Review Article

The Effects of Sedation on Auditory Brainstem Response in Pediatric Population: A Systematic Review

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Highlights

- Intranasal dexmedetomidine sedation failure rate is less than chloral hydrate
- The melatonin reduces the time requires for auditory brainstem response

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ABSTRACT

Background and Aim: Auditory Brainstem Response (ABR) is crucial for evaluating auditory pathway function in pediatric patients. However, obtaining reliable ABR measurements in young children can be challenging due to their inability to stay still and quiet during the test. Sedation is frequently used to facilitate ABR testing in this population, but the most practically effective sedation method and its impact are still uncertain. This systematic review aimed to thoroughly investigate the success rates (completion of ABR in both ears) associated with different sedation techniques.

Recent Findings: In recent review (2000-2022), Ten studies, identified through a comprehensive search of electronic databases, were included in the analysis. The studies reported significant variation in success rates for ABR testing with sedation, ranging from 70% to 100%. This suggests that the effectiveness of sedation may not be uniform across all situations. The included studies employed a wide variety of sedation techniques, highlighting the lack of a standardized approach in this area.

Conclusion: These findings highlight the heterogeneity in sedation practices and success rates for pediatric ABR testing. This emphasizes the importance of tailoring the sedation approach to the specific needs of each child while carefully considering the potential risks associated with each sedation method. Further research is warranted to establish standardized protocols for sedation in pediatric ABR , ensuring optimal test efficacy while prioritizing patient safety. Research Square registration DOI: (https://doi.org/10.21203/rs.3.rs-2388140/v1).

Keywords: Auditory brainstem response; sedation; chloral hydrate; children; dexmedetomidine; intranasal drug administration

Introduction

Auditory Brainstem Response (ABR) is a critical tool in the assessment of auditory function in pediatric populations [1]. ABR measures the electrical activity generated by the auditory nerve and brainstem in response to acoustic stimuli, providing valuable insights into the integrity of the auditory pathway, especially in children who are unable to participate in behavioral hearing assessments [2]. This non-invasive and objective technique has played an indispensable role in the early identification and diagnosis of hearing impairment, guiding treatment decisions and therapeutic interventions, and monitoring the progress of various auditory disorders in the pediatric population [3]. Despite the critical importance of ABR in pediatric audiology, conducting this assessment can be challenging in young children due to their limited capacity to remain still and attentive during the procedure. To mitigate these challenges, sedation has been employed to induce a state of calmness and cooperation, facilitating the acquisition of accurate ABR data [4, 5]. However, the use of sedation in pediatric ABR raises pertinent questions concerning its efficacy, safety, and impact on the accuracy of test results [6-13]. Previous systematic reviews in this field have primarily focused on melatonin for ABR. However, the limited number of studies (e.g. 5 studies in one review) restricts the generalizability of findings. Additionally, methodological variations, such as differences in melatonin dosing and control groups, hinder definitive conclusions about its efficacy in children [6]. A 2022 systematic review by Marra et al. examined the potential of intranasal dexmedetomidine (IN DEX) as a new sedative for ABR evaluation in children. Most studies reported IN DEX to be an effective drug, particularly at a 3 µg/kg dosage. Compared to oral chloral Hydrate (CH) used in some studies, IN DEX demonstrated greater efficiency and fewer side effects. While this review suggests IN DEX as a promising sedative with minimal adverse effects, further comprehensive studies are needed before recommending its clinical application in ABR testing [7]. Another systematic review by Liu et al. investigated the effectiveness and safety of chloral hydrate for ABR evaluation. They found a success rate of around 90% for sedation using chloral hydrate. However, sample size and sleep deprivation significantly impacted sedation failure rates. Smaller samples and less sleep deprivation led to higher failure rates. The authors concluded that the significant side effects and high failure rate of chloral hydrate warrant exploring safer and more effective sedation methods for ABR in children [8]. A comprehensive understanding of the effectiveness and safety of various sedation regimens, their influence on test outcomes, and their potential long-term effects is currently lacking. We aimed to perform a comprehensive search to assess the effect of different sedation methods for ABR in pediatrics. Our primary goal was to evaluate the success rate of a completed ABR procedure in both ears. Secondary goals include determining the time and dose required to complete ABR evaluation in different sedation drugs, evaluating heterogeneity, and finding its potential sources.

