetomidine: 5 hypotension Dexmedetomidine—midazolam 10 hypotension
Lubisch et al. (2009)[24]	Retrospective observational study two treatments	Neurobehavioral disorders $n=315$ Autism 83.1% $n=262$ (6.8 ± 3.9 years; 8 months–24 years)	MRI (77.8%)	Dexmedetomidine Dexmedetomidine + midazolam	IV/oral dexmedetomidine IV/oral/IN—midazolam	Dexmedetomidine: IV 2.6 ± 1.7, oral 3.1 ± 1.2 mg/kg midazolam: IV 0.08 ± 0.09 mg/kg IV, oral 0.45 ± 0.20 mg/kg, IN 0.30 ± 0.16 mg/kg	Dexmedetomidine: 32 on 315 Dexmedetomidine + midazolam: 279 on 283	Not reported for each drug 1 airway obstruction dexmedetomidine + midazolam
Luque et al. (2021)[32]	Retrospective case series observational study	ASD $n=37$ (47 months; 24–96)	ABR	CH Dexmedetomidine	Oral CH IN dexmedetomidine	CH: 50 mg/kg <2 years and 75 mg/kg > 2 Dexmedetomidine: IN 1–3 μg/kg/dose, if rescue of CH 2 μg/kg/dose	CH: 25 on 37 CH + dexmedetomidine: 26 on 28 Dexmedetomidine: 7 on 9	CH: 7 vomiting CH + dexmedetomidine: 4 vomiting

TABLE 1 (Continued)

Article	Type of study	Population (age mean ± standard deviation)	Intervention	Drug	Route of administration	Sedation treatment	Outcome: the number of successful procedure conducted on the total number of procedure	Adverse effect
Mcbride et al. (2020)[38]	Retrospective case series observational study	Autism/intellectual disability $n = 30$ (70.92 months; 32–200)	Ophthalmology exams	Midazolam	Oral	0.5 mg/kg	30 on 30	None
Metha et al. (2004)[17]	Prospectively case series observational study	ASD $n = 27$ (median 6 years; 2.2–16.4)	EEG	Clonidine	Oral	Median 5 mg/kg (2–7 mg/kg)	25 on 27	2 patients heart rate reduction 2 patients asymptomatic systolic blood pressure reduction
Pisalchaiyong et al. (2004)[18]	Prospective, randomised, double-blind, cross-over trial Two treatments	Autism $n = 13$ (8.68 years; 5.8–14.7)	Dental treatment	Diazepam Midazolam	Oral	Diazepam 0.3 mg/kg Midazolam 0.5 mg/kg	Diazepam: 10 on 13 Midazolam:13 on 13	None
Penna et al. (2022)[39]	Parallel, double-blind, controlled, randomised clinical trial Two treatments	ASD $n = 64$ (2–59 years)	Intravenous access	Midazolam Midazolam + ketamine	Oral	Midazolam 0.5 mg/kg Midazolam/Ketamine: midazolam dose was 0.5 mg/kg ketamine dose 3 mg/kg	Midazolam 10 on 32 midazolam + ketamine 18 on 28	Midazolam vs. Midazolam + ketamine: Agitation 3–2 Vomiting 0–1
Ray et al. (2007)[30]	Retrospective case series observational study	ASD $n = 27$ (5.6 ± 2.4 years; 2–11)	EEG	Dexmedetomidine	IV oral	Initial: oral 3.6 ± 0.8 μg/kg (2.9–4.4 μg/kg) or IV 2.1 ± 0.8 μg/kg (0.5–3.5 μg/kg) Followed by IV 1.5 ± 0.2 μg (0.5–2.0 μg/kg)	27 on 27	Not separately reported for ASD
Ross et al. (2005)[27]	Retrospective case–control observational study	ASD $n = 41$ (32.02 ± 3.6 months) Controls 43 (28.16 ± 6.7 months)	MRI	Fentanyl + pentobarbital	IV	Fentanyl 1 μg/kg Pentobarbital 1–3 mg/kg	ASD 41 on 41	None
Sahyoun et al. (2023)[27]	Case series observational study	ASD $n = 29$ (7.2 years; 4.5–11.4)	Blood draw, immunisation, EEG	Dexmedetomidine	IN	Dexmedetomidine 4 μg/kg	28 on 29	3 Prolonged sedation 1 Vomiting 1 Seizure
Shokri et al. (2019)[31]	Prospective randomised parallel group study Two treatments	ASD $n = 40$ (dexmedetomidine 7.94 ± 1.77 years, Midazolam 8.03 ± 1.7)	EEG	Dexmedetomidine Midazolam	IV	Dexmedetomidine initial 1 μg/kg (10′) then, 0.7 μg/kg/h Midazolam initial 0.05 mg/kg (2′) eventually plus 0.05 mg/kg	Dexmedetomidine: 11 on 20 Midazolam: 3 on 20	Dexmedetomidine: Bradycardia 7 Midazolam: Bradycardia 2, agitation 4

