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Original article

Neonatal seizure management with lidocaine: Systematic review and meta-analysis on efficacy and safety

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Abstract. *Background and aim:* Seizures are common in neonates, especially preterm and low-birth-weight infants, with clinical seizures occurring in 1–3 per 1000 live births. Neonatal seizures are associated with increased mortality and risk of developing cerebral palsy. Additionally, these seizures can lead to brain damage, which may result in epilepsy and cognitive impairment. Rapid, protocol-driven therapy and drugs like lidocaine may help, but definitive treatment guidelines are limited. This study aims to systematically review and conduct a meta-analysis to investigate and determine the efficacy and safety of lidocaine treatment for neonatal seizures. *Methods:* A systematic review and meta-analysis followed PRISMA 2020 standards utilizing the PICO framework. Comprehensive screening, data capture, bias risk evaluation, and statistical analysis were conducted to determine the efficacy and safety of lidocaine therapy for neonatal seizures. *Results:* A total of 1,290 publications were obtained from online databases, including Proquest, Scopus, Web of Science, PubMed, Science Direct, and grey literature. Thirteen publications relevant to the meta-analysis were chosen for comprehensive reading and analysis following three rounds of screening. Lidocaine therapy for neonatal seizures showed 73% (RCT) and 75% (observational studies) proportionally in controlling neonatal seizures. The pooled risk ratio of 2.05 [1.47, 2.85] indicates effectiveness with statistical significance ($Z = 4.23$, $p < 0.0001$); lidocaine is better in controlling seizures compared to midazolam. *Conclusions:* Lidocaine is effective in the treatment of neonatal seizures. However, its use must be guided by a thorough understanding of its mechanisms, benefits, and risks. The current evidence supports further investigation into its role alongside other anticonvulsants, focusing on optimizing safety and efficacy for this vulnerable population. (www.actabiomedica.it)

Key words: lidocaine therapy, neonatal seizure management, neonatal seizure treatment, lidocaine for neonatal seizures, seizure therapy in newborns, brain damage, mortality, systemic review neonatal seizures, meta-analysis neonatal seizures

Introduction

Seizures represent the most prevalent neurological condition in neonates, with incidence rates differing significantly according to population and diagnostic standards. Clinical diagnosis frequently under-represents the true incidence of electrical seizures, and the beginning of clinical seizures is inconsistent. No extensive research on outcomes after prospective electroencephalographic (EEG) monitoring is available (1). The estimated prevalence of clinical seizures is approximately 1–3 per 1000 live births, with increased incidence in preterm neonates and those with lower birth weight. Rates reported include 2–3 per 1000 live births in the general population and term neonates, 4.4 per 1000 live births for infants

weighing between 1500 and 2500 g, 55–130 per 1000 live births for children weighing under 1500 g, and up to 64 per 1000 live births for infants weighing under 1000 g (2). The risk of seizures is highest during the first year after birth, particularly within the first month. This risk inversely correlates with gestational age and birth weight (3). Seizures in the neonate period can significantly impact brain development, potentially leading to learning difficulties, behavioral problems, and a predisposition to epilepsy (4). Expedited, protocol-based treatment can diminish seizure frequency; nevertheless, evidence from randomized controlled studies for the selection of antiseizure medications (ASMs) is scarce, hindering conclusive recommendations. Lidocaine is frequently employed as a third-line antiepileptic medication in Europe, whereas its usage among neurologists and neonatologists globally is limited to 1–6%. Lidocaine, however, rarely utilized, has efficacy as a second and third-line treatment for neonate convulsions, with response rates between 60% and 92%. Nonetheless, sample sizes are limited, and treatment protocols differ (5,6). Lidocaine has a distinctive structure comprising an aromatic and amine chain, enabling it to attach to the sodium channel at the pore-lining phenyl-binding site and the exterior amine chain site, diminishing ion transit across the cellular membrane. Other sodium channel-based ASMs generally possess a diphenyl motif, which restricts binding to the pore-lining phenyl sites, thereby blocking sodium ion transport. Thus, lidocaine can offer supplementary sodium channel blocking in refractory seizures by engaging the external amine binding site, even when other sodium channel antagonists are already in use (7). Therefore, it is important to conduct an analysis to gather existing information and determine the efficacy and safety of lidocaine treatment for neonatal seizures. This study aims to systematically review and conduct a meta-analysis to investigate and determine the efficacy and safety of lidocaine treatment for neonatal seizures.

Methods

This systematic review meta-analysis was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards and has been registered with PROSPERO under ID CRD42022309592. This study used the PICO (Population, Intervention, Comparator, and Outcomes) framework, comprising of Population: Neonates with seizures; Intervention: Lidocaine therapy for managing neonatal seizures; Comparison: Efficacy of seizure reduction with other ASMs.

Data sources and search strategy

The authors employed multiple data sources and search methodologies, including the Medical Subject Headings (MeSH) database. A thorough search was performed via Proquest, Scopus, Web of Science, PubMed, Science Direct, and grey literature to uncover relevant studies. This paper includes the keywords lidocaine and neonatal seizures (Table 1). Boolean operators were employed to combine these terms effectively. Filters were applied to limit results to human studies published in English.

Table 1. Detailed summary of the entire search method.

Database	Keyword
PubMed	((“lidocain”[All Fields] OR “lidocaine”[MeSH Terms] OR “lignocain”[All Fields]) AND ((“newborn”[All Fields]) OR “newborn infant”[All Fields] OR “neonatal” [All Fields] OR “neonate”[All Fields] OR “neonates”[All Fields]) AND (“seizural”[All Fields] OR “seizures” [All Fields] OR “seizured”[All Fields] OR “seizures”[MeSH Terms] OR “seizures” [All Fields] OR “seizure”[All Fields] OR “seizuring”[All Fields]))
Science Direct	((lidocain) OR (lignocaine)) AND ((neonatal) OR (neonates) OR (newborn)) AND ((seizures) OR (seizures) OR (convulsion))
Scopus	lidocaine AND neonatal OR neonates OR newborn AND seizure OR convulsion
Web of Science	((ALL=(lidocaine OR lignocaine)) AND ALL=(neonat* seizure OR convulsion)) AND ALL=(therap* OR treatment)
Proquest	lidocaine AND neonatal seizure

Eligibility criteria

This systematic review and meta-analysis included studies that focused on neonates diagnosed with seizures, irrespective of their gestational age or birth weight. Eligible studies assessed the use of lidocaine as a therapeutic intervention for managing neonatal seizures and provided data on efficacy and safety outcomes. Only studies with clear definitions of seizure frequency, duration, and treatment response, as well as those reporting adverse effects related to lidocaine therapy, were considered.

