World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

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Intraventricular hemorrhage in premature neonates: A narrative review of perinatal risk factors, pathophysiology, diagnosis, prevention and management

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World Journal of Advanced Research and Reviews, 2023, 19(03), 964–977

Publication history: Received on 09 August 2023; revised on 17 September 2023; accepted on 19 September 2023

Article DOI: https://doi.org/10.30574/wjarr.2023.19.3.1884

Abstract

Intraventricular hemorrhage (IVH) is a common complication of premature neonates and according to several authors its prevalence varies between 15% - 44.7%. Numerous perinatal risk factors have been associated with the development of IVH. This hemorrhagic situation has been defined as a leading cause of neonatal morbidity and mortality despite the great improvement observed in the clinical management of premature neonates. Rates of neonatal morbidity and adverse neurologic sequelae due to IVH remain high, making clinical decisions regarding treatment and management of IVH, challenging for healthcare professionals working in Neonatal Intensive Care Units. Since IVH is a complex situation that requires the involvement of a multidisciplinary team, we aimed to provide a comprehensive review of the topic. Through up-to-date scientific data, this review summarizes the key aspects of IVH in relation to development, pathophysiology, diagnosis and management via pharmacological and non-pharmacological approaches.

Keywords: Intraventricular hemorrhage; Premature neonate; Diagnosis; Pathophysiology; Prevention; Management

1. Introduction

Intraventricular hemorrhage (IVH) is a relatively common complication of prematurity and one of the leading causes of neonatal morbidity and mortality [1]. It is defined as the presence of blood inside or around the ventricles due to the rupture of blood vessels. The severity of brain injury is determined by the location and extent of the bleeding and in premature neonates it can range from insignificant to life-threatening. Gestational age (GA) is the factor that most decisively influences the risk of IVH development and thus neonates with GA <32 weeks are more prone to it [2]. A premature neonate's vulnerability to brain hemorrhage is primarily because of the intrinsic fragility of the germinal matrix (GM) vasculature, the continuous disturbances in cerebral blood flow (e.g. airway suctioning), the fluctuations of blood pressure and finally, the platelet and coagulation disorders [3]. The 80% of IVH incidences occur within the

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first three days of life [4], usually after delivery. In most cases, the injury begins one day after delivery, progresses in the next two days, and peaks by the end of the first week [5, 6].

In recent years, several interventions and strategies with proven benefits have been recommended for reducing the risk of IVH development, including antenatal corticosteroid administration and neonatal brain-focused clinical practices [7, 8]. In particular, these practices when offered in the early neonatal period are closely linked to the protection of the neonatal central nervous system (CNS), as they aim to assist brain development, prevent or minimize neuronal cell death and lessen adverse neurodevelopmental outcomes in neonates at risk for IVH [3, 8]. Minimal handling, optimized ventilation strategies and novel molecules have been shown to provide effective neuroprotection and are therefore considered critical to confine the burden of IVH.

Although the clinical management of premature neonates has made remarkable progress, rates of neonatal morbidity and adverse neurologic sequelae remain high [9], highlighting the need for healthcare professionals working in neonatal intensive care units (NICUs) to be updated with the latest evidence-based knowledge to provide neonatal care with high-quality standards. This narrative review aims to synthesize and present a concise summary of the most critical and pertinent aspects of the current knowledge on the topic of IVH in premature neonates, derived from peer-reviewed published scientific literature indexed in Pubmed, Scopus and Google Scholar.

2. Prevalence of IVH in premature neonates

The prevalence of IVH remains high in premature neonates, despite significant advances in perinatal and neonatal intensive care. With such high rates reported over the last decade, clinical decisions regarding prevention, diagnosis and treatment of IVH remain a constant challenge for NICU staff, as IVH is closely associated with cerebral palsy and serious long-term neurodevelopmental impairment, including motor, cognitive, neurological, and sensory disability [10]. The following epidemiological data are extracted from the last ten years (2012-2022) and relate only to premature neonates (Table 1).