Methods

The protocol of the present study was registered in ResearchSquare (https://doi.org/10.21203/rs.3.rs-2388140/v1). There was a protocol amendment: We evaluated the quality assessment of trial studies using RoB 2.0 [9] rather than Verhagen. The present study was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. (Appendix 1)

Search strategy

To review the existing literature, we employed a systematic approach for searching and identifying relevant studies. This search was carried out across various electronic databases. including PubMed/MEDLINE, Web of Science, Scopus, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Google scholar from 2000 until May 2022. In addition, clinical trial registries including clinical trial.gov, International Standard Randomized Controlled Trial Number (ISRCT), and International Clinical Trials Registry Platform (ICTRP) will be searched for ongoing trials with no restrictions placed on language. We translated non-English papers using Google Translate. Additionally, grey literature including ProQuest for related thesis/dissertation, Scopus and Web of Science for conference papers, and reference list of primary studies will be searched, and hand searching will be done for the last 6 months' publications from the British Journal of Anesthesia and Anesthesiology. (Appendix 2). According to the Mesh database and previous systematic reviews, the primary search strategy

has been developed in PubMed by using two components of the Population, Intervention, Comparison, Outcomes (PICO) structure including intervention (sedation) and outcome (auditory brainstem response).

Inclusion and exclusion criteria

Studies were included in this systematic review if they met the following criteria: pediatric above 6 months with/without hearing loss and without any comorbidities, any kind of sedation used during the ABR test such as chloral hydrate, melatonin, dexmedetomidine, propofol, benzodiazepines, ketamine, narcotics, midazolam, etc. studies with/without comparison groups, studies that assess the success rate of a completed ABR in both ears as a primary goal, the time required for a successful ABR, and the dose required for a successful ABR in different sedation methods. This systematic review will include any clinical trials (with any study design such as single-group, pre- and post-design studies to two- or multiple-arm, parallel-group design studies with or without random allocation), cohort studies, retrospective, prospective studies, and repeated measure designs. Exclusion criteria included studies that did not focus on pediatrics, studies exclusively involving adults, and studies without clear information about sedation methods and ABR.

Study selection/quality assessment

The results were saved in Mendeley 1.19.4, and duplicates were removed. One researcher performed the initial screening of titles and abstracts according to pre-established inclusion and exclusion criteria. Subsequently, two independent reviewers evaluated the full-text articles of potentially qualified studies for their ultimate inclusion. Any disagreements between reviewers were resolved through discussion and, if necessary, consultation with a third reviewer.

We designed a standardized data extraction template to systematically gather data from the included studies. Data extraction included study characteristics (e.g. authors, publication year, study design), age, sedation drug, sedation method, dose of sedation, time of sedation, and time for completed ABR.

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies and the Risk of Bias 2.0 (RoB 2.0) tool for Randomized Controlled Trials (RCTs) by the two authors independently [9, 10]. Any disagreements between reviewers were resolved through discussion and, if necessary, consultation with a third reviewer.

The data synthesis process involved a narrative approach, as we could not perform a meta-analysis due to expected heterogeneity among included studies. Findings from selected studies were synthesized to provide a comprehensive overview of the efficacy of sedation for ABR.

Results

The search results show in Figure 1. After screening we identified 238 papers, of which 10 met the inclusion criteria and were included in the systematic review.

Characteristics of included studies

Ten studies were reviewed, comprising six cohort studies [5,11-15], and four Randomized Controlled Trials (RCTs) [16-19]. They are offering insights into pediatric ABR with diverse methodologies and patient demographics. Detailed characteristics of the included studies are summarized in Table 1.

Patient demographics

In this section, we provide a comprehensive overview of the demographic characteristics of the pediatric patients included in the studies selected for this systematic review.

Age distribution

The age range varied from infants to 18-year-old adolescents, demonstrating the wide applicability of sedation across age groups.

Gender distribution

A balanced representation of both genders was maintained in the studies.

Medical conditions

All studies focused on pediatric patients without developmental or neurological conditions.