Studies were excluded if they did not specifically evaluate the use of lidocaine in the context of neonatal seizure management, such as case reports and non-peer-reviewed articles. Additionally, studies that focused on non-neonatal populations or those without detailed efficacy and safety outcomes related to lidocaine were not included.

Study selection

An initial screening of titles and abstracts is then conducted to exclude studies that clearly do not meet the inclusion criteria. Two reviewers perform this stage independently to minimize bias and ensure objectivity. Studies that pass this preliminary screening are retrieved in full text for a more detailed assessment. The reviewers carefully evaluate the studies against the inclusion and exclusion criteria during the full-text review. Any discrepancies between reviewers are resolved through discussion or consulting a third reviewer to reach an agreement, ensuring that only the most relevant and high-quality studies are selected.

Data extraction

The authors extracted data in duplicate from the full-text versions of qualifying papers. Data concerning the application of lidocaine in the management of neonatal seizures was gathered at many time intervals. The major source for extraction was data presented in tabular format.

Risk of bias

The risk of bias in each study was evaluated across six categories utilizing the Risk of Bias instrument from the Cochrane Collaboration for clinical trial studies and the Newcastle-Ottawa Quality Assessment Form for cohort studies in observational research. The areas encompassed sequence generation, allocation concealment, blinding, attrition bias, selective outcome reporting, and additional potential causes of bias. Trials were classified as exhibiting high, low, or ambiguous bias in each domain, accompanied by comprehensive reasons for each assessment.

Data synthesis and analysis

The core of the data synthesis involves statistical analysis, with the primary outcome measure being proportions of the use of lidocaine in neonatal seizures and risk ratio (RR) compared with midazolam. The forest plot presents proportions and risk ratio (RR) estimates and their corresponding confidence intervals for each study, facilitating comparison and providing an overall summary estimate. The pooled effect size is then calculated. A fixed-effects model was employed for meta-analysis, conducted using Review Manager Software version 5.4 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) and R version 4.4.1.

Results

A total of 1,290 publications were obtained from online databases, including Proquest, Scopus, Web of Science, PubMed, Science Direct, and grey literature. Following three rounds of screening, twenty-six papers pertinent to the systematic review were chosen for comprehensive reading and analysis (Figure 1). This meta-analysis synthesizes data from thirteen studies examining the efficacy of lidocaine as a treatment for neonatal seizures. The characteristics of the studies are shown in Table 2 and Table 3.

Evaluation study quality

The risk of bias analysis was conducted utilizing the Risk of Bias by Cochrane and Newcastle-Ottawa Quality Assessment Form, UK, and presented in Figure 2 and Figure 3. The risk of bias assessment for

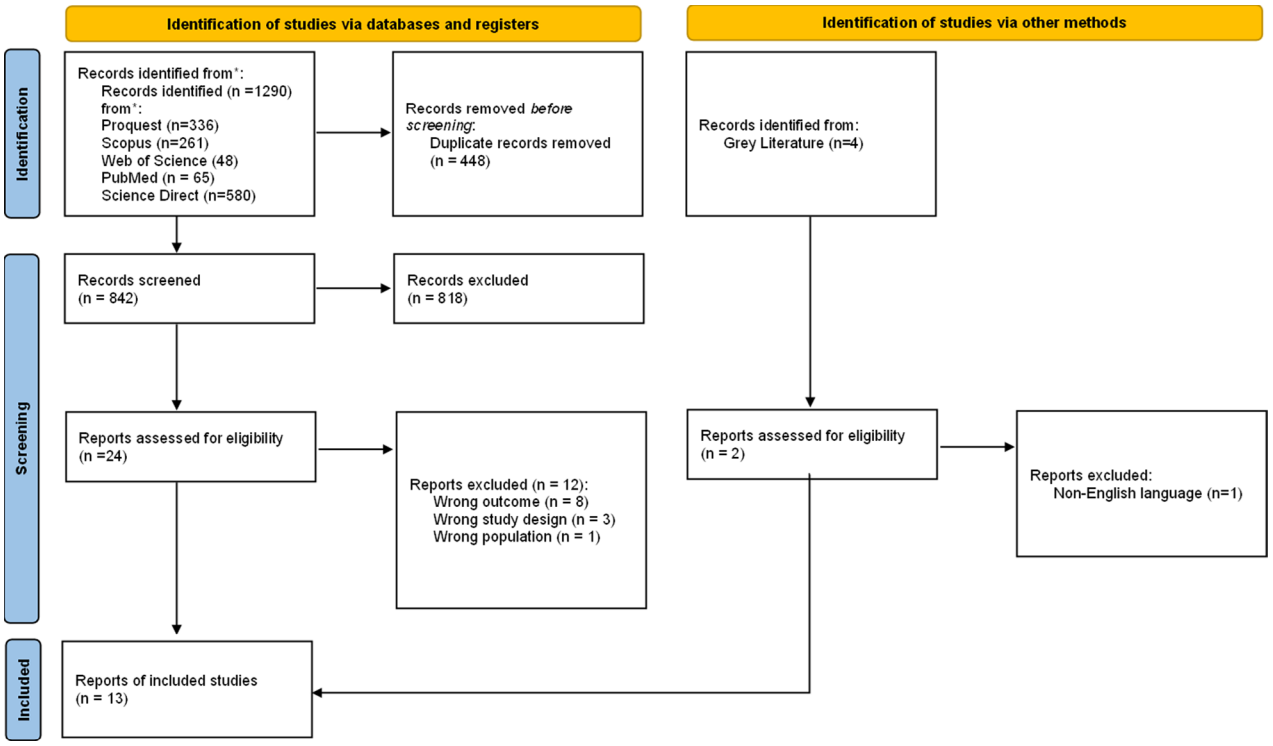


Figure 1. Methodology for study identification and selection for the meta-analysis.