Abbreviations: ABR, auditory brainstem response; CH, chloral hydrate; CT, computerised tomography; EEG, electroencephalogram; IM, intramuscular; IN, intranasal; IV, intravenous; MRI, magnetic resonance imaging.

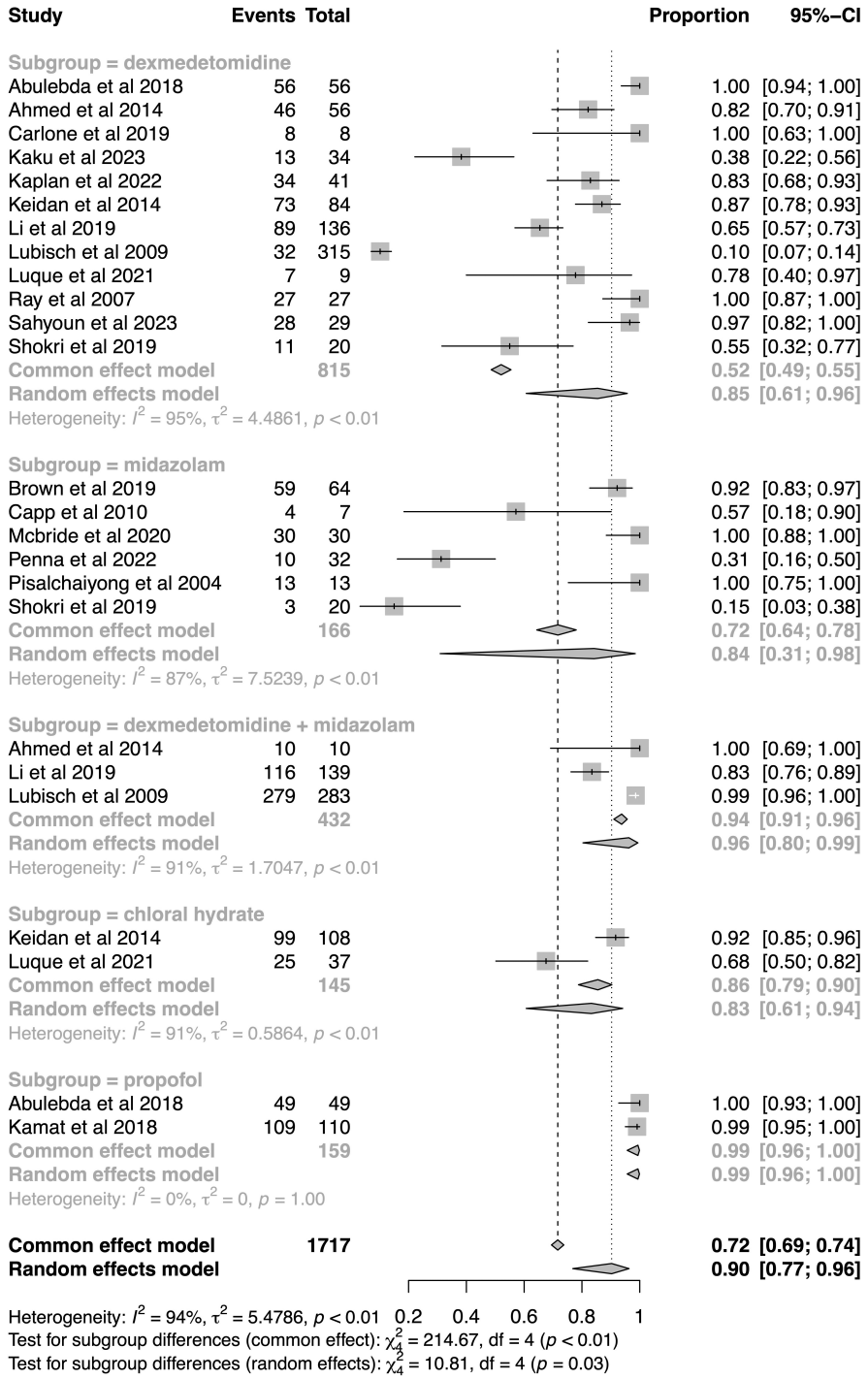

FIGURE 3 Forest plot of the meta-analysis conducted using as outcome the number of the successful procedures completed. Common and random effect model results are reported as well as heterogeneity (I^2 and τ^2). CI, confidence interval; Events, number of successful procedures completed; Total, number of patients.

