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Title

Dexmedetomidine as a Promising Neuroprotective Sedoanalgesic in Neonatal Therapeutic Hypothermia: A Systematic Review and Meta-Analysis

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Short Title: Neuroprotective Role of Dexmedetomidine in Neonatal Hypothermia

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Abstract

Introduction: Hypoxic-ischemic encephalopathy (HIE) is a leading cause of neonatal mortality and neurodevelopmental disabilities. Therapeutic hypothermia (TH) is the standard of care, but optimized sedoanalgesic strategies remain critical. Dexmedetomidine shows promise as an alternative to traditional sedatives, but its role in this context remains systematically under-explored. This meta-analysis aims to address this gap by assessing the safety and efficacy of dexmedetomidine in neonates undergoing TH for HIE.

Methods: A systematic search of Medline, Scopus, EMBASE, WOS, ClinicalTrials, and Cochrane Library identified studies published from January 2014 to October 2024. Studies focusing on dexmedetomidine in neonatal TH with relevant outcomes were included. Selection followed PRISMA guidelines, with independent quality assessments. The protocol was registered in PROSPERO (CRD42024605817). Results are presented as meta-analyses or evidence-based discussions when pooling was unfeasible.

Results: Seven studies involving 609 neonates were included: four cohort studies (n = 486) and three case series (n = 123). Dexmedetomidine provided comparable sedation to traditional agents (MD = -0.01 [-0.68 - 0.66], p = 0.99) and significantly reduced seizure risk (OR 0.31 [0.10 - 0.98], p <0.05) with a non-inferior safety profile. Trends suggested shorter duration of mechanical ventilation and time to full enteral feeding. Substantial heterogeneity in dosing protocols highlights the need for standardization.

Conclusions: Dexmedetomidine appears to be a safe and promising sedative in neonatal TH for HIE, with potential neuroprotective, respiratory, and gastrointestinal benefits. Despite limited evidence and the absence of randomized clinical trials, its non-inferior efficacy and safety warrant further exploration and urges the development of standardized dosing protocols.

Introduction

Hypoxic-ischemic encephalopathy is a serious neurological condition resulting from oxygen and blood flow deprivation to the brain during the perinatal period [1]. It represents a leading contributor to neonatal mortality and neurodevelopmental disabilities, affecting up to 1.5 per 1,000 live births in high-income countries, with significantly higher incidence in low- and middle-income nations [2]. Therapeutic hypothermia is the standard treatment for moderate and severe cases, effectively reducing mortality and long-term impairments by slowing metabolic processes to mitigate neuronal damage in the acute phase [3].

Therapeutic hypothermia requires tailored sedation strategies to optimize neurocritical care and outcomes while managing the physiological stress associated with cooling. However, the absence of precise guidelines for sedoanalgesia in this setting has led to significant variability in clinical practice [4]. This variability underscores the unique challenges of sedoanalgesia during therapeutic hypothermia, where the underlying neurodevelopmental vulnerability of neonates and altered drug metabolism demand agents that deliver effective sedoanalgesia without compromising short- or long-term outcomes [5,6].

In addition to non-pharmacological interventions, opioids and benzodiazepines have traditionally been used for sedation in this setting. However, these agents are associated with significant adverse effects, including respiratory depression and hemodynamic instability, which are particularly concerning in this vulnerable population [4,7]. Dexmedetomidine, an alpha-2 adrenergic agonist, has emerged as a promising alternative due to its stable pharmacokinetics during hypothermia, reduced risk of respiratory compromise, and neuroprotective properties [8].

Respiratory preservation is particularly critical as therapeutic hypothermia is increasingly applied to neonates with moderate hypoxic-ischemic encephalopathy, who, unlike those with severe forms, are often not mechanically ventilated [9]. Furthermore, dexmedetomidine does not interfere significantly with EEG monitoring, enabling continuous aEEG assessment for subclinical seizures during hypothermia [10]. Dexmedetomidine neuroprotective properties, supported by preclinical and clinical evidence, make it particularly valuable in this population [11]. Importantly, compared to opioids and benzodiazepines, dexmedetomidine accumulates less during therapeutic hypothermia, maintaining a stable pharmacokinetic profile and reducing the risk of adverse effects [4,8].

Given these benefits, dexmedetomidine is rapidly emerging as a preferred sedative in this setting, with a recent international survey reporting it as the first-line choice for therapeutic hypothermia in approximately one-third of cases in the United States [2]. Additionally, a study published this year highlighted how dexmedetomidine enabled an '*opioid stewardship*' approach in neonates undergoing therapeutic hypothermia for hypoxic-ischemic encephalopathy, achieving a >90% reduction in opioid use while improving clinical outcomes [12].

