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# Intraventricular haemorrhage in premature infants. Review of diagnostic methods, treatment and influence on neurodevelopment

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## Abstract

Introduction: Preterm infants are at high risk for various neurological complications and mortality caused by hypoxemia, haemorrhage or inflammation concerning preterm delivery. Resulting brain lesions are mostly asymptomatic - they cannot be diagnosed clinically as such neuroimaging of preterm infants has become part of routine clinical care.
In this article, newest studies about intraventricular haemorrhage, its complications and treatment methods were reviewed. The PubMed database was searched using keywords "intraventricular haemorrhage", "preterm infant", "intraventricular haemorrhage treatment", "intraventricular haemorrhage outcome".
State of knowledge: Early diagnosis, appropriate nursing care and treatment can minimise morbidity. Prognosis is mainly determined by the severity of bleeding, occurred complications and neurological irreversible changes. Intraventricular haemorrhage can cause posthemorrhagic hydrocephalus, cerebral palsy, disability and mental retardation in further life. Even mild grades of haemorrhage can result in developmental disorders. Long-term issues such as neurodevelopmental disorders and cerebral palsy are as important as short-term problems. Detection of injuries affecting preterm infants is used to identify complications that might necessitate an intervention.

While head ultrasound is the standard of care for routine neuroimaging screening, the use of brain magnetic resonance imaging has expanded recently.
Conclusions: Considerable advances in neonatal care have resulted in improved survival and prognosis of development of preterm infants with intraventricular haemorrhage. Although there is a wide range of treatment methods, further studies are needed to assess their safety, effectiveness and impact on short- and long-term outcome.

**Keywords:** intraventricular haemorrhage; preterm infant; intraventriculat haemorrhage treatment; preterm delivery; ultrasonography; magnetic resonance imaging

**Complications result from preterm delivery**

Intraventricular haemorrhage is the significant, severe and most frequent complication of preterm birth. According to studies, it affects 20-40% of preterm infants. The incidence has decreased significantly over the last decade due to the global improvements in neonatal care. Despite improving survival, mortality remains high and oscillates between 30-60%. Survivors are at high risk for cerebral palsy, hydrocephalus, seizures, and intellectual disability [1]. The main origin of haemorrhage in the premature infant is the germinal matrix - a structure where neuroblast and glioblast mitotic activity occurs before neural cells migrate to other parts of the brain. Germinal matrix haemorrhage and intraventricular haemorrhage cause disruption of the ventricular lining, the release of blood and neural cells populating the germinal matrix into the cerebrospinal fluid what finally may lead to inflammation and necrosis [2].

Intraventricular bleeding may cause variable short- and long-term complications, such as hydrocephalus, periventricular leukomalacia, epilepsy, cerebral palsy, developmental disorders, visual or hearing impairment and death. Thirty to 50 percent of the infants with severe bleeding develop posthemorrhagic ventricular dilation, typically seen 7 to 14 days later [1, 2].

Although prematurity is the predominant risk factor for intraventricular haemorrhage, additional risk factors include low birth weight (particularly less than 1000g), variation in systemic blood pressure, anaemia, hypo- or hypercarbia, acidosis, patent ductus arteriosus, respiratory distress syndrome and pneumothorax. However, the risk decreases considerably after 32 weeks of gestational age [3].

Cerebellar injury is recognised as a relatively frequent form of brain injury, associated with a broad spectrum of motor developmental disabilities. Cerebellar injury is reported in 10% to 20% of preterm infants less than 32 to 34 weeks of gestational age. Anterior and mastoid fontanel are used as an acoustic window in ultrasound imaging of cerebellum and other structures of posterior cranial fossa. Compared to ultrasound, MRI has the advantage of providing more detailed, quantitative, and functional imaging of cerebellum. Common use of MRI in preterm infants has led to an increased detection of small lesions that usually remain undetected by head ultrasound [4].

Periventricular leucomalatia defines injury of white cerebral matter. It frequently coexists with intraventricular haemorrhage and leads to neuromotofic dysfunction in further life. The extent of changes and the severity of bleeding affect the prognosis. The risk factors include low birth weight (under 1000g), male gender, prolonged mechanical ventilation of infant and the most significant complication is cerebral palsy [5].

Antenatal infection has been reported to be an important risk factor for preterm delivery, responsible for 40% of premature deliveries.

