IJHS
Interamerican Journal of Heath Sciences 4 (2024) - ISSN 2953-3724
DOI: 10.59471/ijhsc2024178

SYSTEMATIC REVIEW

The utility of lidocaine in neonatal conviction syndrome: a systematic review

Utilidad de la lidocaína en el síndrome convulsivo neonatal: una revisión sistemática

Jeune Marie Milange[1], **Marcelo Adrián Estrin**[1]

[1]Universidad Abierta Interamericana. Facultad de Medicina y Ciencias de la Salud. Argentina

Received: 09-08-2023 Revised: 02-12-2023 Accepted: 04-03-2024 Published: 05-03-2024
How to Cite: Marie Milange J, Estrin MA. The utility of lidocaine in neonatal conviction syndrome. Interamerican Journal of Health Sciences. 2024; 4:178. https://doi.org/10.59471/ijhsc2024178

ABSTRACT

Introduction: lidocaine is a drug belonging to the local anesthetics, it is rapidly distributed in the body and metabolized in the liver. At commonly recommended doses, the therapeutic index of lidocaine remains very high and plasma concentrations remain largely below neurotoxic, cardiotoxic and other thresholds. It is used during various medical procedures, and in the nervous system it acts by binding to a specific site which is the sodium channel receptor of the neural membrane and blocking the passage of ions.
Objective: to determine the potential usefulness of lidocaine in neonates with convulsive syndrome.
Methods: in the present systematic review we tried to provide an answer and conducted a literature search through pubmed and others to analyze the usefulness of lidocaine in neonatal convulsive syndrome and its potential benefit.
Results: after applying the inclusion and exclusion criteria, we will be able to identify the groups of neonates at higher risk and the efficacy of lidocaine treatment.
Conclusions: lidocaine is the third drug used in neonatal convulsive syndrome for maintenance where they receive it in continuous infusion, being effective in suppressing electro-clinical crises. Excessive doses of lidocaine should be avoided since it can produce convulsions and other adverse effects in children.

KEYWORDS

Lidocaine, Anticonvulsants, Lidocaine Utility, Seizure Symdrome, Neonatal.

RESUMEN

Introducción: la lidocaína es un fármaco perteneciente a los anestésicos locales, la misma se distribuye rápidamente en el organismo y se metaboliza en el hígado. Con las dosis comúnmente recomendadas, el índice terapéutico de la lidocaína sigue siendo muy elevado y las concentraciones plasmáticas se mantienen en gran medida por debajo de los umbrales neurotóxicos y cardiotóxicos y otros. Se utiliza durante varios procedimientos médicos, y en el sistema nervioso actúa uniéndose a un sitio específico que es el receptor del conducto de sodio de la membrana neural y bloqueando el paso de iones.
Objetivo: determinar la utilidad potencial de la lidocaína en neonatos con síndrome convulsivo.
Métodos: en la presente revisión sistemática tratamos de dar respuesta y realizamos una búsqueda bibliográfica a través de pubmed y otros para analizar la utilidad de la lidocaína en el síndrome convulsivo neonatal y su potencial beneficio.
Resultados: tras la aplicación de los criterios de inclusión y exclusión, podremos identificar los grupos de recién nacidos de mayor riesgo y la eficacia del tratamiento con lidocaína.
Conclusiones: la lidocaína es la tercera droga que se utiliza en el síndrome convulsivo neonatal para mantenimiento

donde lo reciben en infusión continua, siendo efectiva para suprimir las crisis electro clínicas. Se debe evitar las dosis excesivas de la misma ya que puede producir convulsiones y otros efectos adversos en los niños.

PALABRAS CLAVE

Lidocaína, Anticonvulsivantes, Utilidad de Lidocaína, Síndrome Convulsivo Neonatal.

INTRODUCTION

Lidocaine is a local anesthetic in different pharmaceutical forms, such as jelly, spray and ampoule, adhesive dressing, and oral gel. It is administered intravenous, intramuscular, and transdermal routes. The onset of action in the intravenous form is immediate, and the duration of action is 10-20 minutes, while in the intramuscular form, it is 5-10 minutes, and its duration of action is 60-90 minutes, although this depends on the liver function, the initial dose in the newborn is 0,5-1 mg /kg being important not to exceed the total dose 3mg /kg of weight, in recent years new properties have been found beyond its classic characteristics described as a local anesthetic, its chemical structure consists of 4 subunits: Subunit 1 is the aromatic nucleus, formed by a benzene ring that gives liposolubility to the molecule.

