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Intracranial hemorrhage in the preterm infants: An integrative literature review

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***Abstract*—** *Intracranial hemorrhage(ICH) is one of the main reasons for morbidity and mortality in model newborns, being considered the biggest problem of prolonged treatment for units in the world. The research aims to review and analyze, through the relationship of intracranial hemorrhages in preterm newborns. Method: This is a study of bibliographic, descriptive, literature review type, with searches carried out in virtual libraries Scientific Electronic Library Online (SciELO),Biblioteca Virtual em Saúde (BVS) and PubMeddatabase. Ten full articles were selected, available in open access in Portuguese, English and Spanish and published in the years 2015 to 2022. Results: Based on the analysis of the classes, three categories emerged, described below: Class 1 - Factors Associated with Intracranial Hemorrhage in Newborns, Class 2 - Comorbidities Associated with Intracranial Hemorrhage, Class 3 - Outcome of Intracranial Hemorrhage in Child Development. Conclusion: it is essential to understand the risk variables for the development of ICH for the recognition of the choice criteria and the therapeutic conducts in the care of the neonate, as well as the adequate follow-up to alleviate possible injuries.*

I. INTRODUCTION

Intracranial hemorrhage (ICH) is one of the main reasons for morbidity and mortality in premature newborns. The etiology of this hemorrhage is multifactorial and includes the cerebral vascular fragility inherent to prematurity, changes in blood flow and changes in intracranial pressure. The greater the prematurity, the greater the possibilities of developing ICH (Amaral, J, et al, 2022).

The severity of intracranial hemorrhage is associated with its extent, and can range from grade I, mild hemorrhage, to grade IV, severe hemorrhage. Thus, grade I is restricted to the subependymal germinal matrix (caudothalamic sulcus); grade II, without intraventricular ventricular dilatation; grade III, intraventricular with ventricular dilatation; grade IV, parenchymal hemorrhage corresponding to periventricular venous infarctions with hemorrhagic progression (Neves, LAT, et al, 2007).

Clinically, ICH is most commonly asymptomatic, but it can manifest as a subacute intermittent neurological syndrome or, less frequently, when ICH is more significant, as a catastrophic acute neurological deterioration syndrome. (Amaral, J, et al, 2022).

Intracranial hemorrhage is an expressive problem in premature newborns (PTNB) and with birth weight below 2,500 g, called low birth weight newborns (LBW). ICH has great relevance for its immediate and future severity, considering the subsequent neurological disorders (Seki, TN; Balieiro, MMFG, 2009).

Several cases of ICH occur soon after birth or on the first day after birth, therefore, it is closely associated with perinatal aspects. Regarding the moment of occurrence of ICH, almost all of it happens in the first seven days of life, with more than 95% in the first 72 hours of life.(Amaral, J, et al, 2022).

ICH in NB can cause failures in the neuropsychomotor development of these children, mainly because they are associated with prematurity. In this way, the neuropsychomotor development of preterm infants with ICH is present in approximately 30% to 60% of severe cases of ventriculomegaly related to developmental sequelae, such as insufficient muscle tone, inadequate strength and reflexes, and delay in controlling the blood pressure. head (Cerisola, A, et al, 2019).

Trans fontanellar ultrasound (TFUS) is the test of choice for diagnosing intracranial hemorrhages. In addition to the diagnosis, the USTF assists in the staging of ICH and provides information regarding the immediate and long-term prognosis. TUS must be performed, through the anterior or bregmatic fontanelle, in all premature NBs with birth weight below 2,500 g, between 3 and 5 days of life, and reinforced weekly until hospital discharge, regardless of the appearance of symptoms. (Cerisola, A, et al, 2019).

The relevance of ICH in the prognosis of neuropsychomotor development of premature and low birth weight newborns has become more noticeable as diagnostic methods have become more sophisticated and clinical and epidemiological findings have become better known (Neves, LAT, et al, 2007).

According to Amaral, J, et al, (2022), some research shows that there is a tendency for a time of low brain flow that precedes ICH in preterm infants. And that these ranges of vascular passivity to pressure are usual in preterm infants, and are significantly related to low birth weight, low gestational age and systemic hypotension.

Intracranial hemorrhage decreased its incidence by 20% in the late 1980s. However, in the last two decades the occurrence of ICH has remained stationary. In newborns with extremely low birth weight (<750g) it reaches 45%. ICH remains the biggest neurological problem for premature infants in intensive care units worldwide (Neves, LAT, et al, 2007).