Despite promising evidence, dexmedetomidine remains an off-label and novel sedative in neonates, requiring comprehensive evaluation against standard agents [13,14]. High-quality data on its safety and efficacy are limited [15], with early studies presenting mixed findings. While some report improved outcomes and fewer complications, others raise concerns about potential hemodynamic effects, particularly bradycardia and hypotension [8,16].

Previous reviews have predominantly focused on opioids and benzodiazepines for sedoanalgesia during neonatal therapeutic hypothermia, with limited exploration of dexmedetomidine as a primary agent [4,5]. This meta-analysis seeks to address these gaps by systematically reviewing and synthesizing data on dexmedetomidine use in neonates undergoing therapeutic hypothermia, comparing it to traditional regimens. Key outcomes, including seizure control, respiratory and hemodynamic stability, are assessed to inform clinical decision-making, reduce complications, and enhance both short- and long-term outcomes for neonates with hypoxic-ischemic encephalopathy.

Methods

This study protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO) under protocol number CRD42024605817.

Eligibility Criteria

Studies evaluating the safety and efficacy of dexmedetomidine in neonates undergoing therapeutic hypothermia for hypoxic-ischemic encephalopathy were included. Eligible designs were randomized controlled trials (RCTs), observational cohort studies, and dexmedetomidine-focused case series. Included studies had to report safety outcomes (mortality, bradycardia, hypotension, seizures) and/or efficacy outcomes (pain and stress management, mechanical ventilation, full enteral feeding time, and NICU length of stay). Studies without relevant outcomes were excluded. Included studies were grouped based on study type for the analyses.

Information Sources and Search Strategy

A comprehensive literature search was performed in Medline, Scopus, EMBASE, Web of Science, Clinicaltrials, and Cochrane Library covering studies published between January 2024 and October 2024. Last search was conducted on November 2024. A comprehensive search strategy was developed using a combination of MeSH terms and keywords, including "*dexmedetomidine*,""*neonates*,""*therapeutic hypothermia*,""*hypoxic-ischemic encephalopathy*" and "*sedation*." No language restrictions were applied. Reference lists of included studies and relevant reviews were manually searched for additional citations. Grey literature, unpublished studies, conference abstracts, and non-peer-reviewed materials were excluded.

Study Selection

Titles and abstracts identified during the search were independently screened by two reviewers to select potentially eligible studies. Full-text articles meeting inclusion criteria were independently reviewed for eligibility. Discrepancies were resolved through discussion or consultation with a third reviewer. The selection process adhered to PRISMA guidelines, and a flow diagram was used to document the process (Figure 1).

Data Extraction and Risk of Bias Assessment

Data extraction was conducted using a standardized form and independently verified for accuracy. Extracted data included study-level details (authors, publication year, study design, sample size, funding source, and location), participant baseline characteristics (gestational age, sex, birth weight, Apgar scores, cord arterial pH, base excess, lactate levels, and hypoxic-ischemic encephalopathy severity), and intervention/control details (dosing regimen, duration, and co-interventions). Primary outcomes were classified into:

- Safety outcomes: mortality, bradycardia, hypotension, seizures.
- Efficacy outcomes: pain and stress management, mechanical ventilation weaning time, time to achieve full enteral feeding, and NICU length of stay.

Secondary outcomes included the concordance of dexmedetomidine dosing protocols across the included studies. All available data for each outcome, across measures, time points, and analyses, were sought and included in the review. For unclear reports, detailed discussions on the approach used are provided in the Supplementary Results. Missing data were addressed by contacting study authors, and assumptions were avoided whenever possible. Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) [17] for cohort studies, the Joanna Briggs Institute (JBI) critical appraisal checklist for case series [18], and the Cochrane Risk of Bias 2 Tool [19] for randomized controlled trials. Assessments were performed independently by two reviewers, with any discrepancies resolved through discussion.