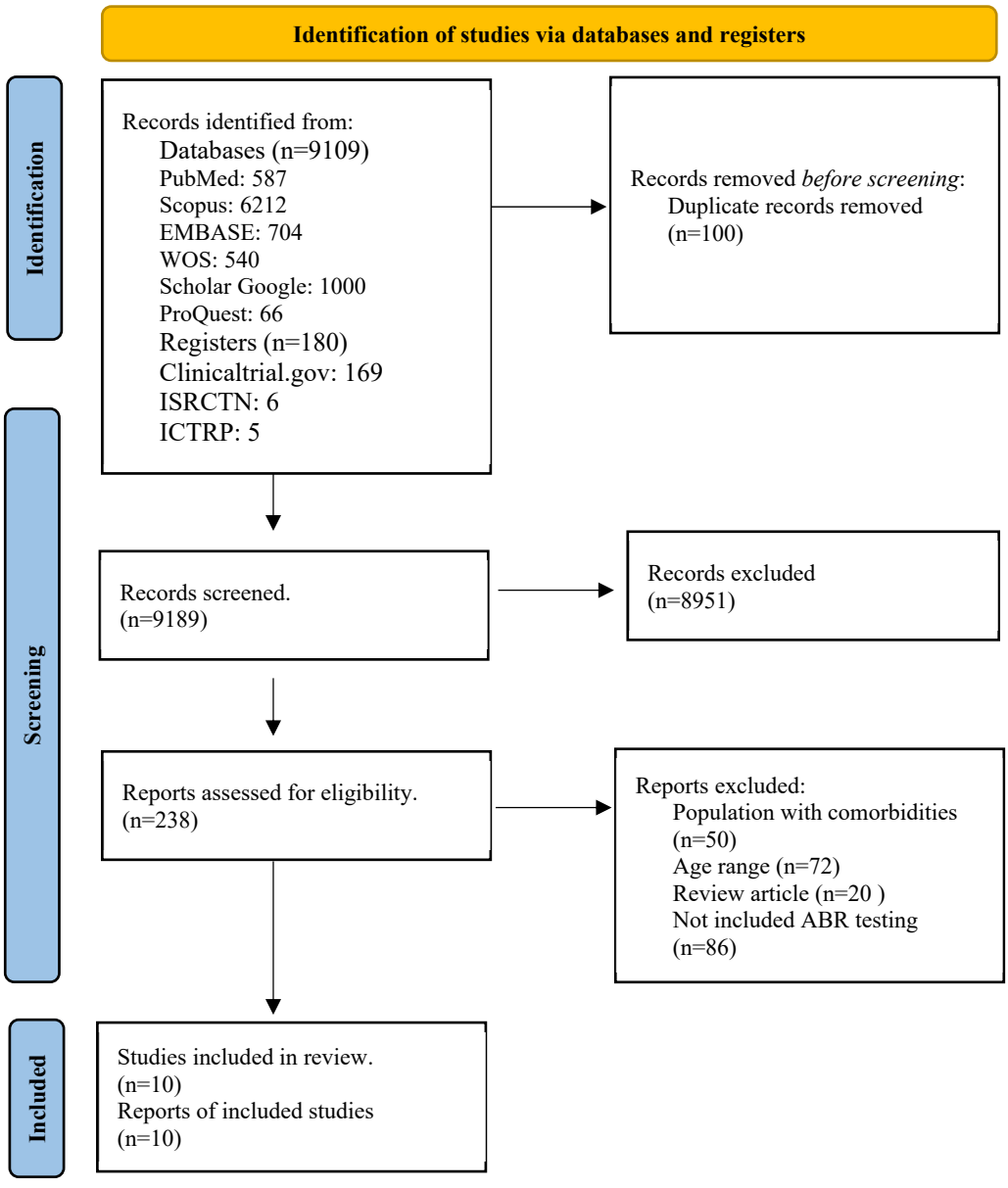

Figure 1. PRISMA flow chart of study

Sedation

Sedation method

Studies examined different sedation methods, each tailored to pediatric needs.

Intravenous sedation

Several of the included studies utilized Intravenous (IV) sedation as a means of facilitating ABR in pediatric patients. IV sedation methods included medications such as propofol, propofol plus ketamine, and midazolam. Intravenous sedation is often chosen for its rapid onset of action and titratable effects, making it suitable for children of different age groups.

Intranasal sedation

Intranasal sedation, a relatively novel approach, has been employed in specific studies to facilitate pediatric ABR. Medications such as dexmedetomidine plus midazolam are administered through the nasal mucosa, allowing for rapid absorption and sedation induction. This method is particularly advantageous in scenarios where intravenous access is challenging or when a less invasive approach is preferred.