II. METHOD

In this sense, the present work aims to review and analyze, through the literature, the relationship of intracranial hemorrhages in preterm newborns, as well as recommendations to prevent them.

This is a bibliographic, descriptive analysis of the integrative literature review type, which made it possible to explore and understand a particular topic based on another independent research. It is revealed that the execution of the research was carried out in five main stages: recognition of the guiding question of the study; research in the literature; establishment of inclusion and exclusion criteria; information analysis; discussion of results and presentation of the review. In this sense, the following guiding question was applied to guide the research: What is the relationship between intracranial hemorrhages in preterm newborns?

To carry out the research, the Scientific Electronic Library Online (SciELO) and Virtual Health Library (BVS) and PubMed databases were consulted. For the search, the descriptors in Health Sciences (DeCS) were used, namely, “intracranial hemorrhages” and “premature infant”, using the Boolean “AND” to process the associations of all the descriptors with each other.

The search was carried out from November 18 to 26, 2021. For the selection of material, the following

inclusion criteria were considered: complete articles, available in open access in Portuguese, English and Spanish and published in the years from 2015 to 2022.

Initially, 2,073 publications were found, however, after applying the inclusion criteria, this number decreased to 291 articles. 178 articles were found in PubMed, 64 in VHL and 49 in SciELO, with 24 duplicate articles in PubMed, 13 in VHL and 7 in Scielo. Thus, after reading the titles, 108 articles were selected and 34 articles by the abstract, leaving 10 studies chosen for reading in full. 1,782 journals were excluded because they were not complete or did not answer the research question. Figure 1 shows the flowchart of the article selection process.

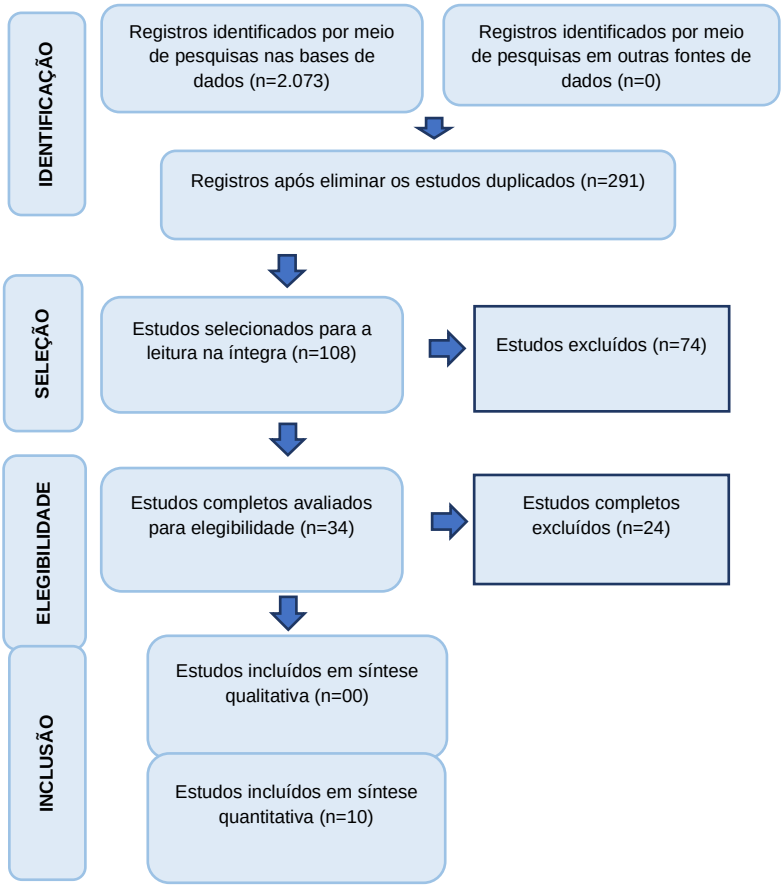

Fig.1: Shows the flowchart of the article selection process.

Source: Study selection flowchart adapted of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA 2009). Belém (PA), Brasil, 2022.

From the pre-reading of each article selected in the research, it was possible to analyze and characterize them in terms of authorship, year of publication, title, virtual libraries, method, levels of evidence.

Studies considered as highevidence quality(meta-analysis of multiple controlled studies - level 1; individual studies with experimental design - level 2), moderate evidencequality(study with quasi-experimental design as a study without randomization, with single test groups before and after, time series or case-control – level 3; studies of non-experimental designs, such as descriptive correlation and qualitative studies or case studies - level 4; case reports or systematically obtained data - level 5), low evidencequality (an authority opinion based on clinical competence or expert committee opinion, including interpretation of non-research-based information - level 6) (Duncombe D. C, 2018).