the included studies on the efficacy of lidocaine as a treatment for neonatal seizures reveals a diverse result. The randomized controlled trial (RCT) by Baquisa et al. (2016) exhibited a minimal risk of bias across all evaluated domains, encompassing random sequence generation, allocation concealment, participant and personnel blinding, outcome assessment blinding, incomplete outcome data, selective reporting, and other bias sources. This strengthens the reliability of its findings, as rigorous methodological standards were followed. Boylan et al. (2014) had an overall unclear majority bias in the binding and concealment of the subject. In the 11 observational cohort studies and case-control studies, including those by Favie, et al (2019), Hellstrom, et al (1992), Lundqvist, et al (2013), Malingre, et al (2006), Shany, et al (2007), Van den Broek, et al (2015), Weeke, et al (2016), Yamamoto, et al (2007) generally exhibited unclear risks of bias. They consistently showed unclear risk in the domains of selection and, outcome assessment. These methodological weaknesses suggest potential biases in how the outcomes were measured and reported, which could affect the validity of the results. Study conducted by Conde, et al (2004), Hellstrom, et al (1988), Rey, et al (1990), and Weeke, et al (2016) showed a low risk of bias across all assessed domains, including selection, comparability, and outcome. Overall, the RCT provided robust evidence with a moderate risk of bias, and the observational studies also had moderate bias due to their design limitations and lack of blinding. The findings from these studies should be interpreted cautiously, considering the potential for bias. This assessment underscores the importance of methodological rigor in clinical research to ensure the reliability and validity of study outcomes, particularly in assessing the efficacy of treatments like lidocaine for neonatal seizures.

Efficacy of lidocaine in neonatal seizure treatment

The forest plot summarizes the efficacy of lidocaine as a treatment for neonatal seizures across two

Table 2. Characteristics of studies included in the systematic review

Author and Year (Origin)	Study Design	Participant Characteristic	Dosage	Observation	Seizure Control Definition
Baquisa *et al*, 2016 (Bangladesh) (8)	RCT	A total of 78 neonates who had neonatal seizures and did not respond to a full dose of Inj. Phenobarbital (40 mg/kg) were randomly divided into two groups: one receiving Inj. Lidocaine (Group A=39) and the other received Inj. Phenytoin (Group B=39).	Lidocaine bolus 2 mg/kg, followed by 4 mg/kg/hr in the first 12 hours followed by 2 mg/kg/hr for the next 12 hours	Clinical	Not mentioned
Boylan *et al*, 2004 (UK) (9)	RCT	Neonates exhibiting seizures verified by EEG and term neonates with electrographic seizures receiving therapy with midazolam (first-line) and lidocaine (second-line).	Lignocaine: bolus of 4 mg/kg in 20 minutes followed by infusion of 2 mg/kg/hour	EEG video	Seizure control was defined as complete if there was no seizure electrographic activity.
Conde *et al*, 2024 (Spain) (10)	Cohort Prospective	Term neonates experiencing electrographic seizures are receiving therapy with midazolam as the primary intervention and lidocaine as the secondary.	Lidocaine: bolus (2-3 mg/kg). Maintenance infusion dose 1-6 mg/kg/hour	EEG video	Seizures ceased if EEG seizure control was obtained after adding lidocaine
Favie *et al*, 2020 (Netherlands) (11)	Cohort retrospective	Data from preterm and (near) term neonates, both with and without therapeutic hypothermia, who were administered lidocaine.	Lidocaine: as per local clinical protocol	aEEG	Seizure control when seizures stop and no additional anti-seizure medication is needed after lidocaine therapy.
Hellstorm-Westas *et al*, 1988 (Swedish) (12)	Cohort prospective	Prior to lidocaine administration, all participants received phenobarbital, and 22 subjects were further administered diazepam. Various dosages of lidocaine were evaluated.	Lidocaine: bolus of 2 mg/kg followed by a 6 mg/kg/hour	aEEG	Not mentioned
Hellstorm-Westas *et al*, 1992 (Swedish) (13)	Cohort prospective	Blood levels of lidocaine and its primary active metabolites, methylethylglycinexylidide (MEGX) and glycinexylidide (GX), were assessed in 24 neonates undergoing anticonvulsant therapy via lidocaine infusion.	Lidocaine bolus 1.6-2.2 mg/kg maintenance dose 4-6 mg/kg/hour	aEEG	Good: seizure stops Intermediate: seizure stops, but then recurs No effect: no change
Lundqvist *et al*, 2013 (Swedish) (14)	Cohort retrospective	A retrospective data study was conducted over a 10-year period for all neonates (gestational age ≥ 37 weeks, age ≤ 28 days) who were administered lidocaine as a second-line therapy for neonatal seizures before receiving phenobarbital.	Lidocaine: continuous infusion of 4-6 mg/kg/hour then rate maintained of 4-8 mg/kg/hour for 11-60 hours	aEEG	Clinically stop on EEG or changes in epileptiform activity on EEG sequences
Malingre *et al*, 2016 (Netherlands) (15)	Cohort prospective	All patients received both loading and maintenance dosages. The efficacy, cardiac toxicity, and plasma levels of lidocaine were subsequently examined.	Lidocaine: bolus of 2 mg/kg in 10 minutes, followed by a continuous infusion of 6 mg/kg per hour for 12 hours, 4 mg/kg per hour for 12 hours and finally 2 mg/kg per hour for 12 hours.	aEEG	Good: seizure stops clinically and on EEG Intermediate: seizures stop, but then recur No effect: no change