Data Synthesis and Statistical Analysis

Mean differences were calculated for continuous outcomes, while odds ratios were determined for categorical outcomes. 95% confidence intervals were calculated for each outcome. The Cai method was used to calculate standardized mean differences and confidence intervals due to small sample sizes, high heterogeneity, and skewed outcomes, as it provides improved accuracy under these conditions [20]. Meta-analyses was conducted on comparative studies (RCT and cohort studies) using both fixed- and random-effects models to account for heterogeneity. Heterogeneity was assessed using I^2 and tau^2 statistics. Fixed-effects models were applied for low heterogeneity ($I^2 \leq 50\%$), and random-effects models for high heterogeneity ($I^2 > 50\%$). Due to the limited number of included studies, the moderate sample size, and the relative rarity of the outcomes, we employed the generalized linear mixed model method for meta-analysis. This approach was chosen for its robustness in handling sparse data, rare events, and variability between studies, while also offering superior capacity to model and account for heterogeneity compared to traditional methods, thus providing more precise and reliable estimates in this setting.

Potential confounders from baseline characteristics were addressed by calculating pooled summary statistics. If significant stratification was detected, multivariate meta-regression was conducted. Missing and unclear data were excluded from the analysis. Summary statistics are reported in tables to increase clarity. Sensitivity analyses, including quality meta-regression and cumulative meta-analysis, were performed to ensure robustness.

As secondary outcome, variability in dexmedetomidine dosing across studies was assessed by calculating pooled means and summary statistics, focusing solely on dexmedetomidine-exposed groups. Case-series studies were included in this analysis. Between-study variability was evaluated using heterogeneity tests, and statistical comparisons of dosing protocols were performed.

A p-value <0.05 was considered statistically significant. All statistical analyses were performed using R version 4.4.2, package *meta*. Plots were created using the *forest* function of this package.

Results

A total of seven studies, involving 609 neonates undergoing therapeutic hypothermia for hypoxic-ischemic encephalopathy, were included in this systematic review, as illustrated in the PRISMA flowchart (Figure 1). Of these, four comparative cohort studies [21–24], involving 486 neonates, were included in the meta-analysis. Among these, 152 neonates received dexmedetomidine as the primary sedative agent, while 334 were managed with opioids (fentanyl and/or morphine) and benzodiazepines. The remaining three single-arm case series [25–27] focused exclusively on dexmedetomidine use in 123 neonates and were analyzed separately to explore heterogeneity in dexmedetomidine dosing protocols. Study characteristics are detailed in Table 1, and outcomes pooled means with corresponding p-values are presented in Table 2. Pooled mean and p-values for baseline characteristics, alongside extensive explanation for each variable, can be found in Supplementary Results.

Comparative Studies

The four comparative studies demonstrated several advantages of dexmedetomidine over traditional sedatives:

- Naveed et al. (2022) [21]: dexmedetomidine reduced the weaning time from mechanical ventilation, reduced seizure incidence, and required fewer additional sedative boluses compared to fentanyl in 45 neonates undergoing therapeutic hypothermia for moderate and severe hypoxic-ischemic encephalopathy.
- Cosnahan et al. (2021) [23]: on a cohort of 70 patients, dexmedetomidine resulted in lower cumulative morphine use while maintaining effective sedation and analgesia, alongside comparable adverse effects, emphasizing its potential to optimize sedation protocols during therapeutic hypothermia.
- Elliott et al. (2022) [22]: in a cohort of 116 neonates, dexmedetomidine was associated with effective sedation and a lower heart rate without significant detrimental effects, reinforcing its safety and promise in this setting.
- Surkov (2019) [24]: involving 205 neonates, dexmedetomidine was linked to reduced seizure rates and improved cerebral oxygenation compared to other sedatives, suggesting potential neuroprotective benefits.

Single-Agent Studies

The case-series studies provided additional insights:

- Acun et al. (2024) [25]: among 97 neonates receiving dexmedetomidine, sedation was effective; however, 41.2% experienced bradycardia (<80 bpm), and hypotension was observed in 7% of cases, though 71% of these instances were detected prior to dexmedetomidine initiation.
- O'Mara and Weiss (2018) [26]: in 19 neonates, dexmedetomidine demonstrated satisfactory efficacy and improved feeding outcomes, with no significant adverse events reported.
- McAdamns et al. (2020) [27]: focused on the pharmacokinetic of dexmedetomidine during hypothermia in 7 patients, with no significant adverse event reported.

Descriptive summaries are provided for outcomes where statistical analysis was not feasible.

Key findings are outlined below, with more detailed data and interpretations available in the Supplementary Results.

Baseline Characteristics

Baseline characteristics, including gestational age, birth weight, Apgar scores, cord arterial gas test results, seizure prior therapeutic hypothermia initiation, and severity of hypoxic-ischemic encephalopathy, were well-balanced between dexmedetomidine and non-dexmedetomidine groups, reducing potential confounding and validating outcome comparisons in our cohort. Details are reported in Supplementary Results.