Subunit 2 is formed by the ester-amide bond that determines the type of drug metabolism, either by plasma pseudocholinesterases (aminoesters) or at the hepatic level (aminoamides). Subunit 3 consists of the hydrocarbon chain influencing liposolubility, duration of action, and toxicity.

Subunit 4, the amine group that confers water solubility and binding to plasma proteins, is considered a weak base since it binds 70 % to plasma proteins, mainly alpha one acid glycoprotein, and interacts with Gram-negative bacteria. [1]

TLR4 mainly activates the nuclear factor kappa light chain enhancer factor kappa of activated B cells (NF-KB), which in turn, however, at lower concentrations have been attributed different effects such as neuroprotection and anti-inflammatory properties. It also blocks the muscarinic system and dopamine in bronchial hyperreactivity.

In general, treating neonatal seizures depends on one's experience, etiology, duration, frequency, and associated dysautonomic signs.

The etiology of neonatal seizures can be primary, with hypoxic-ischemic encephalopathy being the most frequent, pre and perinatal; only 10 % are postnatal, as well as intracranial hemorrhage. Frequent in both term and preterm infants, especially subarachnoid hemorrhage in both cases and intraventricular hemorrhage in preterm infants.

Between 15 and 50 % present metabolic crises such as transient or persistent hypoglycemia (20 mg/dL or less in preterm and 30 mg/dL in term infants), early and late hypocalcemia (less than 7 mg/dL of total calcium or 4 mg/dL of ionic calcium), hypomagnesemia (less than one mEq/L). Others are alterations of natremia, hypo or hypernatremia, infections such as meningitis, encephalitis regardless of their origin, pre or perinatal, which can cause seizures, intoxication, and finally, genetic. [2] Contraindications:

It is contraindicated in cases of hypersensitivity to lidocaine, heart block, severe bleeding, severe hypotension, severe hypotension shock, hepatic or renal dysfunction, malignant hyperthermia, inflammation or infection in the area of application, septicemia, and children < 4 years.

Side effects are described as rash, itching, shallow breathing, dyspnea, dysphagia, drowsiness, cardiac arrhythmias, etc. [3]

Several risk factors are associated with seizure syndrome in newborns. The developing brain is more susceptible to seizure activity, and neonatal seizures can adversely affect neurodevelopment. It is itself a marker of neurological morbidity, may contribute to aggravating the presence of pre-existing brain disease, and affects 2.3/1000 term newborns and 50.130/1000 preterm newborns. Several prenatal and intrapartum maternal factors increased the risk of seizures during admission at birth. Identifying and avoiding neonatal seizure risks may reduce infant neurological morbidity and mortality. [4]

- Factors 1: respiratory distress syndrome, pulmonary air leakage (pneumothorax and pulmonary interstitial emphysema).
- Factors 2: intraventricular hemorrhage, peri-ventricular leukomalacia, patent ductus arteriosus, surgical ligation of patent ductus arteriosus.
- Factors 3: necrotizing enterocolitis and surgical treatment of necrotizing enterocolitis.
- Factors 4: neonatal seizures appear to be associated with major morbidities and surgical interventions in very low birth weight infants. Continuous electroencephalographic monitoring may be warranted in infants undergoing surgical treatment.

The following are the main etiologies in order of frequency or causes:[5]