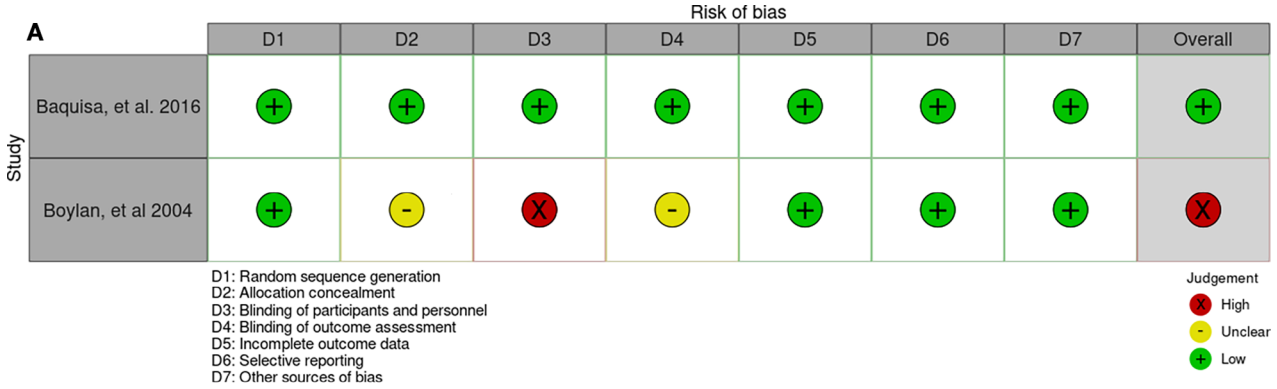
Table 2 (*Continued*)

Author and Year (Origin)	Study Design	Participant Characteristic	Dosage	Observation	Seizure Control Definition
Rey *et al*, 1990 (France) (16)	Cohort prospective	Neonates (five preterm, eight term) with severe seizures and no response to phenobarbital and diazepam received lidocaine (LD) infusion.	Lidocaine: 4 mg/kg/hour on day one, 3 mg/kg/hour on day two, 2 mg/kg/hour on day three, and 1 mg/kg/hour on day four.	Conventional EEG	Seizures or electrical discharges stop within the first 13 hours after the start of lidocaine infusion
Shany *et al*, 2007 (Israel) (17)	Cohort retrospective	Evaluating the efficacy of lidocaine against midazolam in managing intractable seizures in neonates, gestationally aged 36 weeks or older, diagnosed with hypoxic-ischemic encephalopathy, with monitoring cerebral activity.	Lidocaine: 2 mg/kg/hour bolus in 20 minutes followed by 4-6 mg/kg/hour continuous drip.	aEEG	Cessation of seizure activity for 6 hours or longer
Van der Broek *et al*, 2013 (Netherlands) (18)	Cohort prospective	Hypothermic neonates experiencing prenatal asphyxia and receiving lidocaine for seizure management were also incorporated. The effectiveness was evaluated by continuous amplitude-integrated electroencephalography. Safety was evaluated with continuous cardiac monitoring.	Lidocaine bolus 2 mg/kg in 10 min, followed by 4 mg/kg/hour for 6 hours. After 6 hours reduced to 2 mg/kg/hour for 12 hours	aEEG	Reduction of EEG electrographic seizure load by >80% within 4 hours of lidocaine administration
Weeke *et al*, 2016 (Netherlands) (19)	Cohort retrospective	According to aEEG findings, response was categorised as good (>4 hours without seizures and no requirement for rescue medicine); intermediate (0-2 hours without seizures, but requiring rescue medication after 2-4 hours); or no apparent response (rescue medication needed within <2 hours).	Lidocaine bolus 2 mg/kg in 10 minutes, maintenance according to protocol starting from 6 mg/kg/hour decreased to 1.5 mg/kg/hour in 3 stages	aEEG	Cessation of seizure activity for 4 hours or longer
Yamamoto *et al*, 2007 (Japan) (20)	Cohort retrospective	Investigate the history of each case, seizure classification, aetiology of status epilepticus, therapeutic interventions, outcomes, and adverse effects of treatment for patients under one week old presenting with prolonged or frequently recurrent seizures exceeding 15 minutes and resistant to conventional anticonvulsants, including diazepam (DZP), phenobarbital (PB), or phenytoin (PHT).	The mean dose of lidocaine was 1.88 mg/kg/hour).	EEG	Very good: seizures are well controlled with no adverse events. Good: seizures controlled >75% but with manageable side effects Ineffective: no seizure reduction, or seizure reduction of 25-50% with serious side effects

Table 3. Characteristics of studies included in the meta-analysis

No.	Author	Origin	Study Design	Total Sample	Lidocaine		Midazolam		Note
					Events	Total	Events	Total	
1.	Baquisa, et al. (2016)	Bangladesh	RCT	32	24	32			Second line
2.	Boylan, et al. (2004)	UK	RCT	5	3	5	0	3	Second line
3.	Conde, et al. (2024)	Spain	Cohort prospective		15	15	24	39	First line (midazolam) Second line (lidocaine)
4.	Favie, et al. (2019)	Netherlands	Cohort retrospective	92	49	92			Second line
5.	Hellstrom, et al. (1988)	Swedish	Cohort prospective	46	38	46			Second line and third line
6.	Hellstrom, et al. (1992)	Swedish	Cohort prospective	24	15	24			Second line and third line
7.	Lundqvist, et al.(2013)	Swedish	Cohort retrospective	30	19	30			Second line
8.	Malingre, et al. (2006)	Netherlands	Cohort prospective	21	16	21			Third line
9.	Rey, et al. (1990)	France	Cohort prospective	13	11	13			Third line
10.	Shany, et al. (2007)	Israel	Cohort retrospective	27	16 (11)*	27 (22)*	0	8	Second line
					28 (5)*	131 (5)*	21	165	Third line
11.	Van den Broek, et al.(2015)	Netherlands	Cohort prospective	22	20	22			Third line
12.	Weeke, et al. (2016)	Netherlands	Cohort retrospective	358	243 (127)*	358 (186)*	21	165	Second line
					116 (98)*	172 (145)*	61	107	Third line
13.	Yamamoto, et al. (2007)	Japan	Cohort retrospective	16	13	16			Second line