Quality Assessment

The included studies demonstrated high methodological quality, with NOS scores ranging from 8 to 9 and JBI scores of 9 to 10, indicating robust designs, comprehensive reporting, and minimal risk of bias across all assessments. Detailed quality assessments are reported in Supplementary Results.

Safety Outcomes

Mortality

Mortality rates were comparable between groups, with no significant differences observed (OR 1.43, 95% CI 0.61 – 3.33, I2 = 0, p = 0.41, n = 486). Details are provided in Supplementary Results.

Bradycardia and Hypotension

Bradycardia and hypotension have historically been the major concerns with dexmedetomidine use. Bradycardia rates varied across studies due to differing diagnostic thresholds, precluding a pooled meta-analysis. Individual studies did not report significant differences in the incidence of severe bradycardia between dexmedetomidine and control groups. Nevertheless, while not associated with significant adverse events, the consistent trend toward reduced heart rate observed across studies, alongside dexmedetomidine pharmacodynamic profile, highlight the need for vigilant monitoring in neonates undergoing therapeutic hypothermia. Hypotension, though not consistently reported in the studies assessed to approximately 33% in both groups. The available data suggest that dexmedetomidine does not significantly impact hemodynamic stability during therapeutic hypothermia (OR 0.95, 95%CI: 0.55 – 1.63, p = 0.85, $I^2 = 0$, n = 281). Additional details for both outcomes are provided in Supplementary Results.

Seizure Activity

New onset seizure incidence during therapeutic hypothermia was reported before antiseizure therapy in two comparative studies [21,24], while the other two [22,23] used the need for antiseizure medication as a proxy for this outcome. Across these studies, dexmedetomidine was associated with a significant reduction in seizure risk compared to traditional sedatives (OR 0.31, 95% CI: 0.10–0.98, $I^2 = 82\%$, $p < 0.05$, n = 486). This finding aligns with dexmedetomidine pharmacodynamic profile and emerging evidence supporting its neuroprotective properties [28]. Sensitivity analyses, detailed in the Supplementary Results, confirmed the robustness of this result. Nevertheless, it is important to note that this finding could not be adjusted for the severity of hypoxic-ischemic encephalopathy due to the limitations detailed in the Supplementary Results and Limitations sections, thereby reducing the robustness of the result. A visual summary of these results is provided in Figure 2.

Efficacy Outcomes

Pain and Stress Management

The N-PASS score showed no significant differences between groups. Likewise, in studies that did not report N-PASS scores, additional bolus requirements for maintaining effective neonatal sedation and analgesia were comparable or favored dexmedetomidine, highlighting its ability to sustain effective sedation without the need for supplementary interventions.

Mechanical Ventilation Weaning Time

Dexmedetomidine demonstrated a trend toward a shorter ventilation weaning, which did not reach statistical significance (MD = -0.72, 95%CI: -1.62 – 0.18, I2 = 70.0%, p = 0.13, n = 416), likely due to the limited sample size and number of studies available.

Time to Full Enteral Feeding

The time to achieve full enteral feeding did not differ significantly between groups, although a trend toward a shorter duration was observed in the dexmedetomidine group (MD = -1.44 days, 95% CI: -4.19 to 1.30, $I^2 = 57.8\%$, p = 0.3, n = 115). This finding aligns with results from individual studies, where a significant reduction in feeding time was reported [21].

NICU Length of Stay

NICU length of stay showed no significant differences between groups (MD = -0.18, 95% CI -1.46 - 1.09, I2 = 55.1%, p = 0.6, n = 486).

Secondary Outcome

Dosing of Dexmedetomidine

The analysis revealed significant variability in dexmedetomidine starting and maximum dosages across studies ($I^2 > 98\%$, $p < 0.001$), underscoring the lack of standardized dosing protocols. The pooled mean starting dose was 0.3 mcg/kg per hour (IQR: 0.2–0.4, n = 275), while the maximum dose averaged to 0.53 mcg/kg per hour (IQR: 0.28 – 0.78, n = 275). These findings emphasize the need for more specific guidelines. Detailed results of the dexmedetomidine dosing analysis are presented Supplementary Results.

Discussion

Hypoxic-ischemic encephalopathy remains a leading cause of neonatal mortality and neurodevelopmental disabilities, necessitating effective and optimized management strategies. Pain and stress management, integral to the neuroprotection bundle aimed at preventing brain injury, are critical in this context [29]. Our findings demonstrate that dexmedetomidine provides effective pain and stress control in neonates undergoing therapeutic hypothermia, without increasing mortality, morbidity, or NICU length of stay.