(CEM = 0.81; 95% CI = 0.77–0.85; REM = 0.90; 95% CI = 0.76–0.97) and heterogeneity lowered (I^2 = 62.70%; τ^2 = 2.06).

Dexmedetomidine and dexmedetomidine plus midazolam were employed in three studies[24–26]; the OR was 0.05, with both models, indicating more efficacy of the dexmedetomidine plus midazolam regimen as compared to dexmedetomidine alone. Nevertheless, the CEM displayed a limited confidence interval range (0.04–0.08), while the REM contained 1.00 (0.00–1.59). The comparison between dexmedetomidine and chloral hydrate did not support the use of one of the two drugs in terms of sedation effectiveness (Figure 6).

When looking at the routes of administration, oral midazolam (REM = 0.99, CEM = 0.71) and IV propofol (REM = 0.99, CEM = 0.99) had the highest level of efficacy, followed by dexmedetomidine IV (REM = 0.84, CEM = 0.44) and intranasal (REM = 0.82, CEM = 0.73) (Figure S3); with a low adverse event rate (Figures S3–S6).

3.2 | Risk of bias

The risk of bias was assessed using the NHLBI's Study Quality Assessment Tool for Observational Cohort and Cross-Sectional

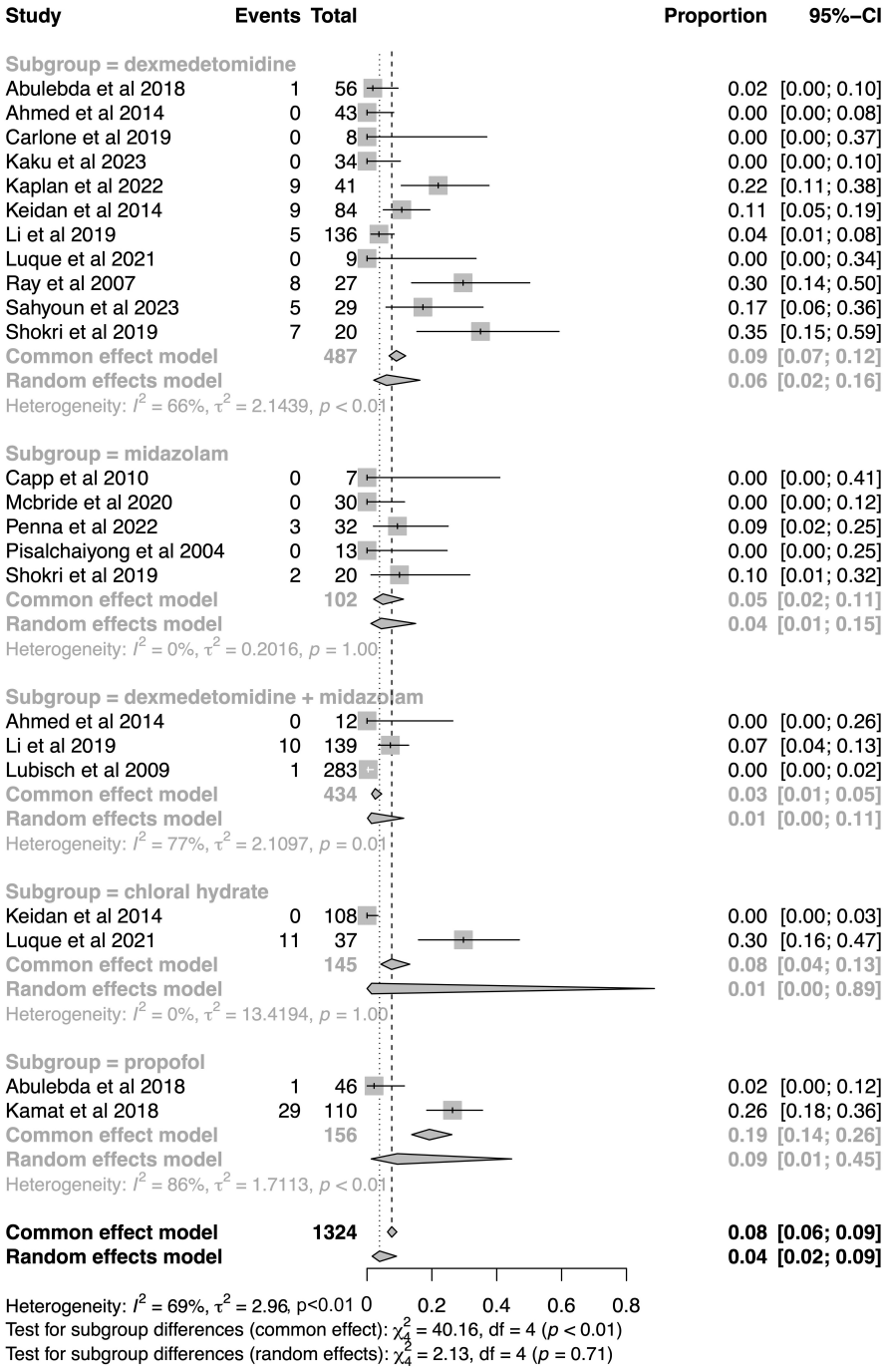

FIGURE 4 Forest plot of the meta-analysis conducted using as outcome the number of side effects. Common and random effect model results are reported as well as heterogeneity (I^2 and τ^2). CI, confidence interval; Events, number of side effects; Total, number of patients.

(Table S1). Ten studies were classified as low and 10 as moderate risk of bias (Figure 7). The main critical item was the blinding of the clinicians involved in evaluating the outcomes. Most studies lacked sample size justification, power description or variance and effect estimates, increasing the risk of bias.