Table 1. Study characteristics

Author, year	Study design	Sample size	Age (year)	Sedation agent	Sedation dosage	Time for completion of ABR (min)	Completed ABR rate
Akin et al. [19]	Control trial	60	4.5	Intravenous propofol versus propofol—ketamine	P:1.5 mg/kg–PK: 1.5 mg/kg propofol+0.5 mg/kg ketamine	9-10	100% in all cases
Della Volpe et al. [17]	Randomized control trial	294	2.5	MELAMIL TRIPTO® (solution that in 0.5 ml contains a 1 mg of melatonin, 20 mg of tryptophan, and 1.4 mg of vitamin B6)	Group A: 6 mg melatonin +120 mg tryptophon +8.4 mg B6 Group B: 3 mg melatonin +60 mg tryptophon +4.2 mg B6 Group C: 1 mg melatonin +20 mg tryptophon +1.4 mg B6	-	100%
Li et al. [16]	Randomized control trial	160	2.5	Intranasal dexmedetomidine and buccal midazolam combination versus oral chloral hydrate	Ch: 50 mg/kg oral with intranasal placebo with 0.9% sodium chloride at 0.03 mg/kg IND: 3 µg/kg plus buccal midazolam at 0.1 mg/kg	12–13	dexmedetomidine: 90% chloral hydrate: 70%
Reynold et al. [18]	Randomized control trial	85	2	intranasal dexmedetomidine versus oral chloral hydrate	CH: 50 mg/kg IND 3 mcg/kg	80–110	Chloral hydrate: 93% dexmedetomidine: 97%
Abulebda et al. [13]	Retrospective cohort	190	2	Intravenous propofol-ketamine versus oral chloral hydrate	IB: Ketamin bolus (0.5 mg/kg<20kg, 0.25 mg/kg>20 kg) followed by induction propofol bolus (1 mg/kg) over 1-to-2-minute CG: propofol infusion (83 mcg/kg/min)	-	100% in all cases
Keidan et al. [15]	Retrospective cohort	200	1.2	chloral hydrate	50–60 mg/kg	-	chloral hydrate without fasting: 97% chloral hydrate with fasting: 92%
Reynold et al. [14]	Retrospective cohort	300	2.3	oral chloral hydrate versus intranasal dexmedetomidine	IND: 4 µg/kg (MAXIMUM 100 µg/kg) CH: not xpressed	-	chloral hydrate: 90% dexmedetomidine: 91%
Hajjij et al. [11]	prospective cohort	247	2.9	Oral melatonin	2–5 mg (1–3 years children) 5–10 mg (3–6 years children)	20–30	83.4%
Levit et al. [12]	Retrospective cohort	501	2	Intravenous triclofos versus propofol	Triclofos: initial dose (50 mg/kg) propofol: 0.8 mg/kg bolus followed by continous infusion at an initial rate of 0.1 mg/kg/min	70–77	100% in all cases
Valenzuela et al. [5]	Retrospective cohort	635	-	oral chloral hydrate	50 mg/kg fpr children under 2 years 75 mg/kg for children over 2 years (max dose 1000 mg)	-	95.9%

Oral sedation

A few studies incorporated oral sedation methods, using medications such as oral melatonin, chloral hydrate, and triclofos. This approach is particularly applicable for children who may have difficulty tolerating intravenous or intranasal sedation and can be administered in a more child-friendly manner.

Sedation dosage

Individualized dosages were calculated, considering patient age, weight, and the sedative agent, balancing sedation effectiveness with safety.

Sedation time required for completion of auditory brainstem response testing

The systematic review revealed significant variability in the time needed for the completion of ABR with different sedation methods. It is worth noting that certain papers within the study did not provide explicit details regarding the duration required for the completion of ABR [5, 13-15, 17], Some sedation techniques led to shorter testing durations ranged from 10–30 min [11, 16, 19], while others were associated with longer periods ranged from 50 to 100 min [12, 18] (Table 1).

Success rate of auditory brainstem response testing with different sedation methods

The primary objective of this systematic review was to evaluate the success rate of ABR when conducted with various sedation methods. The success rate was defined as the completion of ABR in both ears of pediatric patients. This rate ranged between 70% to 100% in different sedation methods. Total success rates were tabulated in Table 1.

Outcome measures

This subsection provides a detailed exploration of the main outcome measures utilized in the studies included in this systematic review. These measures were instrumental in evaluating the effectiveness and safety of various sedation methods in the context of pediatric ABR.

Hemodynamic stability

Akin et al. found that the propofol-ketamine combination outperformed propofol alone. It led to significantly lower systolic and diastolic arterial pressure, heart rate, and respiratory rate. Moreover, this combination resulted in fewer side effects, such as injection pain, apnea, and vomiting [19].