The textual corpus was elaborated with the conclusions of the articles, organizing it in a single text file for Bardin's processing and analysis. According to Bardin (2016), it consists of a method divided into stages: organization of analysis, coding and categorization. Thus, the organization of the analysis is characterized by the exhaustive reading and treatment of the results obtained for interpretation. In addition, in the coding, the units of records in the transcribed material will be classified and in the categorization, the observed results are listed in categories.

In this sense, after the described phase, the studies were analyzed by means of a critical reading of the chosen studies, in order to extract information regarding intracranial hemorrhages in preterm newborns, according to the content of the literature.

III. RESULTS AND DISCUSSION

After selection, only 10 articles met the criteria established in this review, one in 2020 (10%), four in 2019 (40%), one in 2018 (10%), one in 2017 (10%), two in 2016 (20%) and one in 2015 (10%). It was noted that two journals are in the SciELO virtual library (20%), two in the VHL (20%) and six in PubMed (60%).

Regarding languages, six studies were recorded in English (60%), three studies in Portuguese (30%) and one study in Spanish (10%). Regarding the methodology used, all studies were classified as quantitative (100%). Therefore, the articles included in this review are presented, thus exposing the specifications regarding the code of each article, author, year, title, database, method, and levels of evidence (Table 1).

Based on the analysis of the classes, three categories emerged, described below: Class 1 - Factors Associated with Intracranial Hemorrhage in Newborns, Class 2 - Comorbidities Associated with Intracranial Hemorrhage,

Class 3 - Outcome of Intracranial Hemorrhage in Child Development.

Table 1:Integrative review articles

Autor/ Ano		Título	Biblioteca Virtual	Método	Níveis de Evidência
A1	SILVA, Lisandra Radaelli da, et al. 2015.	Pregnancy aspects related to intracranial hemorrhage in newborns of very low weight in South Brazil	SCIELO	Quantitative Analytical Cross-sectional Study, case-control type	Level 2
A2	MARTINO, Márcia Salim de, et al. 2019.	Comparison on cognitive performance among schoolchildren born prematurely according to the presence of intracranial hemorrhage in the neonatal period	SCIELO	Quantitative Analytical Cross-sectional Study, cohort type	Level 2
A3	GRANDI, Carlos, et al. 2016.	Perinatal factors associated with neonatal mortality in very low birth weight infants: A multicenter study	BVS	Quantitative Analytical and Retrospective Study, cohort type	Level 2
A4	SANTOS, Denise Santana Silva dos; PRADO, Marcelle Sanjuan Ganem. 2017.	Occurrence of neurological injuries in newborns diagnosed bytransfontanellar ultrasound	BVS	Descriptive and Retrospective Quantitative Study, of the cohort type	Level 3
A5	KATHERIA, Anup, et al. 2019	Association of Umbilical Cord Milking vs Delayed Umbilical Cord Clamping with Death or Severe Intraventricular Hemorrhage Among Preterm Infants	PUBMED	Randomizedclinicaltrial	Level 1
A6	MAHANEY, Kelly B et al. 2020	Intraventricular Hemorrhage Clearance in Human Neonatal Cerebrospinal Fluid: Associations with Hydrocephalus	PUBMED	Quantitative Analytical and Prospective Study, case-control type	Level 2
A7	GOTARDO, Juliana Wendling, et al. 2019	Impact of peri-intraventricular haemorrhage and periventricular leukomalacia in the neurodevelopment of preterms	PUBMED	Meta-analysis	Level 1
A8	HUANG, Jinglan, et al. 2019	Antenatal infection and intraventricular hemorrhage in preterm infants	PUBMED	Meta-analysis	Level 1
A9	CARDOSO, Gaëlle Pinto, et	Association of Intraventricular Hemorrhage	PUBMED	Quantitative Analytical and Prospective Study,	Level 2

	al. 2018	and Death with Tocolytic Exposure in Preterm Infants		cohort type	
A10	Lu, Hongyan et al. 2016	Risk Factors for Intraventricular Hemorrhage in Preterm Infants Born at 34 Weeks of Gestation or Less Following Preterm Premature Rupture of Membranes.	PUBMED	Quantitative Analytical and Prospective Study, case-control type	Level 2

Source: Own authorship. Belém (PA), Brasil, 2022.

Class 1 - Factors Associated with Intracranial Hemorrhage in Newborns.

