

## Pathophysiology and Management of Intraventricular Hemorrhage in Preterm Infants

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### Abstract

As more and more premature infants are surviving because of the better neonatal care and advanced technology, intraventricular hemorrhage remains an important cause of brain injury in extremely premature infants. Preventive measures to reduce the incidence have limitations because of unmodified risk factors like gestational age and anatomic immaturity. Various treatment modalities are attempted to limit the progression of ventricular dilation and hydrocephalus with limited success. Limitations of the ultrasound in detecting white matter and cerebellar lesions is a major concern for counseling the parents regarding the long-term outcome. Recent findings of adverse neurodevelopmental outcome even with minor grades of hemorrhages is a stimulus for future research for managing these cases. This article is the review of the etiopathogenesis, diagnosis, management and outcome of intraventricular hemorrhage in premature infants.

**Keywords:** *Intraventricular Hemorrhage; Preterm Infants; Hydrocephalus; Brain Injury*

### Abbreviations:

IVH: Intraventricular Hemorrhage; GFAP: Glial Fibrillary Acidic Protein; PVD: Post Hemorrhagic Ventricular Dilatation; LP: Lumbar Puncture; CSF: Cerebrospinal Fluid; VR: Ventricular Reservoir; EVD: External Ventricular Drainage; VSG: Ventriculosubgaleal Shunt; VP: Ventriculoperitoneal; VA: Ventriculoatrial; PVHI: Periventricular Hemorrhagic Infarction

### Introduction

The survival and survival without significant morbidity for premature infants born > 25 weeks significantly improved recently [1]. Intraventricular hemorrhage is the most common ultrasound abnormality seen in preterm infants [2]. The main reason for hemorrhage in extreme premature babies is due to anatomic immaturity, various physiological factors and also because of the intervention done during the first few days to stabilize sick babies [3]. Clinical examination and ultrasonography are useful in diagnosing intraventricular hemorrhage (IVH). The management depends on the clinical severity and associated post hemorrhagic hydrocephalus. Various modalities of treatment include serial lumbar punctures, ventricular tap, ventricular reservoir placement, ventriculosubgaleal shunt, ventriculoperitoneal shunt and endoscopic third ventriculostomy [2]. The choice of the treatment depends on the clinical condition of the patient. The outcome depends on the severity of hemorrhage and its complications. Severe grades of hemorrhage are associated with neurosensory impairment of various magnitude. Contrary to earlier belief, even mild grades of hemorrhages are associated with neurosensory impairment compared to those without IVH [4].

### Methods

EMBASE and PubMed databases were searched using the key words Intraventricular hemorrhage and post hemorrhagic hydrocephalus, preterm, hydrocephalus, ventricular reservoir and ventriculosubgaleal shunt. Cross-references of the relevant articles were also searched for additional studies. No restrictions on language or study designs were applied. Neonatal clinical studies as well as animal and bench research studies were reviewed in preparation for this review.

**Epidemiology**

The incidence of IVH increases with decreasing gestational age. The incidence of grade 1 IVH is 10%, grade 2 IVH- 6%, grade 3 and 4 IVH varies from 7 - 9% [5,6]. Overall, there is reduction in incidence of IVH for preterm infants born at or above 26 weeks of gestation, but not for infants between gestational ages 22 weeks through 25 weeks [7]. The incidence decreased from 19% to 11% at 26 weeks gestation, from 15% to 7% at 27 weeks gestation and from 11% to 5% at 28 weeks gestation [7]. The incidence of grade 4 IVH in infants born at 22 weeks gestation is 30% [2]. The incidence of PVL is approximately 3 - 4% for those babies born between 22 wks through 32 weeks of gestation [5-7]. Post hemorrhagic ventricular dilatation occurs in 30 - 50% of infants with grade 3 or grade 4 IVH, and 25 - 30% of these cases develop progressive ventricular dilatation. Studies have shown that male infants are at greater risk of IVH compared to female infants and severity of IVH is also more in male infants [9]. A multi-center retrospective study by Gamaleldine., *et al.* have shown that IVH is less likely in infants born via Cesarean section between 23 and 27 weeks of gestation [10].

**Pathophysiology of Intraventricular Hemorrhage**

Preterm infants, 32 weeks of gestational age or less, are vulnerable for hemorrhage in to the germinal matrix due to various anatomical and physiological factors. The etiology of IVH is multi-factorial and factors contributing to IVH is summarized in table below (Table 1).