Time efficiency

Della Volpe et al. demonstrated that pre-treatment with MELAMIL TRIPTO® reduced ABR duration by approximately 15 minutes compared to other sedatives. Importantly, the quality of ABR signals remained consistent across treatments [17].

Sedation success

In Li et al. the dexmedetomidine plus midazolam group achieved a significantly higher sedation success rate (97.5%) than the chloral hydrate group (87.5%). Additionally, the former group experienced shorter onset, waiting, and discharge times, along with a quicker return to normal activities. Both groups had similar examination durations and incidence of adverse events [16].

Intranasal superiority

Reynolds et al. reported that intranasal dexmedetomidine was more effective than oral chloral hydrate for pediatric ABR. It resulted in a higher rate of successful sedation (94.6% vs. 77.8%) and reduced the time from sedation initiation to ABR completion. Notably, intranasal dexmedetomidine demonstrated a higher incidence of bradycardia [18].

Efficiency vs. Hypoxemia

Abulebda et al. compared procedural deep sedation with propofol-ketamine to moderate sedation with chloral hydrate. The former was more efficient in terms of procedure time and recovery but carried a higher risk of transient hypoxemia [13].

Impact of fasting

Keidan et al. noted that fasting was associated with an increased sedation failure rate, necessitating higher chloral hydrate doses and prolonged sedation. No

significant differences in adverse effects were observed between the groups [15].

Single-dose efficiency

Reynolds et al. found that intranasal dexmedetomidine (IN DEX) excelled in completing ABR examinations with a single dose of medication, although the study was underpowered to draw definitive safety conclusions [14].

Melatonin as an alternative

Hajjij et al. introduced melatonin as an efficient alternative to sedation, inducing natural sleep, reducing sleep delay, and carrying no adverse effects or respiratory depression risk. Its outpatient feasibility can enhance ABR efficiency, particularly for children [11].

Triclofos and Propofol for evaluating children with Hearing Loss

Levit et al. suggested that triclofos and propofol sedation are safe and effective in improving ABR quality in pediatric patients with hearing loss [12].

Chloral Hydrate Efficacy

Valenzuela et al. confirmed the safety and efficacy of chloral hydrate sedation for ABR in children. They noted a high success rate and provided insights into addressing sedation failure scenarios [5].

Quality assessment

Quality assessment was conducted separately for the two types of studies: cohort studies and randomized controlled trials. All six of the cohort studies achieved a good quality rating on the NOS scale. This means that the studies had a representative exposed and non-exposed cohort, a reliable and valid method for measuring exposure, and adequate control for confounding factors (Table 2 a). Three of the four RCTs achieved a low risk of bias on the RoB 2.0 tool. This means that the studies had a low risk of bias in the domains of selection of participants, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective reporting, and other biases. One RCT had a moderate risk of bias in the domain of allocation concealment. This means that there is some concern that participants may have been assigned to different groups based on their characteristics, which could introduce bias into the trial results (Table 2 b).

Overall, the quality of the included studies was good. The cohort studies all achieved a good quality rating on the NOS scale, and three of the four RCTs achieved a low risk of bias on the RoB 2.0 tool. The quality of the included studies was good. The cohort studies all achieved a good quality rating on the NOS scale, and three of the four RCTs achieved a low risk of bias on the RoB 2.0 tool. This means that the results of these studies can be interpreted with confidence.

Discussion

The comprehensive review of ten selected studies sheds light on the effectiveness and safety of various sedation methods in the context of pediatric ABR. The studies, varying in design and methodology, encompassed

Table 2 a. Quality assessment of 6 cohort studies using Newcastle-Ottawa scale

Author, year	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow-up of cohort	Total score	Overall rating
Abulebda et al. [13]	1	1	1	1	1	1	1	1	8	Good quality
Keidan et al. [15]	1	1	1	1	1	1	1	1	8	Good quality
Reynold et al. [14]	1	1	1	1	1	1	1	1	8	Good quality
Hajjij et al. [11]	1	Not applicable	1	1	Not applicable	1	1	1	6	Good quality
Levit et al. [12]	1	1	1	1	1	1	1	1	8	Good quality
Valenzuela et al. [5]	1	Not applicable	1	1	Not applicable	1	1	1	6	Good quality

Table 2 b. Quality assessment of 4 randomized control trial studies using RoB 2.0 tool

Study ID	Randomization process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Della Volpe et al. [17]	Some concern	Some concern	Low risk	Low risk	Low risk	Some concern
Li et al. [16]	Low risk	Some concern	Low risk	Low risk	Low risk	Some concern
Reynolds et al. [18]	Low risk	Some concern	Low risk	Low risk	Low risk	Some concern
Akin et al. [19]	Some concern	Some concern	Low risk	Low risk	Some concern	Some concern

diverse patient populations, sedation protocols, and outcome measures, offering valuable insights into the complexities of sedating pediatric patients for ABR.