Dexmedetomidine also offers distinct advantages over other sedoanalgesic agents, particularly in preserving spontaneous breathing and gastrointestinal function [30,31]. Consistently, our analysis identified trends toward reduced weaning time from mechanical ventilation and earlier achievement of full enteral feeding, which, although not reaching statistical significance likely due to the limited available evidence, align with findings from individual studies and the broader literature.

Importantly, dexmedetomidine demonstrated significant neuroprotective effects, reducing seizure occurrence after its initiation, as summarized in Figure 2. This aligns with recent reports of dexmedetomidine ability to terminate status epilepticus in adults refractory to conventional antiseizure medications [32–34]. These findings suggest a key role for alpha-2 adrenoceptors in seizure modulation, supported by recent animal studies [35], which may underpin the neuroprotective effects observed in our meta-analysis.

Dexmedetomidine further shows potential for long-term neuroprotection and pro-neurodevelopmental benefits, contrasting with the detrimental effects of opioids and benzodiazepines [36,37]. In animal studies, dexmedetomidine has been shown to enhance neuronal survival after umbilical cord occlusion and to suppress inflammatory cytokine production linked to mortality and brain injury [38,39]. These findings, combined with increasing efforts to reduce neonatal opioid exposure, further support dexmedetomidine role in neonatal hypoxic-ischemic encephalopathy.

Despite these promising findings, our analysis revealed significant variability in dexmedetomidine dosing protocols across studies, highlighting the urgent need for standardized sedation protocols to ensure consistency in clinical practice and optimize care for neonates undergoing therapeutic hypothermia [2,15].

In conclusion, this meta-analysis identifies dexmedetomidine as a safe and promising sedoanalgesic agent for neonates undergoing therapeutic hypothermia for hypoxic-ischemic encephalopathy. Its unique benefits and potential for neuroprotection position it as a compelling alternative to traditional sedation strategies, warranting further exploration to establish standardized guidelines and optimize neonatal outcomes.

Study Limitations

Several limitations of this meta-analysis must be acknowledged. The absence of available RCTs introduces potential selection bias and confounding inherent to observational studies, limiting the strength of conclusions despite moderate to high quality scores. Significant heterogeneity in outcomes and dosing protocols affects generalizability, which may be further constrained by differences in healthcare systems and practices across study sites. Limited studies prevented comprehensive multivariate adjustments and conclusive sensitivity analyses, and short follow-up periods further restricted the evaluation of long-term neurological outcomes, crucial for neonates with hypoxic-ischemic encephalopathy. These findings underscore the need for well-designed RCTs with standardized protocols and extended follow-up to establish more robust evidence. In this regard, an ongoing RCT is expected to provide robust evidence to validate dexmedetomidine role and inform its integration into neonatal care [40].

Conclusions and Future Directions

This systematic review and meta-analysis highlight dexmedetomidine as a safe and promising sedoanalgesic agent for neonates undergoing therapeutic hypothermia for hypoxic-ischemic encephalopathy. The findings emphasize its potential to address critical challenges in this vulnerable population, including neuroprotection and the preservation of respiratory and gastrointestinal functions. With its favorable safety profile and unique advantages, dexmedetomidine emerges as a compelling alternative to traditional sedation protocols in neonatal care. Ongoing and future randomized clinical trials will be pivotal in confirming dexmedetomidine role and establishing comprehensive guidelines to improve outcomes for neonates with hypoxic ischemic encephalopathy.

Statement of Ethics

A Statement of Ethics is not required, as this study is based solely on published literature.

Conflict of Interest Statement

None to disclose.

Funding Sources

None to disclose.

Author Contributions

Enrico Cocchi led the conception and design of the study, while Juleda Shabani developed the search strategy and conducted the database searches, under Arianna Aceti supervision. Both Enrico Cocchi and Juleda Shabani reviewed the retrieved articles and collected data, with Arianna Aceti and Luigi Corvaglia serving as external reviewers to resolve discrepancies. Enrico Cocchi and Arianna Aceti provided methodological guidance and conducted the meta-analyses, with both Enrico Cocchi and Juleda Shabani drafting the manuscript. Arianna Aceti, Luigi Corvaglia, Gina Ancora, and Federico Marchetti critically reviewed and revised the manuscript.

Data Availability Statement

All data relevant to the study are publicly available and included within the article or provided as supplementary information.