There are clinical studies that have reported the existence of a relationship between antenatal infection and intraventricular haemorrhage. Meta-analysis included 23 cohort studies with 13605 infants demonstrating that antenatal infection increases the incidence of intraventricular haemorrhage in preterm infants. Authors analysed different types of antenatal infection - twenty-one studies reported data on chorioamnionitis and two of them on ureaplasma. Not only clinical and histological chorioamnionitis but also ureaplasma antenatal infections increases risk of intraventricular haemorrhage. Additionally, antenatal infection increases the risk of both mild and severe forms of bleeding in premature infants [6].

**Available methods of imaging and its advantages**

Although advanced imaging methods like MRI are getting more available, head ultrasound is still the method of choice. Ultrasound examination is recommended for all infants born before 32 weeks to exclude intracranial haemorrhage. Cranial ultrasound has several advantages - non-invasive examination, safety, elimination of radiation, repeatability, availability, low cost and no need for special preparation. Obtaining view through fontanels gives good visualisation of most important intracranial structures - the ventricular system, white matter and cerebellum. Ultrasound is ideal for quickly detecting intraventricular haemorrhage, large cerebellar bleeds, cysts and echogenic areas in white matter. The disadvantage is operator-dependent - subtle lesions may be missed in less experienced hands [7, 8].

Formerly CT has been used to assess structural abnormalities, but this is now largely displaced by MRI due to the ionising radiation required for imaging. Except for emergencies, CT scans are now generally avoided for newborn imaging [7].

Since the first published report of brain MRI in the early 1980s, its use has expanded to newborns. MRI enables noninvasive exploration of acute injury and postinjury alterations in structural and functional connectivity, offers the highest resolution for detecting and quantifying lesions in white matter, early intraventricular haemorrhage, cerebral malformation, abnormalities of posterior cranial fossa and even can help with diagnosing inborn errors of metabolism. Those pathologies are not always easy to interpret and may be a main cause of concern for parents. White matter injury is the most common finding seen on MRI in preterm infants. Nonetheless, this is an expensive, time- and resource-consuming technique that is not always available, often requires transport, and may require sedation [7, 8]. Abnormal findings on MRI at term equivalent in very preterm infants strongly predict adverse neurodevelopmental outcomes. These findings suggest a role for MRI at term equivalent in risk stratification for infants [9, 10].

Overall, head ultrasound remains reliable for detecting intraventricular haemorrhage and severe cystic lesions in white matter. When it comes to cerebellar haemorrhages and punctate, non-cystic white matter injuries, MRI overcomes ultrasound in detecting such subtle lesions. It either enhances the ability to predict neurodevelopmental outcomes.

**Classification of findings and its correlation with prognosis**

The most commonly used Papile grading was originally based on computer tomography and it defines four stages of haemorrhage (Table 1) [11].

Table 1: Papile's classification of intraventricular haemorrhage

| | |
|---|---|
| Grade I | Haemorrhage to the germinal matrix (the main origin of haemorrhage in the premature infant) |
| Grade II | Intraventricular bleeding without ventricular dilation |
| Grade III | Intraventricular bleeding coexisting with ventricular dilation |
| Grade IV | Periventricular hemorrhagic infarction - intraventricular haemorrhage with bleeding into the parenchyma. |

According to Bolisetty, although lower grade of haemorrhage gives better prognosis, in extremely preterm infants grade I-II, even with no documented white matter injury or other late ultrasound abnormalities, is associated with adverse neurodevelopmental outcomes. The same outcome concerns grade III–IV of haemorrhage and other lesions noted on ultrasound including periventricular leukomalacia, porencephaly and ventriculomegaly [12].

On the other hand, Yong Wang's study indicated that preterm infants of <30 weeks' gestational age with I-II grade of haemorrhage had similar neurological outcomes and mortality compared to those without intraventricular haemorrhage, while III-IV grade was associated with cerebral palsy, disability and death at 18–24 months of corrected age [13].

There is no consensus on the long-term outcome of children experiencing intraventricular haemorrhage. Some papers report that less than 50% of adolescents born before 32 weeks gestation have a normal school performance. While intraventricular haemorrhage, even the lower grades, was related to disability at the age of 5 years, van de Bor's study demonstrated that it also has an unfavourable additional effect on school performance [14]. However, low-grade IVH was not demonstrated in another study to be a risk factor associated with lower long-term outcomes in intelligence, academic achievement or problem behaviour at age 3, 8 and 18 years [15].

**Treatment and prevention of intraventricular haemorrhage**

Intraventricular haemorrhage treatment is focused on preventing, reducing bleeding and improvement of short- and long-term neurodevelopment outcome. Vitamin K is not indicated specifically for prevention but is routinely administered to newborns to minimise bleeding caused by lack of coagulation factors [1].