One prominent aspect illuminated in this review is the diversity of sedation methods employed. Intravenous sedation, particularly the propofol-ketamine combination, emerged as a viable option due to its ability to maintain hemodynamic stability. This is crucial when conducting ABR, as fluctuations in vital signs can affect the accuracy of results. The combination not only ensured stable hemodynamics but also minimized common side effects associated with sedation [19].

In contrast, intranasal sedation, though relatively new, demonstrated superior efficacy, especially in terms of time efficiency. Studies highlighted that intranasal dexmedetomidine enabled rapid absorption and sedation induction, leading to shorter testing durations. However, it's worth noting that this method did exhibit an increased risk of bradycardia, which should be weighed against its benefits [16].

The efficacy of oral sedation methods was also observed. The use of melatonin as a sedative was particularly promising, as it reduced the time required for ABR and eliminated adverse effects, making it a suitable alternative for inducing natural sleepin pediatric subjects. Such sedation protocols are feasible in outpatient settings and could substantially reduce waiting times [11].

Furthermore, the review disclosed critical details regarding the dosage of sedative agents. Tailoring dosages to factors such as patient age and weight proved instrumental in achieving the right balance between sedation adequacy and safety. These findings underscore the need for personalized approaches to sedation in pediatric ABR.

This review's primary objective was to assess the success rate of ABR with different sedation methods, focusing on successful completion in both ears. The collected data showed varying success rates ranging from 70% to 100%. This variance is influenced by multiple factors, including the sedation method employed and the patient population.

Despite the invaluable insights offered by these studies, it is essential to acknowledge their limitations. Some studies lacked detailed information regarding the time required for ABR, which hinders the ability to draw comprehensive conclusions about the efficiency of different sedation methods. Moreover, certain studies had sample limitations and might not have been sufficiently powered to detect differences in the low incidence of adverse effects, limiting the capacity to make broad safety assertions.

Conclusion

In conclusion, the review underscores the diversity and adaptability of sedation methods for pediatric auditory brainstem response. While certain sedation approaches exhibit advantages in terms of stability and time efficiency, it is imperative to consider the specific needs of individual patients and the potential risks associated with each method. Further research in this field is required to enhance our understanding and refine the protocols, ultimately ensuring that pediatric patients receive safe and effective sedation during ABR.

Ethical Considerations

Compliance with ethical guidelines

The authors certify that this work was completed in compliance with ethical standards.

Funding

There was no external funding.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

TF: Study design; MAS: Study design; MM: Interpretation of results; FJ: Interpretation of results; AP: Statistical analysis.

Conflict of interest

The authors have no conflicts of interest to declare.

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Appendix 1. PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Line 2
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	9-20
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	47-49
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	49-54
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	84-102
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	60-73
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	107
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	113
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	124
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	124
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	118
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	124
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	-
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	-
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	-
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	-
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	-
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	118
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	132
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	237
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	-
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	-
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	-
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	-
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	-
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	266
	23b	Discuss any limitations of the evidence included in the review.	299
	23c	Discuss any limitations of the review processes used.	302
	23d	Discuss implications of the results for practice, policy, and future research.	309

Continued Appendix 1

Section and Topic	Item #	Checklist item	Location where item is reported
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	57
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	57
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	58
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	315
Competing interests	26	Declare any competing interests of review authors.	318
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	316