ICH is a disease of multifactorial etiology, associated with intrinsic fragility of the vasculature of the germinal matrix, changes in cerebral blood flow and hemostasis and coagulation disorders, which may be symptomatic or asymptomatic, depending on the area and extent of the lesion(Santos, GC, 2019).

Therefore, among the reasons that correlate with the genesis of ICH are maternal or obstetric, prenatal, perinatal conditions, those typical of preterm newborns and those associated with ventilatory support and systematizations and techniques commonly performed in Neonatal Intensive Care Units (Santos, GC, 2019). By analyzing A10 based on the logistic regression performed in the study, the lower gestational age, low birth weight, the greater the risk of developing ICH, in addition, asphyxia resuscitation and maternal chorioamnionitis were evaluated as independent risk factors for ICH.

According to the A3, Low Weight Preterm Newborns (PTNB) tend to have a higher positive predictive factor for the frequency of ICH as well as higher associated mortality, which may also be related to maternal characteristics such as age, which include pregnant women under 18 years of age or over 30 years of age, prenatal characteristics, such as length of gestation, which is related to a greater chance of developing ICH, given that preterm neonates with a GA of less than 28 weeks had higherintracranial hemorrhageproportions(Santos, GC, 2019).

In this way, maternal risk factors are understood above all with the circumstances that result in premature birth, such as low adherence to adequate prenatal care, previous hypertensive disorders (systemic arterial hypertension - SAH) and those that originate from pregnancy (Hypertensive Disorders of Pregnancy - HDP), in addition to preeclampsia and eclampsia (Santos, GC, 2019). Factors that include inflammatory markers and oxidative stress are also associated, such as those related to maternal infections during pregnancy, accounting for 40% of preterm births (López, CC&Vólquez, RSC, 2019).

In addition, recent research indicates that exposure to intrauterine infection/inflammation results in more serious injuries than just preterm birth, including neonatal sepsis, bronchopulmonary dysplasia, and patent ductus arteriosus, and a higher incidence of intraventricular hemorrhage has been found. This last factor is justified because the preterm newborn does not have a mature self-regulation function in relation to cerebral blood pressure, which can be induced to instabilities of this factor and consequently leading to an increased risk of HIV, which was recorded in about 24% of subjects evaluated in A10 after Premature Membrane Rupture, while the incidence of maternal chorioamnionitis was 43.8%(López, CC&Vólquez, RSC, 2019).

Low APGAR scores can be considered a good measure of the gestational and intrapartum events that result in ICH, as the effects of perinatal asphyxia, such as the presence of hypoxemia, acidosis and hypercapnia, often reduce platelet survival, its aggregatory purposemodifying the balance between bleeding and the coagulation cascade. These disorders impair the homeostasis of newborns affected by asphyxia and may be involved in the etiology of ICH.(Santos, GC, 2019).

In addition, in A1, it was highlighted that the characteristic of the mode of delivery does not significantly interfere with the occurrence of ICH. Differently from what other studies address, which report that it was determined in the analysis of the study that cesarean delivery has a protective factor related to intraventricular hemorrhage, since premature vaginal delivery presented frequent complications in the survey, excoriations and ecchymosis, clavicle fracture, brachial plexus injury , respiratory failure, difficulty in sucking, rupture of the large venous sinuses of the brain and a higher number of deaths. It is worth mentioning that there was a difference between the number of cesarean and

normal deliveries performed in the compared studies (Sanchez, YBV, 2020**).**

In view of these risk factors, A9 identifies tocolysis as a measure to alleviate negative outcomes for Preterm Newborns and women in preterm labor, as it is associated with a decrease in death or severe ICH in preterm infants, suggesting that tocolysis is safe and may even bring neonatal benefits, such as the use of nifedipine and atosiban in the development of the central nervous system. Tocolytics do not act directly on the uterus and cross the placental barrier. Thus, they have multiorganic effects and can bypass molecular pathways that result in a mature functional blood-brain barrier.

Such aspects are relevant for conducting comparative research, since another treatment with high-dose erythropoietin to extremely preterm infants up to 32 weeks, administered within 24 hours after birth, did not result in a lower risk of high neurodevelopmental impairment or of death at two years old (Juul, SE, et al, 2020).

In addition, we compared cord milking versus delayed cord clamping among preterm infants born at less than 32 weeks' gestation, noting that there was no statistically significant difference in the composite outcome rate of death or severe intracranial hemorrhage, but there was a statistically significantly higher rate of severe intraventricular hemorrhage in the cord milking group (Katheria, A, et al, 2019).