Antenatal steroids are commonly administered to women in preterm labour. Steroids reduce risk of IVH, respiratory distress, infection, and mortality in infants. Furthermore, the same clinical trial noted that caesarean section delivery has an important role in lowering the risk of early-onset intraventricular haemorrhage [16].

Nowadays angiogenic inhibitors have demonstrated potential in treatment by stabilising the germinal matrix vasculature and preventing intraventricular haemorrhage. Both celecoxib and the vascular endothelial growth factor (VEGF) inhibitor ZD6474 reduce the incidence and severity of germinal matrix haemorrhage in human preterm infants [17].

Surgical methods are mostly focused on reducing the amount of cerebrospinal fluid to control intracranial pressure and prevent hydrocephalus. The very first method was lumbar puncture and cerebrospinal fluid drainage, replaced with a ventricular access device obtaining repeated aspiration [2]. Nowadays DRIFT, which means drainage, irrigation, and fibrinolytic therapy, gives a promising outcome with reported reduction of mortality and objectively demonstrates sustained cognitive improvement. Its effectiveness was verified in a randomised control trial of 77 children. Evaluated outcome involved cognitive assessment undertaken by psychologists, cerebral visual function, sensorimotor disability and behavioural function. DRIFT had a significant effect on cognition but did not appear to improve motor function [18].

Alternative surgical intervention include ventricular endoscopic lavage. A study of 19 newborns demonstrated Endoscopic lavage was associated with fewer numbers of overall necessary procedures, infections and supratentorial multiloculated hydrocephalus in comparison with standard treatment. However, there is a lack of long-term data on outcomes from these children [19].

Despite a wide range of surgical treatment methods, there is no consensus on the optimal timing of intervention. Complications resulting from intraventricular haemorrhage lead to irreversible neurological changes. Posthemorrhagic ventricular dilatation occurs in 30% to 50% of infants with high grade of haemorrhage (III/IV). Leijser et al. performed a multicenter, observational cohort study of 127 preterm infants. It proves that intervention at an early stage, based on ventricular ultrasound measurements, is associated with favourable neurodevelopmental outcomes. In contrast, later intervention based on intracranial pressure, increases the risk of unfavourable outcome and surgery-related complications. Cranial ultrasound remains reliable for following the progression of ventricular dilatation and the result of this study supports early intervention based on ventricular dimensions [20].

The latest innovations focus efforts on treating secondary brain injury. They include administration of GSK3b (intracellular kinase) inhibitors and transplantation of mesenchymal stem cells. Both are suspected to be connected with risk of oncogenesis. While these therapies seem promising, they require further study before wide admission into clinical care [1].

Therapeutic neuroprotective strategies for severe brain injury of preterm infants are not yet accessible for clinical use. Experimental data support high efficiency for nasal application of growth factors and stem cells for rescuing neonatal brain injury. Breast milk contains plenty of both. A retrospective summary of 31 very low birth weight preterm infants with intraventricular haemorrhage proved that nasal drops of fresh breast milk lowers incidence for severe porencephalic defects. Authors emphasise the need for further investigations [21].

A study in two Dutch tertiary neonatal intensive care units was performed to investigate the effect of a nursing intervention bundle, applied during the first 72 hours of life, on the incidence of germinal matrix-intraventricular haemorrhage in very preterm infants. The bundle consisted of maintaining the head in the midline, tilting the head of the incubator and avoiding rapid withdrawal of blood and sudden elevation of the legs. Control group obtained routine care. The group of patients with the nursing intervention bundle was associated with reduced risk of developing a germinal matrix-intraventricular haemorrhage, cystic periventricular leukomalacia and mortality compared to infants of the control group. The beneficial effect was more pronounced in extremely preterm infants [22].

**Summary**

Intraventricular haemorrhage and its consequences remains a significant clinical issue. Preterm infants require extraordinary, qualified medical and nursing care to avoid neurodevelopmental impairment and give a chance for normal further life without disability. Head ultrasound is reliable for fast detecting intraventricular haemorrhage and severe cystic lesions. MRI overcomes ultrasound in detecting subtle lesions and enhances the ability to predict neurodevelopmental outcomes. An easy access to both imaging methods should become a standard of units managing treatment and care over preterm infants. Although there is wide range of treatment methods, further studies are needed to assess their safety, effectiveness and impact on short- and long-term outcome.

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