* (n) = represents the number that can be compared with midazolam



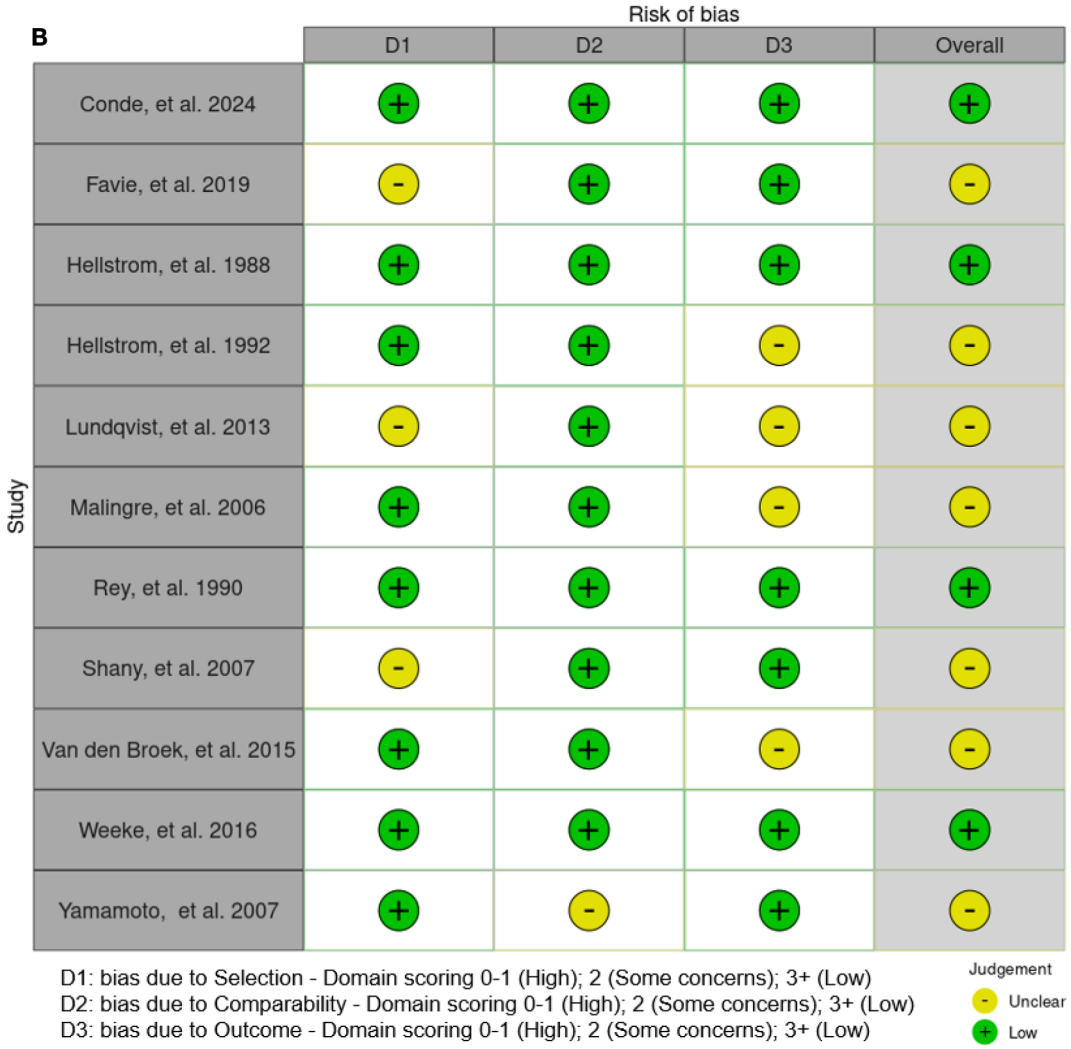


Figure 2. Summary of bias risk: evaluations by review authors regarding each bias risk criterion for every included study. (a) Risk of Bias in RCT, (b) Risk of Bias in Observational Study.

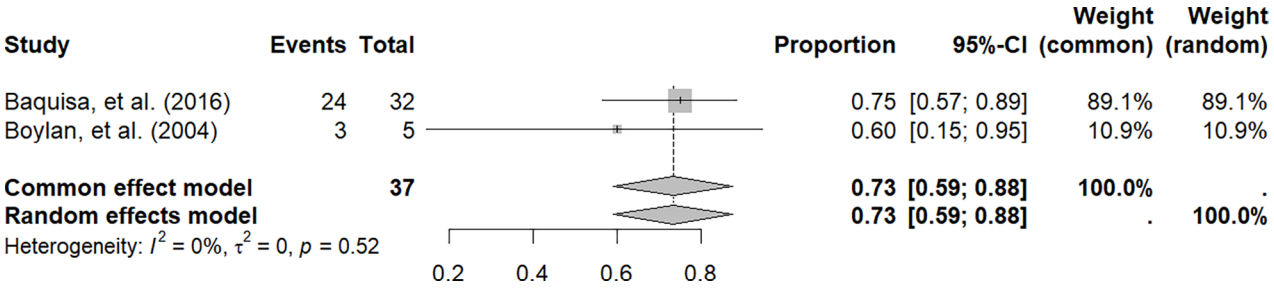


Figure 3. Forest Plot: Meta Proportion Efficacy of Lidocaine in Neonatal Seizure Treatment in RCT.