Table 1 Reported prevalence of IVH in premature neonates between 2012-2022

Authors	Prevalence
Robinson, 2012 [11]	15%-20% in neonates born <1,500 gr
Schmid et al., 2013 [12]	20%-25% in neonates born <30 weeks or weighing <1,500gr
Ballabh, 2014 [3]	12,000 premature neonates/year in the United States
Mukerji et al., 2015 [13]	25%-30% in preterm infants weighing <1,500gr 45% in preterm infants weighing <1,000gr
Szpecht et al., 2016 [4]	15%-20% in neonates born <32 weeks of GA
Lu et al., 2016 [14]	19.7% in all preterm infants
Coskun et al., 2017 [15]	10%-20% of all live-born premature neonates
Roberts et al., 2018 [16]	25% of extremely premature very low birth weight infants in the United States
Poryo et al., 2018 [17]	15%-25% in neonates born <32 weeks of GA
Novak et al., 2018 [10]	32% in neonates born <28 weeks of GA and <1,500 gr
Murosko et al., 2020 [18]	25%-30% of all preterm infants born annually
Özek et al., 2020 [19]	10%-20% in infants born <30 weeks of GA
Deger et al., 2021 [20]	20%-40% of all infants weighing <1,500 gr worldwide
Al-Mouqdad et al., 2021 [21]	12,000 in the United States annually 13%-27% of all live-born premature neonates in Saudi Arabia
Basiri et al., 2021 [22]	36% in neonates with GA 22-28 weeks
Egesa et al., 2021[23]	14.7%-44.7% among preterm infants globally
Garvey et al., 2022 [24]	25% in all infants born <32 weeks of GA

GA: gestational age

2.1. Perinatal risk factors for IVH development in premature neonates

Several perinatal risk factors have been associated with the development of IVH but the determinants are low birth weight and the GA (especially <34 weeks of gestation) of the neonate. Other perinatal risk factors described to have a relation to IVH development in premature neonates are outlined extensively in Table 2.

Table 2 Perinatal risk factors for IVH development in premature neonates

Original Research - Authors	Perinatal Risk Factors
Linder et al., 2003 [25]	High fraction of inspired oxygen in the first 24 hours of a neonate's life Pneumothorax Early sepsis Failure usage of antenatal steroid treatment (for every dose of antenatal steroid treatment there is a lower risk of high-grade of IVH) Low first hematocrit level (43.96 ± 7.94) during the first 24 hours of neonate's life Higher FiO_2 (%) during the first day of life (80.83 ± 23.38) High $PaCo_2$ (lowest 33.6 ± 5.8) - each decrease in a mmHg unit of $PaCo_2$ during the first day of life was correlated to a lower risk of IVH (OR: 0.91; 95% CI: 0.83-0.98)
Jain et al., 2009 [26]	Low GA Mode of delivery (higher rates of IVH in cesareans with no trial of labor compared to cesareans after trial of labor and higher rates in vaginal unassisted delivery than in instrumental vaginal delivery)
Lee et al., 2010 [27]	Metabolic acidosis Use of inotropes
Lu et al., 2016 [28]	Low GA (29.3 ± 2.8 weeks) Low birth weight (986 ± 122 gr) Fetal distress and asphyxia resuscitation Low apgar score at 5 minutes Chorioamnionitis Prolonged rupture of the membranes Asphyxia Resuscitation in preterm infants following premature rupture of the membranes
Helwich et al., 2017 [29]	Lack of antenatal corticosteroids admission Invasive mechanical ventilation Vaginal birth
Roberts et al., 2018 [16]	Low birth weight (<1,000gr) Low GA (<30 weeks) Seizures Sepsis Surgery Pneumothorax Thrombocytopenia Cardiopulmonary resuscitation at labor Intubation at labor Disseminated intravascular coagulation
Vesoulis et al., 2019 [30]	Unstable mean arterial blood pressure (extended period outside of the optimal range)