3.3 | Certainty assessment

Certainty was assessed following the GRADE guidelines (Table 3). The overall judgement was 'moderate', such as the 'research conducted so far provides a good indication of the likely beneficial effect. The likelihood that the effect will be substantially different from what the study shows is moderate'.

4 | DISCUSSION

We conducted a meta-analysis of the available literature on procedural sedation in patients with ASD and found that all the studies described the significant efficacy of procedural sedation to complete medical procedures in children with ASD, independent of the drugs

TABLE 2 Summary of the meta-analysis findings.

Drug	No of studies	No of patients	No of events	%	CEM (95% CI)	REM (95% CI)	τ^2	I^2
Number of Successful sedation/procedures conducted								
Dexmedetomidine	12	815	424	52%	0.52 [0.49; 0.55]	0.85 [0.61; 0.96]	4.49	95.30%
Midazolam	6	166	119	71%	0.72 [0.64; 0.78]	0.84 [0.31; 0.98]	7.52	87.50%
Dexmedetomidine + midazolam	3	432	405	94%	0.94 [0.91; 0.96]	0.96 [0.80;0.99]	1.71	91.10%
Chloral hydrate	2	145	124	85%	0.86 [0.79; 0.90]	0.83 [0.61; 0.94]	0.59	91.20%
Propofol	2	159	158	99%	0.99 [0.96; 1.00]	0.99 [0.96; 1.00]	0.00	0.00%
Number of side effects								
Dexmedetomidine	11	487	44	9%	0.09 [0.07; 0.12]	0.06 [0.02; 0.16]	2.14	65.60%
Midazolam	5	102	5	5%	0.05 [0.02–0.11]	0.04 [0.01–0.15]	0.20	0.00%
Dexmedetomidine + midazolam	3	434	11	2.5%	0.03 [0.01; 0.05]	0.01 [0.00–0.11]	2.11	76.60%
Chloral hydrate	2	145	11	8%	0.08 [0.04; 0.13]	0.01 [0.00; 0.89]	13.42	0.00%
Propofol	2	156	30	19%	0.19 [0.14; 0.26]	0.09 [0.01; 0.45]	1.71	86.2%

Abbreviations: CEM, common effect model; CI, confidence interval; NR, not reported; REM, random effect model.