1. Hypoxic-ischemic encephalopathy: the most frequent, pre- and perinatal, only 10 % are postnatal.
2. Intracranial hemorrhage: frequent in both term and preterm infants, especially subarachnoid hemorrhage in both cases and intraventricular hemorrhage in preterm infants. Between 15 and 50 % present crises.
3. Metabolic.
   A). Transient or persistent hypoglycemia (20 mg/dL or less in the preterm and 30 mg/dL in the term infant).
   B). Early and late hypocalcemia (less than 7 mg/dL total calcium or 4 mg/dL ionic calcium).
   C). Hypomagnesemia (less than 1 mEq/L).
   D). Others are alterations of natremia, hypo or hypernatremia (< 130mEq/L or more than 150mEq/L), and hyperbilirubinemia. Blood tests, blood glucose, serum electrolytes, calcium, and magnesium should be performed even if a clear etiology of seizures, such as hypoxic-ischemic encephalopathy, is suspected.
4. Infections (sepsis, meningitis and encephalitis). Regardless of their origin, pre- or perinatal, they can cause seizures, so at the slightest suspicion, lumbar puncture should be performed.
5. Cerebral malformations: virtually all disorders of neuronal migration and cortical organization can present severe neonatal seizure phenomena.
6. Toxic and drug deprivation. Of increasing frequency related to deprivation of analgesics-narcotics, hypnotics, sedatives, alcohol, and heroin, in the case of methadone, the possibility of its later presentation (up to four weeks after its suppression) should be retained. A little-known cause is the accidental injection of local anesthetics (in surgical maneuvers), which can produce tonic crises six hours after their injection, accompanied by other symptoms such as loss of lateral ocular motility and alteration of pupillary reflexes.
7. Genetically determined CNS processes. Disorders of amino acid metabolism and the urea cycle, in which seizures are clinical elements of the first order, mitochondrial, lysosomal, peroxisomal, and other metabolic disorders (biotinidase deficiency, hydrocarbon metabolism, pyridoxine dependence, folinic acid deficiency, glucose transporter protein deficiency, cerebral creatine deficiency, etc.) and degenerative disorders (Alpers).
8. Genetic (channelopathies): benign familial neonatal seizures (KCNQ 2, on chromosome 20 and KCNQ 3, on chromosome 8).
9. Benign idiopathic neonatal idiopathic neonatal epileptic syndromes:
   a. Benign idiopathic neonatal seizures, “fifth-day seizures,” “fifth-day seizures,” and “fifth-day seizures.”
   b. Benign familial idiopathic neonatal seizures.
10. Neonatal epileptic encephalopathies:
    a. Ohtahara syndrome (early infantile encephalopathy).
    b. Aicardi syndrome (early myoclonic encephalopathy).
11. Neonatal convulsive mal seizure states.
12. Symptomatic epilepsies.
13. Unknown.

Signs and symptoms of neonatal seizures.

Neonatal seizures are usually focal and may be difficult to distinguish from normal neonatal activity because they may manifest as chewing or “cycling” movements with the legs. Frequent manifestations are migratory myoclonic jerks, alternating hemiconvulsions, and primitive subcortical seizures (causing respiratory arrest, chewing movements, persistent eye deviations, and episodic alterations of muscle tone). One type of clinical classification of neonatal seizures, according to their motor manifestations, subdivides them into the following types: focal or multifocal clonus, focal or multifocal tonic seizures, focal or multifocal myoclonus, subtle seizures, epileptic spasms. [6]

Diagnostic methodology of neonatal seizure disorders

The evaluation begins with a detailed family history and physical examination. Startles (alternating contraction and relaxation of antagonistic limb muscles) should be distinguished from true seizure activity. Startles are usually stimulus-induced and can be stopped by holding the limb still; in contrast, seizures are spontaneous, and motor activity is perceived even if the limb is still.

Electroencephalography (EEG)

EEG is essential, and prolonged recording may sometimes be required, especially when it is difficult to determine whether the newborn is having seizures. EEG is also useful for monitoring response to treatment. EEG should capture active and quiet sleep periods and may require ≥ 2 hours of recording. A normal EEG with expected

variation during sleep stages indicates a good prognosis; an EEG with severe diffuse alterations (e.g., voltage suppression pattern or flares) indicates a poor prognosis. Bedside ECG with video monitoring for ≥ 24 h can detect ongoing clinically silent electrical seizures, especially in the first few days after a stroke. [5]

Laboratory tests
Laboratory tests Laboratory studies should be performed immediately to look for underlying treatable disorders; studies should include pulse oximetry, determination of serum concentrations of glucose, sodium, potassium, chloride, bicarbonate, calcium, and magnesium; and lumbar puncture for cerebrospinal fluid analysis (cell count and formula, glucose, protein) and culture. Urine culture and blood culture are also performed. [7]
The need for other metabolic tests (e.g., arterial pH, blood gases, serum bilirubin, amino acids, and organic acids in urine) or investigation of common drugs of abuse (transferred to the newborn via transplacental or breast milk) depends on the clinical picture. Genetic evaluation should be considered in children with recurrent or refractory seizures of undetermined cause. [7]