Khanafer-Larocque et al., 2019 [31]	Lack of antenatal corticosteroids admission Low GA and birth weight Maternal chorioamnionitis Apgar score <5 at 5 minutes Umbilical cord pH <7 Patent ductus arteriosus Respiratory distress syndrome Early onset sepsis Prolonged intubation Inhaled nitric oxide, use of opioids, bicarbonate, inotropes or normal saline boluses Metabolic derangements Hypercarbia Hyperglycemia Hypothermia
Wu et al., 2020 [32]	Maternal lower genital tract infection Invasive respiratory support, pulmonary surfactant, dopamine and antibiotic administration
Al-Mouqdad et al., 2021 [21]	Neonatal pulmonary hemorrhage Neonatal hydrocortisone administration Patent ductus arteriosus Low hematocrit in the first three days of life Lack of antenatal steroid admission Use of inotrope
Basiri et al., 2021 [22]	Low GA (mean 29.5 weeks) Low 5 minute apgar score (mean 7.23) Low birth weight (mean 1,423.42 gr) Pneumothorax
Iwahata et al., 2022 [33]	Clinical chorioamnionitis Absence of prenatal $MgSO_4$ administration
Zhao et al., 2022 [34]	Birth weight (≤1,000gr) GA (≤32 weeks) Vaginal delivery 5-minute apgar score ≤7 Early onset neonatal sepsis Lack of antenatal glucocorticoid use

FiO_2: fraction of inspired oxygen; GA: gestational age; HIV: human immunodeficiency virus; $MgSO_4$: magnesium sulfate; $PaCo_2$: partial pressure of carbon dioxide in arterial blood; pH: potential of hydrogen

2.2. Pathophysiology of IVH

Intraventricular hemorrhage is a cerebrovascular lesion that typically begins in the periventricular GM. The GM is a transitional gelatinous area in the developing fetal brain that gives rise to the neuronal cells that will later form the grey matter of the brain. It is located at the level of the foramen of Monro and underneath the lateral ventricles. It is a major source of neuronal and glial precursor cells. During human embryogenesis, it is the area where neurons proliferate and migrate to other areas of the brain [35]. Around mid-pregnancy, the generation of neurons stops but that of glial cells continues. The bulk of migration is usually completed by 22 weeks of gestation. At 24 weeks of GA, the GM begins to appear thinner and as pregnancy progresses, it almost disappears. The GM promotes neural proliferation and differentiation until the 32nd week of gestation. After this point, it is unusual to observe GM because these cells migrate

out to the cerebral cortex and by 40 weeks of gestation its existence as an individual fetal structure ceases and the immature vascular network remodels to constitute adult vascular patterns [35-37].

The site of origin of IVH is believed to be in the fragile capillary network of the subependymal GM of the brain. When the hemorrhage is substantial, the ependymal lining, a protective barrier between the brain and cerebrospinal fluid, may be disrupted. Blood may then progress into the adjacent lateral ventricle [36].

The pathogenesis of IVH in premature neonates is complex and multifactorial, and is a combination of endovascular and extravascular factors that contribute to blood vessel rupture. It is mainly attributed to the increased vascular fragility of the GM, the fluctuations in cerebral blood flow and the immature cerebral autoregulation in premature neonates [23]. In contrast to mature vessels, these of the GM are thin-walled and have deficiency in a) pericytes, b) fibronectin in the basal lamina and c) glial fibrillary acidic protein in astrocyte endfeet. These components create vulnerability in the blood - brain barrier and thus, increase susceptibility to hemorrhage [38]. Furthermore, cerebral blood flow in premature neonates is closely related to fluctuations in systemic blood pressure, contrary to full-term neonates and adults in whom cerebral blood flow is maintained constant regardless of blood pressure. In case of hypotension there is a greater risk of ischemia in the final perfusion areas of the brain while in hypertension there is a greater risk of hemorrhagic lesions caused by the rupture of the cerebral vessels. Factors closely linked to fluctuations in cerebral blood flow are numerous and involve the pre-, peri-, and postnatal period. The most important risk factors are: clinical practices in neonatal intensive care units (e.g. suctioning, positioning and handling), respiratory distress syndrome and hypercarbia, pneumothorax, patient - ventilator asynchrony, patent ductus arteriosus, sepsis, inotrope administration, fluid boluses and rapid infusion of sodium bicarbonate. Finally, impaired cerebral autoregulation is associated with prematurity less than 32 weeks of GA, birth weight less than 1,500 grams and is usually observed in ventilated, critically-ill and hemodynamically unstable premature neonates [3, 23, 39].