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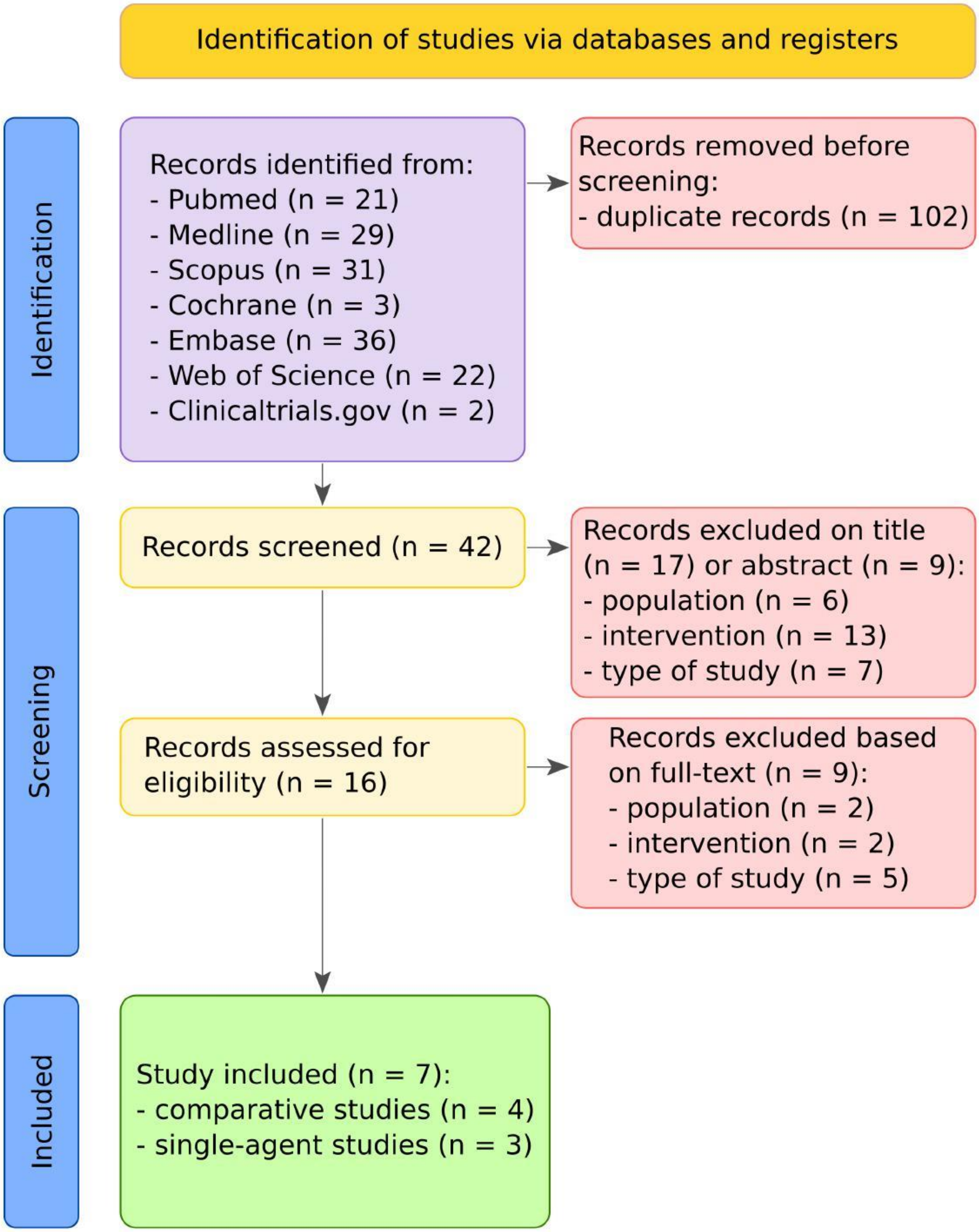
Figure Legends