Anatomic factors	Fragility of germinal matrix blood vessels Decreased expression of glial fibrillary acidic protein Paucity of pericytes Decreased fibronectin, laminin and collagen
Physiological factors	Alteration in cerebral blood flow Increased cerebral venous pressure Impaired autoregulation
Neonatal morbidities	PDA Pneumothorax Mechanical ventilation Hyperosmolar fluid/medications Hypotension Inotropes Hypercapnia/hypocapnia Thrombocytopenia Sepsis Hypernatremia Inhaled nitric oxide

Table 1

Germinal matrix is the area of active neuronal proliferation from where the neuron migrates toward the cortex and because of the high metabolic demand from the proliferating cells, there is rich vascularity in this part of the brain compared to the other areas [2,11,12]. Reduced expression of Glial Fibrillary Acidic Protein (GFAP), which covers perivascular area in germinal matrix of premature infants could potentially result in reduction of structural integrity of the blood vessels [11]. Morrison., *et al.* had demonstrated that the concentration of GFAP was induced by hydrocortisone which could explain the protective effect of prenatal steroids against the development of IVH [13]. Autopsy studies have shown lower level of fibronectin in the basal lamina of the blood vessels in germinal matrix of premature infants resulting in decreased stability of blood vessels [11]. Pericytes, which provide stability and integrity for blood vessels are relatively less in germinal matrix blood vessels compared to other parts of the brain [14].

The physiological factors which contribute for the development of IVH include alteration in cerebral blood flow, cerebral venous pressure changes and impaired autoregulation of cerebral blood flow [2,11]. Ventilator-patient asynchrony alters the cerebral blood flow and predispose to IVH [11]. Recent study published by Mian Q., *et al.* showed that high tidal volume (> 6 ml/kg) delivered by mask positive pressure ventilation at birth during resuscitation is associated with severe IVH [15]. The other neonatal conditions associated with IVH include PDA, pneumothorax, inhaled nitric oxide, early onset sepsis, use of catecholamines, hypercapnia, hypernatremia and rapid infusion of hyperosmolar fluid [2,3,11]. Mechanical ventilation and pneumothorax increases the central venous pressure. PDA results in fluctuation of cerebral blood flow. Hypercapnia causes cerebral vasodilatation resulting in increased cerebral blood flow. Fabres J., *et al.* in a retrospective study, demonstrated that both extremes and fluctuation in arterial CO<sub>2</sub> are associate with IVH [16]. Hypotension decreases cerebral perfusion and result in IVH [17]. Some studies have shown that it is the hypoperfusion-reperfusion injury, rather than hypotension per se, is responsible for IVH [2,11]. Impaired autoregulation of cerebral blood flow is seen in sick, extremely premature infants. But direct relation between impaired autoregulation and development of IVH need further studies. Thrombocytopenia is seen in 70 - 80% of very low birth weight infants [18]. But a retrospective study published by Linderin., *et al.* demonstrated that even though IVH ≥ grade 2 occurs more often in thrombocytopenic infants, there is no relation with severity of thrombocytopenia [19].

### Clinical features

Clinical features depend on the severity of the bleeding. Most of the mild grades of IVH are detected by routine ultrasound examination (clinically silent- 25 - 50% of cases). Saltatory course is characterized by decreased spontaneous movements, hypotonia, alteration of consciousness, changes in eye movement and disturbances in respiratory status. These features evolve over hours to days. The laboratory tests may show fall in hematocrit and rise in bilirubin levels. Rare catastrophic presentation evolves over minutes to hours and may results in stupor, coma, apnea, decerebrate posturing, seizures, dilated pupil, bulging fontanelle, irregular respiration, increased ventilatory requirement, hypotension, bradycardia and metabolic acidosis [20].

### Diagnosis

Ultrasound is the readily and easily available imaging modality used to diagnose IVH. The initial classification by Papile., *et al.* used computerized tomography to classify IVH, still being used in several centers. The classification is as follows [21]:

- Grade I: Subependymal hemorrhage
- Grade II: IVH
- Grade III: IVH with ventricular dilatation
- Grade IV: IVH with ventricular dilatation and parenchymal extension

The terminology grade 4 IVH, is now replaced by periventricular hemorrhagic infarction (PVHI) [2].

There are some pitfalls in Papile's classification. Subependymal hemorrhage is graded as grade 1 IVH even though there is no blood in the ventricle. The ventricular size of premature infants depends on the gestational age and degree of maturation. The accurate interpretation of ventricular size depends on the measurements in different planes. The ventricular enlargement could be due to brain volume loss from ischemia or could be from partial obstruction of the ventricle due to IVH [22,23]. The parenchymal hemorrhage associated with IVH is believed to be due to venous obstruction of the terminal vein rather than direct extension of the IVH [24]. Also, parenchymal hemorrhage without any IVH, which has worse prognosis, is not included in Papile's classification.