2.3. Diagnosis of IVH

The diagnosis of IVH can be based on physical examination and clinical signs but the use of a neuroimaging tool is vital for precise assessment. The most preferred and practical neuroimaging technique used in NICUs for diagnosis and classification of brain injury is cranial ultrasound (CUS) while conventional magnetic resonance imaging (MRI) may be performed at term corrected age in neonates who reveal moderate to severe abnormalities during ultrasonography [40-42]. Currently, computerized tomography (CT) is not considered as part of routine imaging techniques for the premature brain [43].

2.3.1. Clinical signs of IVH

IVH manifests in three ways - clinically silent, salutatory and catastrophic. Most cases are asymptomatic and are usually detected through routine screening. However, several clinical symptoms can occur including change in the level of consciousness, hypotonia, decerebrate or decorticate posturing, lethargia, seizures, bulging fontanel, recurrent apnea, unexplained pallor, respiratory distress, acidosis, hypoglycemia, hyperglycemia, rapid decrease in blood pressure and temperature instability [19, 23].

2.3.2. Laboratory signs

IVH is a hemorrhagic disease and a sudden and significant reduction in the hematocrit may occur in the event of severe hemorrhage. Failure of hematocrit to rise with transfusion or unexplained persistent hyperbilirubinemia should cause concern and be considered suspicious signs of IVH [19, 23].

2.3.3. Cranial Ultrasound

Cranial ultrasound is the most widely used method of brain imaging in NICUs as it has multiple capabilities and advantages and few disadvantages, such as the fact that it is highly operator-dependent. Advances in ultrasound technology have led to the ability to focus at different depths in the neonatal brain, resulting in more detailed imaging of its anatomical structures.

The locations where the transducer can be placed are the anterior or posterior fontanelle and the mastoid process. The CUS is a non-invasive technique that monitors the cerebral circulation and provides direct information about the arteries and cerebral blood flow (CBF) [44]. CBF fluctuations have been highly correlated with the resistive index, pulsatility index, and end-diastolic blood flow velocity. In preterm infants prone to develop IVH, CBF changes are observed. For instance, high levels of pulsatility due to infarction of the blood vessels in the GM and low resistive index accompanied by bleeding can be observed [45]. CUS has a limited capacity due to single local measurements of velocities

and resistive index in large arteries. In recent years, ultrafast plane-wave Doppler imaging has overcome this limitation and thus, can be considered as an alternative neuroimaging method [46].

A sonographic grading system was first proposed by Papile in 1978 and included four criteria. Volpe later adapted this classification [47].

Currently, the American Academy of Paediatrics (AAP) suggests that CUS as a screening tool for IVH should be performed on all premature neonates delivered before the 30th week of GA. Specifically, the first CUS is recommended to take place between the 7th and 10th day of life to detect IVH, while the European Foundation for Care of Newborn Infants (EFCNI) suggests a more intensive screening for premature neonates (Table 3).

Table 3 AAP and EFCNI recommendations regarding neuroimaging of the premature infant

	Gestational age	**Infant age**	**Recommendation**
American Academy of Pediatrics [48]	≤30 or >30 weeks at high risk for brain injury OR clinical signs and symptoms suggestive of brain injury	<7 days of age	Initial CUS
	≤30 weeks	7 to 10 days of age 4 to 6 weeks of age & before hospital discharge	Routine CUS Repeat CUS
	high-risk infant <37 weeks	at term equivalent age	MRI optional, based on physician-family discussion and ideally non sedated
European Foundation for Care of Newborn Infants [49]	<28 weeks	1-3-7-14-21-28 days of age and then every 2 weeks until 34 weeks gestational age and at term equivalent age	Routine CUS
	>28 weeks	1-3-7-14-21-28 day, at 6 weeks and at term equivalent age	Routine CUS
	>28 weeks OR <28 weeks	In case of abnormalities or after episode of clinical deterioration	Intensify CUS
	<28 weeks	Around term equivalent age	Routine MRI
	<37 weeks	Neurological symptoms of unknown origin	As soon as possible MRI