Brain Imaging Studies
Imaging studies are usually performed unless the cause is immediately obvious (e.g., glucose or electrolyte disturbance). MRI is preferred but may not be readily available; in such cases, a brain CT scan is performed.
For infants who cannot be moved to radiology, a bedside cranial ultrasound may be performed; it may detect intraventricular but not subarachnoid hemorrhage. MRI or CT is performed when infants are stable.CT of the brain can detect intracranial hemorrhage and some encephalic malformations. MRI shows malformations more clearly and can detect ischemic tissue within a few hours of the onset. [8]
MRI spectroscopy can help determine the extent of an ischemic lesion or identify the accumulation of certain neurotransmitters associated with an underlying metabolic disorder.

Treatment
Brain flow increases during status epilepticus, so the amount of drug in circulation through the brain is increased. Lidocaine is used as the third-line drug. [8]
In one study,[9] they evaluated 20 newborns with seizures refractory to treatment with Phenobarbital and Midazolam, who received a continuous infusion of lidocaine. It was effective in suppressing electroclinical crises in 76 % of the newborns. None of them presented cardiac arrhythmias, a previously reported complication if there is a rapid exit of the drug from the central nervous system, and this will affect the dose of lidocaine to be used since the dose during status epilepticus may vary from 2 to 10 times the normal dose.

METHOD

This work is a systematic review of the literature and was carried out from July 2023 to October 2023 in Buenos Aires, Argentina. For the present work, an exhaustive search was carried out in the following databases: PubMed, SciELO, Scopus, with the following filters: free full text, without language restriction, between the period of 2012-2023. Subsequently, the MESH (Medical Subject Heading) terms “Lidocaine”, “Utility in neonatal seizures”, “Older newborns”, “Irrational use”, “Falls” and the Boolean operator AND were used to restrict the data. Of the scientific articles found, we excluded those that did not contain information relevant to the central research topic, those that did not address convulsive syndromes in neonates, and others that did not belong to the established databases.

Inclusion criteria
We considered scientific articles in Spanish and English language for this systematic review work dealing with neonatal patients, of both sexes, patients with congenital brain malformation and patients with pre-existing brain alterations.

Exclusion criteria
Scientific articles referring to neonatal patients whose mothers were not monitored during pregnancy, neonatal patients with intoxications and neonatal patients with genetic alterations were excluded.

RESULTADS

Table 1. Distribution according to types of neonatal crises

Type of neonatal crises	Frequency (%)
Clonic	50
Subtle	10-35 According to gestational age
Tonics	20
Myoclonic	5

Source:[10]

Table 2. Relationship between clinical and electroencephalographic crises

Clinical crises	Electroencephalographic seizures	
	Frequent	Infrequent
Subtle		+
Focal Clonic	+	
Multifocal Clonic	+	
Focal Tonics	+	
Generalized Tonics	+	
Focal myoclonic, multifocal		+
Generalized Myoclonic	+	

Source:[11]

Tabla 3. Etiology of neonatal seizures in relation to the time of presentation of seizures and their relative frequency

Etiology	Start-up time (days)			Relative frequency	
	0-3	>3	>7	RNPT	RNT
Hypoxic-ischemic encephalopathy	+	-	-	++++	+++
Intracranial hemorrhage	+	-	-	++	+
Hypoglycemia	+	-	-	+	+
Hypocalcemia	+	+	-	+	+
CNS infection	-	+	-	++	++
Cerebral dysgenesis	+	+	-	++	++
Drugs	+	+	-	++	++
Pyridoxine dependence	++	-	-	+	+
Congenital infection	+	-	-	+	+
Non-ketotic hyperglycinemia	+	+	-	+	+
Peroxisomal disease	+	+	-	+	+
Other EIM	-	-	+	+	+
Folic acid deficiency	-	-	+	-	+
Benign neonatal seizures	-	+	-	-	+

Source:[4,11]