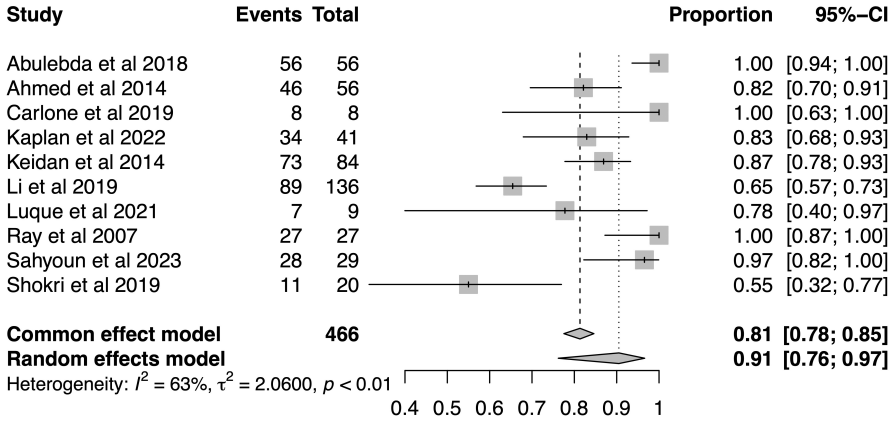

FIGURE 5 Forest plot of the meta-analysis conducted using as outcome the number of side effects and removing outliers.[23,24] Common and random effect model results are reported as well as heterogeneity (I^2 and τ^2). CI, confidence interval; Events, number of side effects; Total, number of patients.

employed. The two most investigated single-drug regimens were dexmedetomidine and midazolam, primarily for diagnostic imaging. These regimens were safe and effective.

Considering the studies as single arm based on the pharmacological agents used, propofol had the highest efficacy. However, it was employed only in two studies with numerous adverse events and requires intravenous access which can be difficult to obtain in these patients, often requiring physical restrains or other interventions such as topical anaesthesia or pre-medication for anxiolysis.

The second most effective drug was dexmedetomidine used in 12 of the 20 studies with 815 patients. The third was midazolam and the last chloral hydrate. However, midazolam, as a single agent, had the highest number of sedation failures.

Dexmedetomidine appeared to be a safe alternative for sedation in infants and children. It could be administrated via different routes such as the intranasal (IN), intramuscular (IM) and intravenous (IV).[27] In our meta-analysis, seven studies employed intravenous,[23–25,28–31] four intranasal,[16,26,27,32] two oral (O)[24,30] and one intramuscular.[33] The studies analysed documented 27 cases of adverse events, specifically, one apnoea, one desaturation, 15 bradycardia, five hypotension, three prolonged sedations, one vomiting and one seizure. As expected, the few adverse events were mainly linked to hemodynamics, such as bradycardia and hypotension, with minimal impact on respiration. It is well established that in the setting of dexmedetomidine related adverse effects, interventions are rarely required and may be strongly influenced by underlying and/or concomitant abnormalities, such as myocardiopathies, arrythmia, drug induced bradycardia and/or hypotension.[34] Considering the route of administration, the use of the IV or IN route appeared to be similar when using the REM model. The use of the IN route appeared to be superior in term of successful procedures with respect to the IV when the CEM model was applied. This may be due to a bias related to both the analysis (REM is considered more conservative and more appropriate to heterogeneous studies with respect to CEM[35]) and to the type of procedure. Sedation of short and/or non-painful procedures, such as EKG or EEG, will require a lower sedation level compared to a sedation performed for MRI or a painful procedure, showing a major effectiveness versus a non-intravenous approach.[34]

Midazolam had mild adverse events, mainly concerning agitation, but the efficacy was as the lowest among the studies analysed.[18,31,36–39] It was mainly administered by orally ($n = 3$), while IN ($n = 1$) and IV routes ($n = 1$) were less represented.