CUS: cranial ultrasound; MRI: magnetic resonance imagining

2.3.4. MRI

Nowadays, advanced MRI has become increasingly preferable due to its detailed imaging. Advanced MRI neuroimaging tools include MR spectroscopy, functional MRI and susceptibility-weighted imaging (SWI) for evaluation of premature infants. However, further clinical surveys are needed to confirm their detective and predictive role regarding IVH [50].

The correct evaluation of the images emerging from the neonate's brain requires specialized knowledge, such as the etiology and pathophysiology of brain injury, brain anatomy, embryology, the advantages and disadvantages of different imaging techniques and optimal imaging time. In addition, transporting and sedating critically ill neonates is often a major challenge for NICU staff. During the examination the neonate is wrapped tightly so as to be immobilized and maintain a constant body temperature. The recording of vital signs and the presence of personnel highly skilled and

experienced in neonatal cardiorespiratory resuscitation is essential. In addition, ear protection is considered necessary for the neonate as exposure to gradient noise may lead to negative effects on the neonate [51, 52].

2.3.5. Biomarkers

In recent years, the scientific community has shown significant interest in involving biomarkers for the early diagnosis of IVH and other types of brain injury. To date, numerous biomarkers in different biological fluids have been investigated in neonates with promising results (Table 4). For instance, Activin A, S100B, IL-6 and many others have been associated with a variety of roles in the neuronal injury response [53-55]. However, further investigation needs to prove the predictive value of different biomarkers regarding neonatal brain injury [56].

Table 4 Biomarkers studied in premature infants related to IVH

Authors	**Biomarker(s)**	**GA (weeks)**	**Biological fluid(s)**	**Results**
Florio et al., 2006 [57]	Activin A	≤32	Plasma (cord blood)	↑ Levels were significantly higher in preterm infants who developed IVH compared to those who did not develop IVH.
Rao et al., 2009 [58]	BDNF	<34	Serum (peripheral and cord blood)	↓ Cord blood concentrations did not correlate with IVH although they were lower in infants who developed IVH compared to those who did not develop IVH.
Bhandari et al., 2010 [59]	EPO IL-6	23-34	Serum (cord blood)	↑ EPO ↑ IL-6 Elevated EPO may predict newborns at risk for IVH.
Abdel-Wahed et al., 2012 [60]	Activin A	<34	Serum	↑ Infants with IVH had higher serum levels compared to infants without IVH.
Sannia et al., 2013 [61]	Activin A	27-30	Urine (five predetermined time-points: 0-6, 6-12, 12-24, 24-48 and 48-72 hours after birth)	↑ Infants who developed IVH had significantly higher levels than controls at all monitoring time-points.
Efstathiou et al., 2015 [62]	S100B EPO NSE SDF-1	<34	Serum or plasma (peripheral)	↑ S100B ↑ EPO ↑ NSE ↑ SDF-1 Levels of S100B were significantly higher in the case group (IVH or PVL) compared to controls on the 1st day of life. NSE levels were significantly higher in the case group compared to controls on the 18th day of life. Both EPO and SDF-1 were higher in the case group compared to controls early after birth. EPO was higher on days 1 and 3 of life, whereas SDF-1 was higher on the 3rd day of life.