Class 2 - Comorbidities Associated with Intracranial Hemorrhage.

The greater the degree of hemorrhage, the more frequent complications such as hydrocephalus and encephalomalacia, which can cause severe cognitive and motor impairments(A6). According to Ezperanza, MA (2014), any degree of intracranial hemorrhage predisposes to neurocognitive developmental dysfunctions with later rates of cerebral palsy for grades I (8%), II (11%), III (19%) and IV (50%).

Neurological damage resulting from ICH can be varied, such as cerebral palsy, visual and hearing impairment, mental retardation, post-hemorrhagic hydrocephalus, and periventricular hemorrhagic infarction, the last two being very frequent complications. ICH is also described as the main cause of brain death. (A6).

In some newborns they present themselves as subtle changes in the level of consciousness, tone, movement, breathing; and eventually there is catastrophic deterioration happening like coma, decerebrate posturing, generalized tonic seizures and quadriparesis (Amaral, LF, 2016).

One of the important mediate complications of intracranial hemorrhage is post-hemorrhagic hydrocephalus. This can be a communicative or non-communicative manner that happens because of impaired CSF (Cerebrospinal Fluid) reabsorption or obstruction of the foramen of Monroe. Posthemorrhagic hydrocephalus should be suspected in any preterm infant with ICH who has a rapidly growing head circumference. There are several suggested treatment strategies for hydrocephalus with elevated intracranial pressure, including subgaleal shunt placement, ventricular reservoir placement, or ventriculoperitoneal shunt placement(Esperanza, MA, 2014).

The prognosis of neonates with ICH varies by initial identification, but is generally good (Amaral, LF, 2016). Thus, diagnostic methods are important not only for improving the prognosis and future quality of life of newborns, but also essential for interventions in the progress of intracranial hemorrhage(A4).

Class 3 - Outcome of Intracranial Hemorrhage in Child Development.

Prematurity and the existence of intracranial hemorrhage in the neonatal period are causes of risk for development at different stages of development, particularly at school age, when cognitive adversities are more pronounced.(A2).

According to Santos DSS dos & Prado MSG (2017), situations may be responsible for changes in global development when genetic or acquired causes occur in limiting circumstances in structural and functional fields of the nervous system, as can occur with intracranial hemorrhages.

It is still not adequately understood whether children who were born preterm and manifested ICH in the neonatal period, when they reach school age, will or will not present changes in the cognitive assessment (A2). However, studies indicate specific cognitive alterations, such as memory, attention, visual-motor skills, difficulty with numerals and deficits in function(A7).

Considerable inequalities are found in the general cognitive ability (IQ), language, phonetics, sensitization, articulation and school development of children born extremely preterm and/or with intracranial hemorrhages, compared to their age-matched peers who were born without any pathology (Martino, MS, et al, 2019).

Martino, MS, et al, (2019), it is estimated that a considerable number of children who were born

prematurely with ICH manifest subtle developmental disorders, which are often not observed or are diagnosed late. It also pointed out that premature children with ICH are at risk for behavioral disorders with a prevalence of attention deficit, autism and hyperactivity.

In this way, verifying and monitoring the development of these children is important, since the various types of diseases, whose effects appear throughout the child's life, can be prevented early, through guidance to parents and assistance from specialized professionals(Santos DSS dos, Prado MSG, 2017).

As a result, parents or guardians need to receive guidance on essential developmental stimulation. Thus, actions such as playing, reading, and having a motor and tactile stimulus aimed at the period of early childhood, from zero to three years, contribute to improving neuro-cognitive functioning throughout life(A7).

IV. CONCLUSION

Considering the NB in all its peculiarities from pregnancy to the birth process, there are numerous changes that make them susceptible to complications such as intracranial hemorrhage, prematurity and low birth weight.

Among the factors related to the occurrence of intracranial hemorrhages, associated conditions such as maternal, obstetric, prenatal, perinatal and those of the preterm newborn, which result in weaknesses that favor the involvement of ICH.

In view of this, it is essential to understand the risk variables for the development of ICH (5th minute Apgar score below six, low birth weight, modes of delivery, maternal age greater than 30 years or less than 18, prenatal care). inappropriate Christmas, etc.). Thus, well-defined clinical approaches and effective prophylactic strategies still need to be established.

The recognition of factors associated with ICH reinforces the criteria for choosing and therapeutic approaches in the care of the neonate, as well as in the management, with the aim of preventing future comorbidities associated with adequate follow-up to alleviate possible injuries.

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