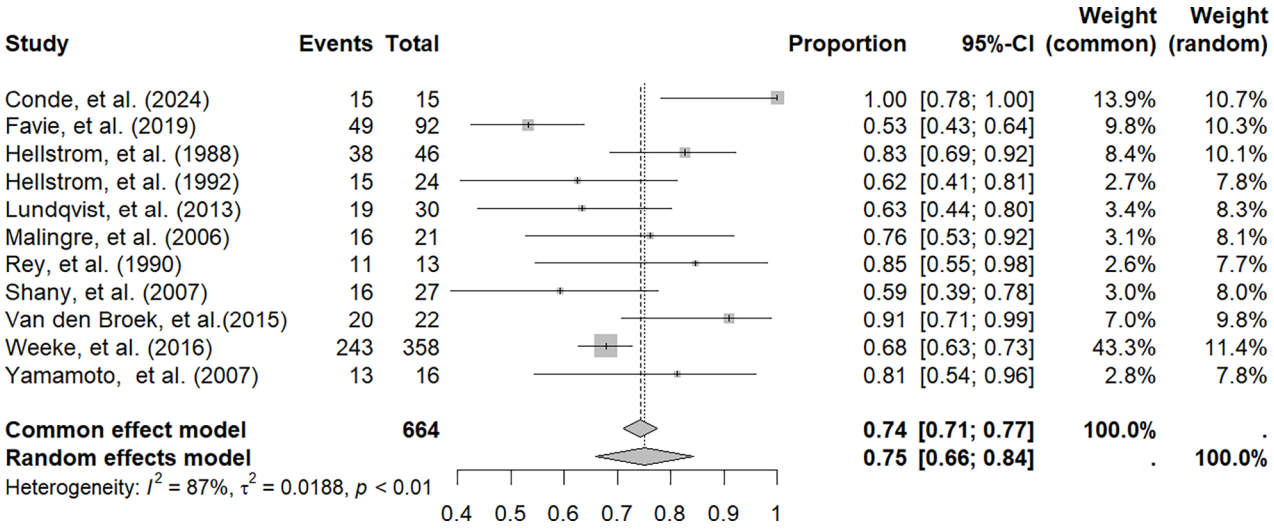


Figure 4. Forest Plot: Meta Proportion Efficacy of Lidocaine in Neonatal Seizure Treatment in Observational Study.

RCT studies: Baquisa et al. (2016) and Boylan et al. (2004). The meta-analysis study used a clinical trial research design and included 37 patients. The results showed an improvement in seizure incidence of 73% (95% CI 0.59-0.88). Data were heterogeneous with p>0.05 (Figure 3).

In observational studies obtained from 11 studies consisting of Conde, et al (2004), Favie, et al (2019), Hellstrom, et al (1988), Hellstrom, et al (1992), Lundqvist, et al (2013), Malingre, et al (2006), Rey, et al (1990), Shany, et al (2007), Van den Broek, et al (2015), Weeke, et al (2016), and Yamamoto, et al (2007), with a total of 664 patients, from heterogeneous data with p<0.01, a seizure improvement of 75% (95% CI 0.66-0.84) was obtained (Figure 4). In the results of the meta-proportion analysis of lidocaine as a second-line neonate seizure therapy (Figure 5), the efficacy was 74% (95% CI 0.57-0.91), while the use in the third line (Figure 6) obtained an efficacy of 82% (95 CI 0.70-0.94).

The outcome used the proportion incidence of cessation of seizure after lidocaine treatment. Each study contributes its own estimate of lidocaine's efficacy, with varying statistical significance levels.

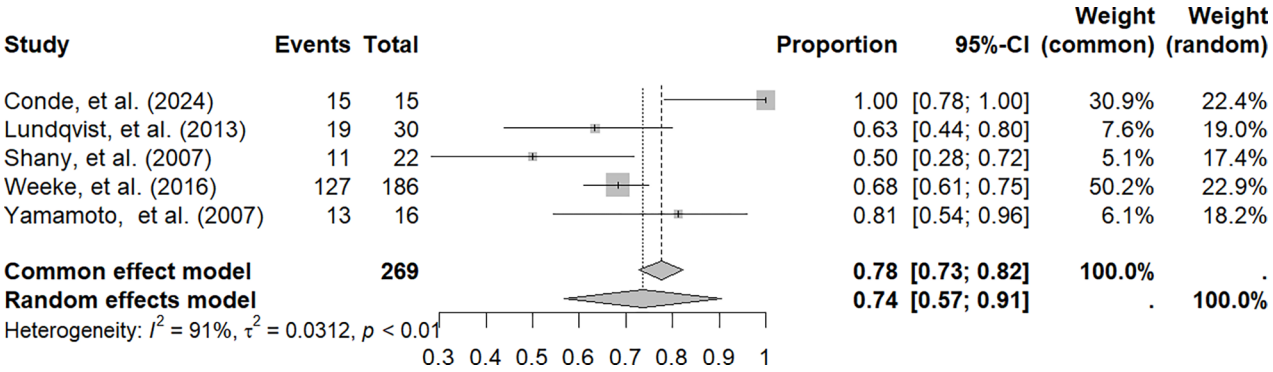


Figure 5. Forest Plot: Meta Proportion Lidocaine as second-line treatment in Neonatal Seizure in Observational Study.

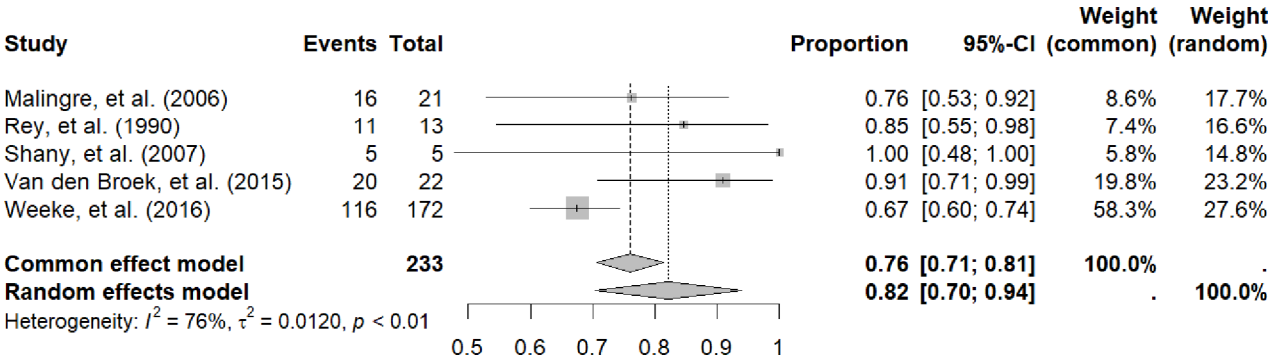


Figure 6. Forest Plot: Meta Proportion Lidocaine as third-line treatment in Neonatal Seizure in Observational Study.

Efficacy of lidocaine comparing with midazolam in neonatal seizure treatment

In the subanalysis of lidocaine as the second line and midazolam as the second-line administration, the Risk Ratio was 2.05 CI (1.47-2.85) with p<0.0001. This shows that the research data is homogeneous, with the use of the second lidocaine providing a better anti-seizure effect than the use of midazolam. This can be seen in Figure 7.