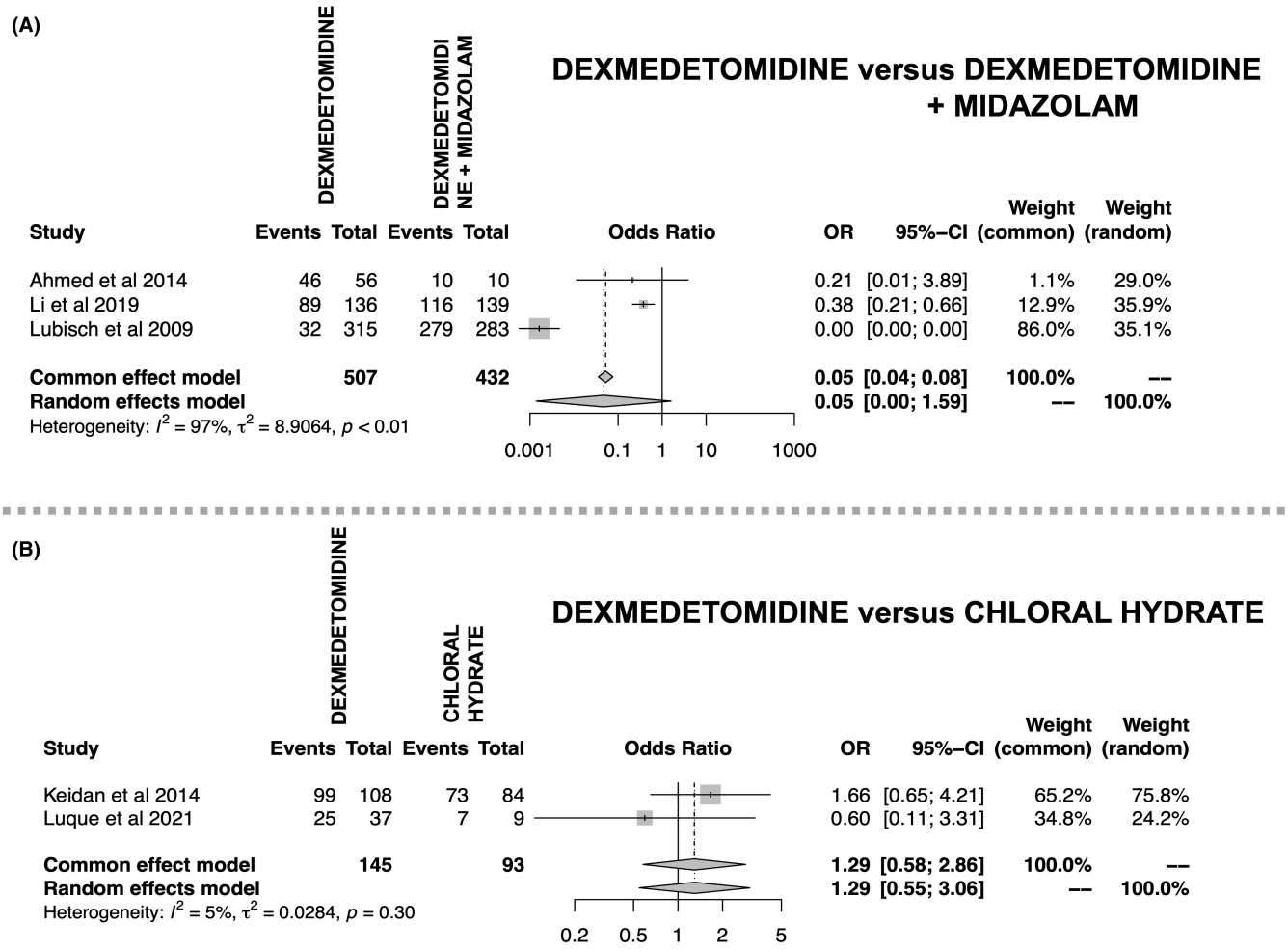

FIGURE 6 Forest plot of the meta-analysis conducted on the studies where two different drugs are employed. The outcome is the number of the successful procedures completed. Common and random effect model results are reported as well as heterogeneity (I^2 and τ^2). (A) Dexmedetomidine versus dexmedetomidine plus midazolam. (B) Dexmedetomidine versus choral hydrate. CI, confidence interval; Events, number of successful procedures completed; OR, Odds Ratio; Total, number of patients.

Chloral hydrate has a history of severe adverse events and fatalities and its production was suspended in the United States in 2012[40] and banned in some European countries. Nevertheless, its use in procedural sedation in children with ASD showed medium-high efficacy and few adverse events.[29,32]

Due to its adverse effects and the availability of safer and more effective pharmacological choices, the Chloral hydrate use should be limited to settings without any other possible pharmacological option.