Appendix 2. Search syntax

Search round	Syntax
PubMed	(Sedative[all] OR sedation*[all] OR chloral hydrate[all] OR melatonin[all] OR dexmedetomidine[all] OR propofol[all] OR benzodiazepines[all] OR ketamine[all] OR narcotics[all] OR midazolam[all]) AND (ABR [all] OR "short-latency auditory evoked potential*" [all] OR "Auditory Evoked Potential*" [all] OR ("Evoked Potential*" [all] AND Auditory[all]) OR "Auditory Evoked Response*" [all] OR ("Evoked Response*" [all] AND Auditory) OR "Auditory Evoked Potential*" [all] OR "Brainstem Auditory Evoked Potential*"[all] OR ("Evoked Potential*"[all] AND Auditory[all] AND Brainstem[all]) OR "Auditory Brainstem Evoked Response*"[all] OR ("Evoked Response*"[all] AND Auditory[all] AND Brainstem[all]) OR "Acoustic Evoked Brain Stem Potential*"[all] OR "Auditory Brain Stem Evoked Response*"[all] OR ("Evoked Response*"[all] AND Auditory AND Brain Stem[all]) OR "Auditory Brain Stem Response*"[all] OR "Brain Stem Auditory Evoked Potential*"[all] OR "Acoustic Evoked Brainstem Potential*"[all] OR "Auditory Brainstem Response*"[all] OR ("Brainstem Response*"[all] AND Auditory[all]) OR (Response*[all] AND "Auditory Brainstem" [all])) AND 2000/01/01:2022/07/31[dp]
Scopus	(TITLE-ABS(Sedative) OR TITLE-ABS (sedation*) OR TITLE-ABS(chloral hydrate) OR TITLE-ABS(melatonin) OR TITLE-ABS(dexmedetomidine) OR TITLE-ABS(propofol) OR ALL(benzodiazepines) OR ALL(ketamine) OR ALL(narcotics) OR ALL(midazolam)) AND (ALL(ABR) OR ALL("short-latency auditory evoked potential*") OR ALL("Auditory Evoked Potential*") OR (ALL("Evoked Potential*") AND ALL(Auditory)) OR ALL("Auditory Evoked Response*") OR (ALL("Evoked Response*") AND ALL(Auditory)) OR ALL("Auditory Evoked Potential*") OR ALL("Brainstem Auditory Evoked Potential*") OR (ALL("Evoked Potential*") AND ALL(Auditory) AND ALL(Brainstem)) OR ALL("Auditory Brainstem Evoked Response*") OR (ALL("Evoked Response*") AND ALL(Auditory) AND ALL(Brainstem)) OR ALL("Acoustic Evoked Brain Stem Potential*") OR ALL("Auditory Brain Stem Evoked Response*") OR (ALL("Evoked Response*") AND ALL(Auditory) AND ALL(Brain Stem)) OR TITLE-ABS("Auditory Brain Stem Response*") OR TITLE-ABS("Brain Stem Auditory Evoked Potential*") OR TITLE-ABS("Acoustic Evoked Brainstem Potential*") OR TITLE-ABS("Auditory Brainstem Response*") OR (TITLE-ABS("Brainstem Response*") AND TITLE-ABS(Auditory)) OR (TITLE-ABS(Response*) AND TITLE-ABS("Auditory Brainstem"))) AND PUBYEAR > 1999 AND PUBYEAR < 2023 AND NOT PUBDATETXT ("august 2022" OR "September 2022" OR "October 2022" OR "November 2022" OR "December 2022")
ProQuest	(AB,TI(Sedative) OR AB,TI(sedation*) OR AB,TI(chloral hydrate) OR AB,TI(melatonin) OR AB,TI(dexmedetomidine) OR AB,TI(propofol) OR ALL(benzodiazepines) OR ALL,FT(ketamine) OR ALL,FT(narcotics) OR ALL,FT(midazolam)) AND (ALL,FT(ABR) OR ALL,FT("short-latency auditory evoked potential*") OR ALL,FT("Auditory Evoked Potential*") OR (ALL,FT("Evoked Potential*") AND ALL,FT(Auditory)) OR ALL,FT("Auditory Evoked Response*") OR (ALL,FT("Evoked Response*") AND ALL,FT(Auditory)) OR ALL,FT("Auditory Evoked Potential*") OR ALL,FT("Brainstem Auditory Evoked Potential*") OR (ALL,FT("Evoked Potential*") AND ALL,FT(Auditory) AND ALL,FT(Brainstem)) OR ALL,FT("Auditory Brainstem Evoked Response*") OR (ALL,FT("Evoked Response*") AND ALL,FT(Auditory) AND ALL,FT(Brainstem)) OR ALL,FT("Acoustic Evoked Brain Stem Potential*") OR ALL,FT("Auditory Brain Stem Evoked Response*") OR (ALL,FT("Evoked Response*") AND ALL,FT(Auditory) AND ALL,FT(Brain Stem)) OR AB,TI("Auditory Brain Stem Response*") OR AB,TI("Brain Stem Auditory Evoked Potential*") OR AB,TI("Acoustic Evoked Brainstem Potential*") OR AB,TI("Auditory Brainstem Response*") OR (AB,TI("Brainstem Response*") AND AB,TI(Auditory)) OR (AB,TI(Response*) AND AB,TI("Auditory Brainstem"))) AND YR(20000101-20220731)