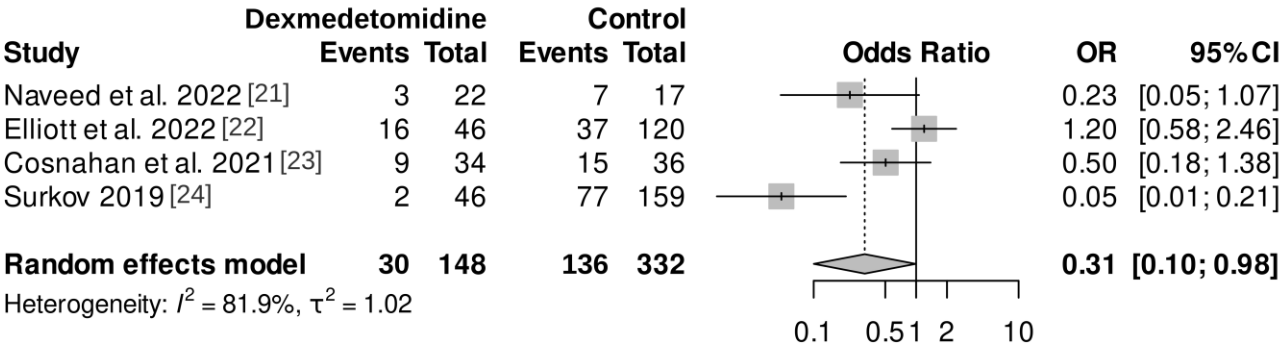
Figure 1: PRISMA Flowchart for Study Selection
The flowchart outlines the systematic process of study identification, screening, eligibility assessment, and inclusion according to the PRISMA guidelines. A total of 144 records were identified through database and registry searches. After removing 102 duplicate records, 42 unique records underwent screening. 17 records were excluded based on titles, and 9 were excluded based on abstracts, primarily due to population (n = 6), intervention (n = 13), or study type (n = 7). 16 full-text articles were assessed for eligibility, with 9 excluded for reasons including population (n = 2), intervention (n = 2), and study type (n = 5). Ultimately, 7 studies were included in the systematic review, comprising 4 comparative cohort studies and 3 single-agent case series studies.

Figure 2: Effect of Dexmedetomidine on New Onset Seizure Occurrence in Neonates Undergoing Therapeutic Hypothermia

Forest plot of the effect of dexmedetomidine on new onset seizure occurrence during therapeutic hypothermia. The odds ratios (ORs) and 95% confidence intervals (CIs) are shown for each included study and for the overall pooled analysis using a random-effects model. Events represent the number of seizures observed in the dexmedetomidine and control groups. Naveed et al. (2022) and Surkov (2019) reported new onset seizure incidence before antiseizure therapy initiation, while Elliott et al. (2022) and Cosnahan et al. (2021) reported the need for antiseizure medication as a proxy for this outcome. The diamond at the bottom represents the overall effect estimate (OR 0.31, 95% CI: 0.10 - 0.98), indicating a statistically significant reduction in seizure occurrence associated with dexmedetomidine. Heterogeneity among studies is represented by I^2 = 81.9%, suggesting substantial variability. Individual study weights are represented by the size of the gray squares.



Identification of studies via databases and registers
Identification
Records identified from:
- Pubmed (n = 21)
- Medline (n = 29)
- Scopus (n = 31)
- Cochrane (n = 3)
- Embase (n = 36)
- Web of Science (n = 22)
- Clinicaltrials.gov (n = 2)
Records removed before screening:
- duplicate records (n = 102)
Screening
Records screened (n = 42)
Records excluded on title (n = 17) or abstract (n = 9):
- population (n = 6)
- intervention (n = 13)
- type of study (n = 7)
Records assessed for eligibility (n = 16)
Records excluded based on full-text (n = 9):
- population (n = 2)
- intervention (n = 2)
- type of study (n = 5)
Included
Study included (n = 7):
- comparative studies (n = 4)
- single-agent studies (n = 3)



Dexmedetomidine
Control
Study
Events Total
Events Total
Odds Ratio
OR
95%CI
Naveed et al. 2022 [21] 3 22 7 17 0.23 [0.05; 1.07]
Elliott et al. 2022 [22] 16 46 37 120 1.20 [0.58; 2.46]
Cosnahan et al. 2021 [23] 9 34 15 36 0.50 [0.18; 1.38]
Surkov 2019 [24] 2 46 77 159 0.05 [0.01; 0.21]
Random effects model 30 148 136 332 0.31 [0.10; 0.98]
Heterogeneity: I^2 = 81.9%, τ^2 = 1.02
0.1
0.5
1
2
10

Tables

Table 1. Summary of Selected Studies. This table outlines key characteristics of the identified studies, including their design, patient demographics, treatment protocols, and sedation efficacy measurements. It highlights the varying methodologies and sedation practices employed across different institutions, providing insight into the effectiveness and safety of dexmedetomidine compared to other sedatives in this vulnerable population. Abbreviations: Dex = dexmedetomidine, NOS = Newcastle Ottawa Scale, JBI = Joanna Briggs Institute Critical Appraisal Checklist.