In the sub analysis of lidocaine as the third line and midazolam as the third-line treatment of neonatal seizure administration, the Risk Ratio was 1.67 (95% CI 1.00-2.77) with heterogeneity p=0.26. This shows that the study data is homogeneous, with the use of lidocaine in the third line providing a better anti-seizure effect than the use of midazolam but not significant between the two. This can be seen in Figure 8.

Comparison of lidocaine administration as neonatal seizure treatment in preterm and aterm patients

We conducted a sub-analysis of lidocaine administration between patients with preterm and at term gestational age. There were 4 study that analyzed this outcome (Figure 9). From these results, it was found that lidocaine administration in preterm patients had no difference in providing seizure control effects compared to aterm patients with Risk Ratio of 0.9 (95% CI 0.29-2.80).

In conclusion, based on the pooled data from these studies, lidocaine appears to be an effective treatment for neonatal seizures. The statistically significant overall efficacy supports its use. However, the substantial heterogeneity among the studies suggests that the results should be interpreted with caution. Further research is necessary to understand the sources of this variability and to confirm the findings in larger, more homogenous study populations.

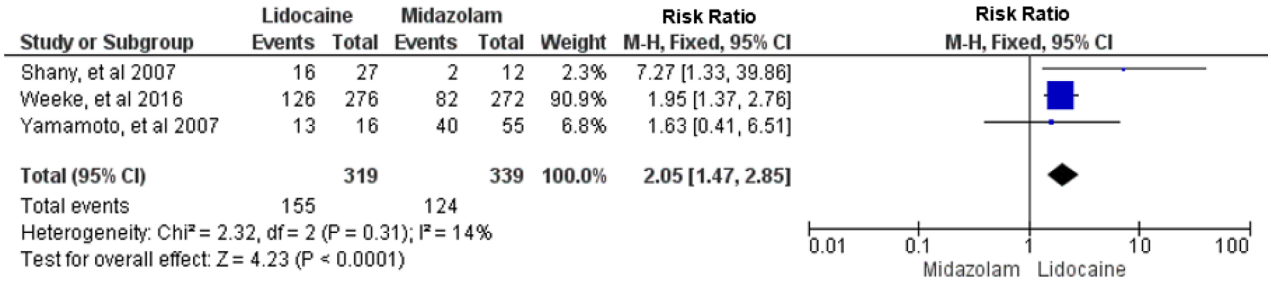


Figure 7. Forest plot: comparison between patients with lidocaine as second line and midazolam as second-line therapy in neonatal seizure**.**

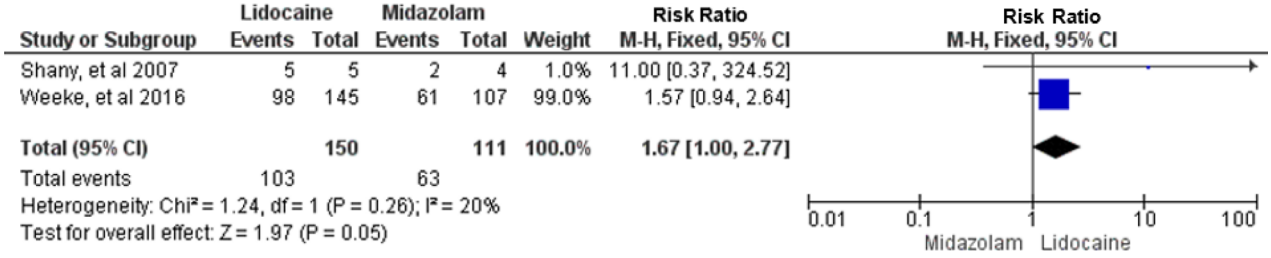


Figure 8. Forest plot: comparison between patients with lidocaine as third line and midazolam as third-line therapy in neonatal seizure.

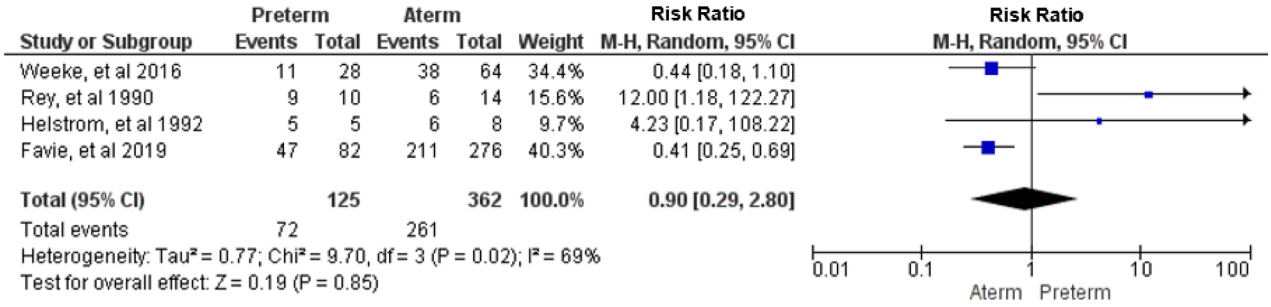


Figure 9. Forest Plot: Comparison of lidocaine administration as neonatal seizure treatment in preterm and aterm patients.

Side effects of lidocaine administration in neonatal seizures

There are 8 studies that also reported the incidence of side effects of lidocaine administration, which can be seen in Table 4.

Publication bias

The studies included in this research were deemed to have no publication bias, as evidenced by the nearly symmetrical appearance of the funnel plot in the meta-proportion (Figure 10).