WOS	(TS=(Sedative) OR TS= (sedation*) OR TS=(chloral hydrate) OR TS=(melatonin) OR TS=(dexmedetomidine) OR TS=(propofol) OR ALL=(benzodiazepines) OR ALL=(ketamine) OR ALL=(narcotics) OR ALL=(midazolam)) AND (ALL=(ABR) OR ALL=("short-latency auditory evoked potential*") OR ALL=("Auditory Evoked Potential*") OR (ALL=("Evoked Potential*") AND ALL=(Auditory)) OR ALL=("Auditory Evoked Response*") OR (ALL=("Evoked Response*") AND ALL=(Auditory)) OR ALL=("Auditory Evoked Potential*") OR ALL=("Brainstem Auditory Evoked Potential*") OR (ALL=("Evoked Potential*") AND ALL=(Auditory) AND ALL=(Brainstem)) OR ALL=("Auditory Brainstem Evoked Response*") OR (ALL=("Evoked Response*") AND ALL=(Auditory) AND ALL=(Brainstem)) OR ALL=("Acoustic Evoked Brain Stem Potential*") OR ALL=("Auditory Brain Stem Evoked Response*") OR (ALL=("Evoked Response*") AND ALL=(Auditory) AND ALL=(Brain Stem)) OR TS=("Auditory Brain Stem Response*") OR TS=("Brain Stem Auditory Evoked Potential*") OR TS=("Acoustic Evoked Brainstem Potential*") OR TS=("Auditory Brainstem Response*") OR (TS=("Brainstem Response*") AND TS=(Auditory)) OR (TS=(Response*) AND TS=("Auditory Brainstem"))) AND py=(2000-2022)
CENTRAL	(Sedative OR sedation* OR chloral hydrate OR melatonin OR dexmedetomidine OR propofol OR benzodiazepines OR ketamine OR narcotics OR midazolam) AND (ABR OR 'short-latency auditory evoked potential*' OR 'Auditory Evoked Potential*' OR ('Evoked Potential*' AND Auditory) OR 'Auditory Evoked Response*' OR ('Evoked Response*' AND Auditory) OR 'Auditory Evoked Potential*' OR 'Brainstem Auditory Evoked Potential*' OR ('Evoked Potential*' AND Auditory AND Brainstem) OR 'Auditory Brainstem Evoked Response*' OR ('Evoked Response*' AND Auditory AND Brainstem) OR 'Acoustic Evoked Brain Stem Potential*' OR 'Auditory Brain Stem Evoked Response*' OR ('Evoked Response*' AND Auditory AND Brain Stem) OR 'Auditory Brain Stem Response*' OR 'Brain Stem Auditory Evoked Potential*' OR 'Acoustic Evoked Brainstem Potential*' OR 'Auditory Brainstem Response*' OR ('Brainstem Response*' AND Auditory) OR (Response* AND 'Auditory Brainstem'))
Cliniclatrial.gov	ABR in outcome measure
Isrctn	ABR in outcome measure
ICTRP	Auditory brainstem response in title
Scholar	ABR+sedation
EMBASE via embase.com	(Sedative OR sedation* OR chloral hydrate OR melatonin OR dexmedetomidine OR propofol OR benzodiazepines OR ketamine OR narcotics OR midazolam) AND (ABR OR 'short-latency auditory evoked potential*' OR 'Auditory Evoked Potential*' OR ('Evoked Potential*' AND Auditory) OR 'Auditory Evoked Response*' OR ('Evoked Response*' AND Auditory) OR 'Auditory Evoked Potential*' OR 'Brainstem Auditory Evoked Potential*' OR ('Evoked Potential*' AND Auditory AND Brainstem) OR 'Auditory Brainstem Evoked Response*' OR ('Evoked Response*' AND Auditory AND Brainstem) OR 'Acoustic Evoked Brain Stem Potential*' OR 'Auditory Brain Stem Evoked Response*' OR ('Evoked Response*' AND Auditory AND Brain Stem) OR 'Auditory Brain Stem Response*' OR 'Brain Stem Auditory Evoked Potential*' OR 'Acoustic Evoked Brainstem Potential*' OR 'Auditory Brainstem Response*' OR ('Brainstem Response*' AND Auditory) OR (Response* AND 'Auditory Brainstem')) AND [2000-2022]/py