Zhou et al., 2015 [63]	S100B MBP	<34	Plasma (Peripheral blood)	↑ S100B ↔ MBP Within 1st day and on the 3rd day after birth, the serum levels of S100B in PVH-IVH group were significantly higher than those in no brain damage group. The plasma levels of MBP within 1st day and on the 3rd, 7th and 14th day after birth, did not differ significantly between PVH-IVH group and no brain damage group.
Khosravi et al., 2016 [64]	IL-6 EPO	27-37	Plasma (cord blood)	↑ IL-6 ↑ EPO Higher levels of both biomarkers in infants with IVH compared to controls.
Elfaragy et al., 2017 [65]	Activin A EPO	28-37	Serum and Plasma (cord blood and venous samples)	↑ Activin A ↑ EPO Infants with IVH had significantly higher plasma Activin A concentration than infants without IVH. Infants with IVH had significantly higher cord blood EPO levels than infants without IVH.
Shahid et al., 2017 [66]	Activin A	<34	Serum (cord or peripheral blood) Amniotic Fluid	↑ Serum levels of amniotic fluid, cord blood and 3rd day peripheral blood were significantly higher in infants with IVH or PVL than the control group.
Metallinou et al., 2020 [54]	S100B	<34	Serum (peripheral or umbilical)	↑ Cases with IVH had higher concentration when compared to neonates with PVL.
Gasparroni et al., 2021 [67]	S100B	Preterm infants	Urine (four time-points: first void, 24, 48 and 96 hours after birth)	↑ Elevated S100B levels were detected in infants with IVH at all monitoring time-point particularly at first void.
Metallinou et al., 2021 [55]	Activin A	<34	Serum (peripheral or umbilical)	↑ Significantly higher levels in infants with IVH or PVL during the first two days of life compared to infants without brain injury.
Metallinou et al., 2022 [2]	GFAP	<34	Serum (peripheral or umbilical)	↔ No significant differences were observed in levels between infants with IVH or PVL and infants without brain injury.

BDNF: brain-derived neurotrophic factor; EPO: erythropoietin; GFAP: glial fibrillary acidic protein; MBP: myelin basic protein; NSE: neuron-specific enolase; PVH: periventricular - intraventricular hemorrhage; PVL: periventricular leukomalacia; SDF-1: stromal cell-derived factor-1; ↔: biomarker concentrations did not differ significantly; ↑: significantly higher concentrations of biomarker; ↓: significantly lower concentrations of biomarker.

2.4. IVH prevention and management

Prevention and management of neonatal IVH involve various strategies aimed at reducing the risk factors, detecting and monitoring the condition and providing appropriate medical and non - medical interventions. Some key approaches [3, 68-72] involve:

2.4.1. Antenatal care

Adequate antenatal care is important to minimize the risk of IVH. This includes regular prenatal check-ups, screenings, obstruction of premature labor and interventions to manage conditions that might contribute to IVH, such as preeclampsia or maternal infections. In suspicion of possible premature birth, maternal transportation to a specialized hospital is vital, as the fetus will be transferred "in utero" conditions and in case of perinatal asphyxia, both of them will receive optimal perinatal care. Furthermore, previous studies have shown that neonates whose mothers received antenatal steroids were less likely to develop IVH and had significantly lower mortality rates [54], suggesting that steroids may play a crucial role in IVH prevention.

2.4.2. Birth practices

Careful management of labor and delivery can help reduce the risk of IVH. Avoiding unnecessary trauma during delivery, ensuring adequate oxygen supply and delay cord clamping, preventing prolonged labor and minimizing the use of forceps or vacuum extraction can be preventive measures. All healthcare professionals being involved in intrapartum care should be acquainted with the latest neonatal cardiopulmonary resuscitation guidelines.

2.4.3. Monitoring neonatal vital signs

Systematic monitoring of vital signs, especially blood pressure, heart rate and oxygen saturation levels, can help in detecting any signs of distress or instability and that may indicate a potential risk or presence of IVH.

2.4.4. Control of blood pressure and oxygen levels

Proper control of blood pressure and oxygen levels is crucial in managing IVH. Maintaining stable blood pressure within the normal range and avoiding extreme fluctuations reduces the risk of bleeding and further damage to the brain. IVH is primarily attributed to increased vascular fragility and disturbance in CBF thus the prevention strategies should focus on CBF stabilization. Fluctuations in the CBF have been associated with daily clinical practices such as suctioning, handling and placing intravenous lines. Furthermore, respiratory distress syndrome, patent ductus arteriosus, apneic episodes, seizures, hypoxemia, hypercarbia and abrupt administration of colloids or other solutions are situations in premature neonates that have been correlated with the occurrence of IVH.