Discussion

Neonatal seizures arise from an imbalance between excitatory and inhibitory signals in the brain, largely due to the developmental stage of the neonatal brain. The balance between the primary excitatory neurotransmitter glutamate and the inhibitory

Table 4. Side effects of lidocaine administration in neonatal seizure therapy

No.	Study	Side Effects
1.	Hellstrom, et al. (1988)	7 changes in blood pressure, 22 decreases in heart rate per minute
2.	Rey, et al. (1990)	No side effects found
3.	Hellstrom, et al. (1992)	Acidosis and bradycardia
4.	Malingre, et al. (2006)	No side effects of cardiac arrhythmia
5.	Yamamoto, et al. (2006).	6.3% hypotension, decreased urine *output*, tracheal hypersecretion, abdominal distension
6.	Van den Broek, et al. (2015)	No side effects of cardiac arrhythmia
7.	Lundqvist, et al. (2013)	1 bradycardia
8.	Baquisa, et al. (2016)	1 apnea, 2 bradycardia, 1 lethargy

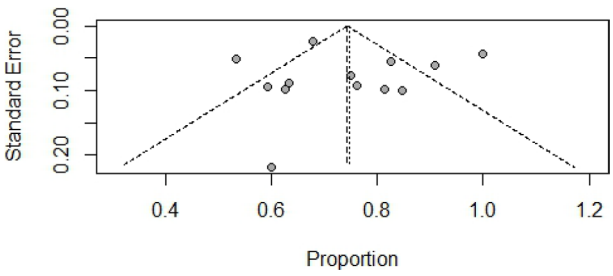


Figure 10. Funnel Plot of the included studies.

neurotransmitter GABA is disrupted in neonates. GABA, which typically has an inhibitory role in adults, can act excitatory in neonates due to the high expression of the NKCC1 cotransporter. Additionally, the increased density of NMDA and AMPA receptors in the neonatal brain lowers the seizure threshold and makes neonates more susceptible to seizures (21). Metabolic factors, such as hypoxia-ischemia and hypoglycemia, also contribute to neonatal seizure susceptibility by disrupting cellular energy and neurotransmitter levels. Hypoxia impairs the Na-K ATPase pump due to decreased ATP production, leading to excessive neuronal depolarization and seizures. Similarly, hypoglycemia results in reduced energy substrates and neurotransmitter imbalances, further increasing seizure risk. The immaturity of the neonatal brain's electrical and biochemical systems, including fewer inhibitory synaptic connections and less developed glial cells, exacerbates this susceptibility and leads to a higher propensity for seizures and associated complications (22,23). Lidocaine, a commonly used local anesthetic, has been investigated for its potential use in treating neonatal seizures, particularly as an alternative to traditional anticonvulsants like phenobarbital. Studies suggest lidocaine can act as a sodium channel blocker, which may help stabilize neuronal membranes and reduce seizure activity (24,25). This mechanism is particularly relevant in neonates, where excessive neuronal depolarization and imbalance in sodium channel activity contribute to seizure susceptibility. Lidocaine's ability to modulate neuronal excitability through sodium channel blockade offers a therapeutic advantage, potentially reducing seizure frequency and severity in neonates (26,27). The results of this meta-analysis provide compelling evidence for the efficacy of lidocaine in treating neonatal seizures. The meta proportion gives a value 73-82% of subjects' cessation of seizures after being given lidocaine. The pooled risk ratio (RR) of lidocaine as secondary and third-line treatment compared to midazolam in neonatal seizure is 2.05 [1.47, 2.85] with $p<0.0001$ and 1.67 [1.00-2.77] with $p=0.05$ respectively, suggests a benefit of lidocaine in controlling seizure activity compared to midazolam. This indicates that neonates treated with lidocaine are approximately twice in second-line treatment statistically significantly more likely to experience a reduction in seizure frequency or severity than those receiving midazolam interventions. The statistical significance of these findings supports the effectiveness of lidocaine as a therapeutic option for neonatal seizures. The observed effect size reflects a meaningful clinical impact, suggesting that lidocaine may offer a viable adjunctive treatment or, in some cases, a primary treatment option for managing seizures in neonates. This aligns with previous studies that have suggested the potential of lidocaine as a sodium channel blocker to stabilize neuronal membranes and reduce excitatory neurotransmission, thereby mitigating seizure activity (28,29). The comparison between preterm and term subjects was RR 0.9 (95% CI 0.29-2.80) $p = 0.85$. This shows no significant difference between lidocaine

administration in preterm and term neonates. Favié et al. found that although the overall effectiveness of lidocaine was lower in preterm infants compared to term infants (55.3% vs 76.1%), lidocaine still showed a significant response rate, with an overall effectiveness of 71.4% (11). This suggests that although preterm infants may respond less favorably to lidocaine, lidocaine remains a viable option when other treatments fail. Furthermore, Lundqvist et al. reported that lidocaine led to seizure termination in 63% of term infants when used as a second-line treatment, which suggests that efficacy may vary based on gestational age and specific clinical context (14). Monitoring is crucial when administering lidocaine to preterm infants, as they are susceptible to fluctuations in drug levels and potential side effects. Continuous electroencephalography (EEG) monitoring is recommended to detect subclinical seizures and assess treatment efficacy in real-time (30). This is especially important in the preterm population, where the incidence of electrographic seizures is high, and timely intervention can significantly impact outcomes (31). The use of lidocaine in neonates presents several concerns despite its potential benefits in managing seizures. Side effects such as cardiovascular and central nervous system toxicity necessitate careful monitoring, as high doses or prolonged use can lead to adverse reactions, including bradycardia, hypotension, and additional seizures, which can complicate seizure management (32). Furthermore, the long-term impact of lidocaine on brain development and cognitive outcomes is not well understood, warranting further investigation to assess its potential developmental effects alongside its immediate benefits (33,34). Careful monitoring and dose adjustment are essential to minimize risks associated with lidocaine therapy. Additionally, the impact of lidocaine on neurodevelopment and cognitive outcomes remains an area requiring further research (35). To the best of our knowledge, this is the first and only comprehensive systematic review and meta-analysis to study lidocaine efficacy in neonatal seizure treatment. However, this study is limited in several ways. The variability in study designs and heterogeneity of patient populations across the included studies need further consideration that would provide a more nuanced interpretation and understanding of the findings. Differences in dosage regimens, treatment duration, and baseline characteristics of neonates may contribute to variability in treatment outcomes. Future research needs to standardize protocols and ensure homogeneity in study populations to better understand the optimal use of lidocaine for neonatal seizures (36). Expanding the study on the role of lidocaine as a combination therapy and evaluating long-term neurodevelopmental outcomes will make future research better, more extensive, and thorough.

Conclusion

Lidocaine is effective in the treatment of neonatal seizures. However, its use must be guided by a thorough understanding of its mechanisms, benefits, and risks. The current evidence supports further investigation into its role alongside other anticonvulsants, with a focus on optimizing safety and efficacy for this vulnerable population.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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