	Naveed et al. 2022 [21]	**Elliott et al. (2022)** [22]	**Cosnahan et al. (2021)** [23]	**Surkov (2019)** [24]	**Acun et al. (2024)** [25]	**McAdams et al. (2020)** [27]	**O'Mara and Weiss (2018)** [26]
Type of Study	Retrospective cohort	Retrospective cohort	Retrospective cohort	Prospective cohort	Case Series	Case Series	Case Series
Place	Chicago (US)	Charlottesville (US)	New York (US)	Dnipro (UA)	Cleveland (US)	Seattle (US)	Gainesville (US)
Sedation Efficacy Measurement	N-PASS	/	N-PASS	/	N-PASS	N-PASS	N-PASS
Total Number of Patients	45	166	70	205	97	7	19
Dex Number of Patients	26 (57.8%)	46 (27.7%)	34 (48.6%)	46 (22.4%)	97 (100%)	7 (100%)	19 (100%)
Non-Dex Number of Patients	19 (42.2%)	120 (72.3%)	36 (51.4%)	159 (77.6%)	/	/	/
Dex-Group Sedative Monotherapy	Yes	No	No	Yes	No	Yes	No
Dex-Group Additional Sedative	/	Fentanyl	Morphine	/	Opioid ± Benzodiazepines	/	Fentanyl
Dex-Group Sedative Infusion	Continuous	Continuous	Continuous	Continuous	Continuous	Continuous	Continuous
Dex-Group Additional Sedative Infusion	/	Bolus	Bolus	/	Bolus	/	Continuous ± Bolus
Non-Dex Group Sedative	Fentanyl	Fentanyl	Morphine	Morphine ± Oxybutynin ± Diazepam	/	/	/
Non-Dex Group Sedative Infusion	Continuous ± Bolus	Continuous ± Bolus	Bolus	Continuous ± Bolus	/	/	/
Anti-Convulsant Agent	/	Phenobarbital	Phenobarbital, Phenytoin, Levetiracetam, Midazolam, Lorazepam	/	/	/	Phenobarbital, Phenytoin, Levetiracetam, Lorazepam
NOS/JBI Score	9/9	9/9	9/9	8/9	9/10	10/10	9/10

Table 2. Clinical Outcomes of Neonates with Hypoxic-Ischemic Encephalopathy Undergoing Therapeutic Hypothermia. This table summarizes key variables among the overall meta-analysis cohort (n=486), dexmedetomidine cohort (n=152), and non-dexmedetomidine cohort (n=334). The values represent means ± standard deviations (SD) or counts (%). I² indicates the percentage of variation across studies attributed to heterogeneity, while p-values assess statistical significance for each variable. Abbreviations: Dex = dexmedetomidine, HIE = Hypoxic Ischemic Encephalopathy, TH = Therapeutic Hypothermia, NICU = Neonatal Intensive Care Unit.

	Overall cohort		**Dex cohort**		**Non-Dex cohort**			
variable	***num***	***Mean ± SD or count (%)***	***num***	***Mean ± SD or count (%)***	***num***	***Mean ± SD or count (%)***	***I^2 (%)***	***p-value***
N-PASS score during TH	115	1.03 ± 3.78	60	1.03 ± 2.99	55	1.02 ± 4.43	0	0.99
seizure during TH	244	89 (36.48%)	68	5 (7.35%)	176	84 (47.73%)	49.7	<0.001
phenobarbital	236	77 (32.63%)	80	25 (31.25%)	156	52 (33.33%)	46.4	0.69
phenobarbital total dose	236	40.71 ± 21.75	80	31.08 ± 15.01	156	39.36 ± 23.09	0	<0.001
mechanical ventilation	281	153 (54.45%)	106	58 (54.72%)	175	95 (54.29%)	0	0.8
mechanical ventilation weaning time (days)	416	6.08 ± 42.41	118	5.59 ± 34.34	298	6.51 ± 58.33	70.0	0.13
vasopressor usage	281	89 (31.67%)	106	36 (33.96%)	175	53 (30.29%)	0	0.7
mortality	486	26 (5.35%)	152	10 (6.57%)	334	16 (4.79%)	0	0.4
length of NICU stay (days)	486	13.34 ± 9.96	152	13.38 ± 8.36	334	13.49 ± 14.23	55.1	0.6
time to full enteral feeding (days)	115	8.37 ± 42.12	60	7.51 ± 30.1	55	9.42 ± 72.21	57.8	0.3