2.4.5. Treatment of coagulopathies

Neonates with clotting disorders or coagulopathies may have an increased risk of IVH. Coagulation normalization can be set via fresh frozen plasma, vitamin K and coagulation factors infusion. Identifying and treating such conditions promptly can help reduce the risk of bleeding in the brain.

2.4.6. Supportive care

Creating an optimal, calm and stress-free environment for the neonate can support its overall well-being and recovery from IVH. Today, a neonatal care bundle for IVH prevention has been established and aims to reduce the rates of this specific brain injury occurrence. This bundle includes eight basic principles: 1) nursing care, 2) care procedures, 3) stimulation/pain management, 4) infant positioning, 5) light and sound environment, 6) medical procedures, 7) cranial ultrasound and 8) review of practice.

More specifically, NICU staff has to avoid prone positioning during the first week of a neonate's life. It is recommended that neonates should be placed at supine midline position during the first three days of life. Also, neutral head positioning is suggested and the incubator's mattress slope has to tilt at 10 to 30 degrees upper to provide an optimum body elevate positioning during the first week of life. A head rotation has to be avoided. Regarding "nursing care" and "care procedures", these should be combined and adapted to the neonate's sleep-wake cycles. The care provision has to be individualized for each neonate and is suggested to be performed in six care rounds in each day between three to five hours. Neonatal care has to be performed by experienced nurses/midwives, especially during the first week of life. Simple daily procedures such as the change of neonate's linen and body weight measurement have to be performed by two midwives/nurses. Extensive cleaning of the incubator and bathing has to be avoided during the first seven days of life. On mechanically ventilated infants a closed suction system is required.

As for stimulation and pain management, the use of individual tactile stimulation during neonatal care can be useful. Generally, stress and pain have to be avoided and in case of painful or stressful procedures the NICU staff has to apply pain scale reports.

The NICU environment has to be free of constant light and sound exposure such as alarm tones and noisy conversations close to the incubator. To avoid extensive noise, alarm tones can be set as quietly as possible and light can be isolated from infant's field of vision by covering the incubator.

Regarding medical procedures, endotracheal intubation has to be performed by an experienced neonatologist during the first week of life. To avoid blood pressure fluctuation, drawing of blood samples from arterial lines with subsequent flushing should be performed slowly (1.5mL/30 sec). Routine cranial ultrasound is often performed in premature neonates for the early detection of signs suggesting IVH. This technique contributes also to the classification and monitoring the severity of IVH, described extensively in this article before. All serious IVH cases (≥ grade 3) should be discussed within the case conference.

Other measures that have been mentioned as IVH prevention bundle is the frequent multidisciplinary assessments and education, the stabilization and transition of the neonate (e.g. use of a preheated gel mattress, prepare an incubator at delivery room or use of a plastic bag at birth), the optimal respiratory management, the hemodynamic management and the set-up of a process for discussing inconsistent reporting.

Finally, certain neuroprotective strategies may be considered in specific cases to minimize brain injury and optimize outcomes for neonates with severe IVH. However, the use of pharmacological and non-pharmacological brain-focused clinical practices for premature neonates, extensively described previously [8], should be individualized and carefully evaluated on a case-by-case basis.

3. Conclusions

Intraventricular hemorrhage in premature neonates is a complex condition. Although major efforts have been made to manage this intricacy of brain injury the last decades, its incidence remains high. The future of neonatal IVH will involve a multidisciplinary approach, combining advances in medical technology, genetics, and personalized medicine, along with a focus on early detection and intervention. Ultimately, the goal is to reduce the occurrence of IVH and improve the long-term outcomes for affected neonates. However, it's important to note that research in this field is ongoing, and it may take years before many of these advancements become standard in daily clinical practice.

Compliance with ethical standards

Disclosure of conflict of interest

All authors declare that they have no conflicts of interest.

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