Six studies investigated the combination of two drugs.[19,23–26,39] In three papers,[24–26] the same combination, dexmedetomidine plus midazolam, showed high efficacy and low rate of adverse events. Few studies directly compared different drugs (dexmedetomidine versus dexmedetomidine plus midazolam[24–26] and dexmedetomidine versus choral hydrate[29,32]) but the meta-analysis did not indicate the superiority of one drug over the other; however, a trend suggested that successful sedation was more likely to occur when children were sedated with the combination of the dexmedetomidine plus midazolam, rather than the dexmedetomidine alone.

4.1 | Limitations

The main limitation of this meta-analysis was the high frequency of observational nature of the studies selected. Eleven were retrospective observational studies, including three case–control studies. Three studies were prospective observational studies with one case–control study, finally two were case series papers. Only four works were randomised prospective trials. However, these studies were too few to conduct a sub-analysis of the current regimens employed in the procedural sedation of patients with ASD.

Another limitation is the route of administration, as most of the studies used the IV route. Intravenous access is a procedure that in this population, as a rule, may require interventions, not only in terms of distraction, but often physical restraint or a premedication. When looking at the route of administration, IV, IN or O did not appear to be different in term of efficacy with REM, although IV appeared to be inferior respect to IN or O, when using the CEM. Adverse effects did not vary between the routes of administration. Finally, the limited number of studies did not allow to

FIGURE 7 Risk-of-bias visualisation by using the 14 items of the NHLBI (National Heart, Lung and Blood Institute)'s Study Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies reported in detail in Table S1. (A) 'Traffic plot' of risk of bias' results in each study for each question and (B) weighted bar plots representing the distribution of risk-of-bias evaluation within each of the 14 bias items. Two of the authors evaluated independently the selected articles and they classified each item as low, moderate, high or critical risk of bias. An overall classification was then performed, considering the scale with the following numerical values: Low = 0, moderate = 1, high = 2 and critical = 3. The numerical sum of each item was employed for the 'overall' classification in the four areas, low = 0–10 (0%–25%), moderate = 11–21 (25%–50%), high = 21–31 (50%–75%) and critical = 32–42 (75%–100%).

TABLE 3 GRADE summary of findings table.

Certainty assessment								
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Impact**	**Certainty**
Outcome: number of successful procedures								
20	Observational studies	Not serious	Serious due to high heterogeneity	Not serious	Not serious	None	The procedural sedation is an effective treatment to allow the success of the medical procedures in children with ASD	⨁⨁⨁◯ Moderate due to inconsistency
Outcome: number of side effects								
20	Observational studies	Serious due to no reporting of mild severe effects	Serious due to high heterogeneity	Not serious	Not serious	None	Low number of side effects shows the safety of the procedures in children with ASD	⨁⨁◯◯ Low due to risk of bias and inconsistency

define whether the likelihood of success of each drug, or combination of drugs, was proportional to the type of procedure or to the route of drug administration performed.

In patients with ASD non-pharmacologic strategies can play a significant role in a successful preparation for sedation, with a significant impact on quality of care. These strategies should include a previous knowledge of patients' and parents' fears and preferences, anticipated knowledge of possible distraction strategies, creation of patient-centred, adequate and quiet environment, with reduced noise and light stimuli. Additionally, desensitisation techniques for venipuncture or intranasal administration can be employed to improve the overall experience.

5 | CONCLUSION

Multiple effective drug regimens currently exist for procedural sedation in children with ASD. Considering the traumatic experience that children with ASD often encounter in their medical encounters, non-IV regimens would be preferable with respect to the IN or oral and should be considered to facilitate venous access when deeper levels of sedation are required. These alternatives are not only effective but tend to be more acceptable from the parents' and patients' perspective. The results of this meta-analysis highlighted the efficacy of most of the regimens already in use, moreover, these data could support the development of evidence-based guidelines for procedural sedation in children with ASD.

AUTHOR CONTRIBUTIONS

Luisa Zupin: Conceptualization; data curation; methodology; writing – original draft. **Cyril Sahyoun:** Writing – review and editing; conceptualization; visualization. **Baruch Krauss:** Conceptualization; visualization; writing – review and editing. **Arianna Dagri:** Writing – review and editing; data curation. **Elisabetta Maria Rocco:** Data curation; writing – review and editing. **Egidio Barbi:** Conceptualization; visualization; supervision; writing – review and editing; methodology. **Fulvio Celsi:** Conceptualization; methodology; data curation; visualization; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors have no relevant financial or non-financial interests to disclose.

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Additional supporting information can be found online in the Supporting Information section at the end of this article.

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