The ultimate goal in the management of a child with severe neurological injury will be to preserve adequate blood flow to the brain at all times, avoiding factors that impair neurological function, such as hypoxemia, considering

that most severe neurological injuries are represented at some point in their evolution by an increase in intracranial pressure (ICP) and that this increase can lead to a decrease in cerebral perfusion pressure (CPP), an understanding of the pathophysiology of this alteration is the basis for rational and objective treatment. [12]

DISCUSSION

The present review aimed to demonstrate the efficacy of lidocaine in the management of neonatal convulsive syndrome as an important analgesic adjuvant, as well as its efficacy as a maintenance drug in which it was administered as a continuous infusion, effectively suppressing electroclinical crises and thus reducing the side effects of this syndrome, ultimately favoring a brief recovery. To assess efficacy, patients receiving a lidocaine infusion were analyzed.

CONCLUSION

Lidocaine is one of the most widely used drugs as a local anesthetic and is readily available in both public and private hospitals, as well as offering new uses and benefits. The re-emergence of this drug for the new properties described opens a promising outlook as new randomized clinical trials in humans will confirm or not all the effects described, analyzing the convenience of non-classical uses of other common drugs such as lidocaine.

BIBLIOGRAPHIC REFERENTES

1. Gerardo Ochoa-Anaya, Claudia Patricia Aguirre-Ibarra, Montserrat Franco-Cabrera. Lidocaína: aspectos generales y nuevas implicaciones en la inflamación. 2017;(3).

2. Castelló JC, Gómez LA, Villar GV, Serrano MM. Convulsiones neonatales. Protocolo de manejo.

3. Lidocaína | Asociación Española de Pediatría [Internet]. [citado 3 de agosto de 2023]. Disponible en: https://www.aeped.es/comitemedicamentos/pediamecum/lidocaina

4. Glass HC, Pham TN, Danielsen B, Towner D, Glidden D, Wu YW. Antenatal and Intrapartum Risk Factors for Seizures in Term Newborns: A Population-Based Study, California 1998-2002. The Journal of Pediatrics. 1 de enero de 2009;154(1):24-28.e1.

5. Alonso García B, Samper Villagrasa MP. Crisis convulsivas en el neonato. Zaragoza: Universidad de Zaragoza; 2019.

6. REVISION BIBLIOGRÁFICA CONVULCIONES NEONATALES.pdf [Internet]. [citado 3 de agosto de 2023]. Disponible en: https://www.kerwa.ucr.ac.cr/bitstream/ handle/10669/79937/REVISION %20BI BLIOGR %c3 %81FICA %20CONVULCI ONES %20 %20NEONATALES.pdf?se quence=1&isAllowed=y

7. Troncoso A L, Menéndez G P, Hernández Ch M. Convulsiones neonatales: diagnóstico y manejo. Revista chilena de pediatría. mayo de 2001;72(3):190-8.

8. Feld DV. CONVULSIONES NEONATALES. Normas de evaluación, diagnóstico y tratamiento.

9. a9_1_tr_convulsionesneonatales.pdf [Internet]. [citado 2 de agosto de 2023]. Disponible en: https://www.revistachilenadeepilepsia. cl/revistas/revista_2008/a9_1_tr_conv ulsionesneonatales.pdf

10. a9_1_tr_convulsionesneonatales.pdf [Internet]. [citado 3 de agosto de 2023]. Disponible en: https://www.revistachilenadeepilepsia. cl/revistas/revista_2008/a9_1_tr_conv ulsionesneonatales.pdf

11. Evans D, Levene M. Neonatal seizures. Arch Dis Child Fetal Neonatal Ed. enero de 1998;78(1):F70-5.

12. Barba DJP. EVALUACIÓN Y MANEJO DEL NIÑO CON LESION NEUROLÓGICA GRAVE.

FINANCING

The authors received no funding for the development of this research.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORSHIP CONTRIBUTION

Conceptualization: Jeune Marie Milange, Marcelo Adrián Estrin.
Research: Jeune Marie Milange, Marcelo Adrián Estrin.
Methodology: Jeune Marie Milange, Marcelo Adrián Estrin.
Writing - original draft: Jeune Marie Milange, Marcelo Adrián Estrin.
Writing - revision and editing: Jeune Marie Milange, Marcelo Adrián Estrin.