Volpe's classification is based on neuropathologic finding and the parenchymal hemorrhage is mentioned separately [22].

- Grade I: Germinal matrix hemorrhage with no or minimal intraventricular hemorrhage (< 10% of intraventricular area on parasagittal view)
- Grade II: Intraventricular hemorrhage (10 - 50% of ventricular area on parasagittal view)
- Grade III: Intraventricular hemorrhage (> 50% of ventricular area on parasagittal view; usually distends lateral ventricle)
- Separate notation Periventricular echo density (location and extent)

A new scoring system was developed by Abdi based on ultrasound finding and laterality which predicts the death and neurodevelopmental outcome at 3 years of age [25,26]. As per this study, the developmental outcome was more severe if the involvement is bilateral compared to unilateral IVH. But the drawbacks included the small size of the study population and its retrospective nature.

## Complications

The complications of IVH depends on the severity and location of hemorrhage. The blood in the ventricle may result in post hemorrhagic ventricular dilatation, the most common complication of higher grades of hemorrhage. The infant may develop acute hydrocephalus if the blood in the ventricle obstruct the flow of CSF or more commonly late onset non-communicating hydrocephalus from inflammatory destruction of arachnoid villi. The bleeding in the brain parenchyma may evolve over weeks and lead to the periventricular leukomalacia [27]. Vasileiadis GT, *et al.* in a prospective cohort study, demonstrated that even uncomplicated IVH was followed by reduced cortical volume at term corrected age [28].

## Post hemorrhagic Ventricular Dilatation (PVD)

Post hemorrhagic ventricular dilatation is defined as rapid increase in ventricular diameter within one week of IVH or progressive dilatation of ventricle after 14 days of occurrence of IVH. Ventricular dilatation is quantified by measuring the width of the anterior horn of lateral ventricle from the medial wall to the floor of lateral ventricle at the widest point. The reference range for premature infants from 23 weeks through 33 weeks has been defined as 0 - 2.9 mm. Quantitatively mild, moderate and severe ventricular dilatation is defined as anterior horn width of > 6 mm, > 14 mm and > 22 mm respectively [29]. The PVD occurs in 4% of infants with grade 1 IVH, 12% of infants with grade 2 IVH, 55% of infants with severe grades of hemorrhage and up to 80% if there is parenchymal hemorrhage also [22,29]. The ventricular dilatation can progress either rapidly or slowly. Spontaneous arrest occurs in 65% of cases and in 30 - 35% of cases the ventricular size can increase rapidly [27]. The brain damage from PVD occurs at the time of hemorrhage itself and from ischemic changes due to increased vascular resistance caused by the dilated ventricles [27]. The ventricular dilatation is diagnosed by rapid increase in head circumference (> 1.25 cm/wk), bulging fontanelle, increase in ventilatory setting, seizures or apnea. Serial ultrasonography every 5 - 7 days is recommended for early detection of progressive ventriculomegaly [27].

## Prevention of IVH

There are several prenatal and neonatal interventions proposed for the prevention of IVH. The prenatal measures include in utero transfer of high risk deliveries, prompt treatment of antenatal complications like PIH, antepartum hemorrhage, chorioamnionitis, delaying preterm delivery by tocolytics and antenatal corticosteroids [30]. A Cochrane review in 2006 demonstrated that antenatal steroids reduces IVH compared to the placebo (relative risk 0.54, 95% confidence interval 0.43 to 0.69) [31]. An observational study has demonstrated that the antenatal steroid reduced the incidence of IVH in the gestational age group between 22 weeks to 30 weeks, but no benefit for infants born after 30 weeks of gestation [32]. Corticosteroids help in the maturation the germinal matrix vasculature and catecholamine response, thereby decreasing the need for inotropes. Assisted vaginal delivery and cesarean section have shown to be beneficial compared to vaginal delivery without forceps for prevention of IVH. Compared to general anesthesia, babies born to mothers who received epidural anesthesia have better apgar scores and also fetoplacental circulation is less affected by epidural anesthesia [30].

## The postnatal interventions

The postnatal intervention starts from the delivery room. The measures include avoiding excessive tidal volume at the time of resuscitation, administer vitamin K soon after delivery, avoiding ventilator-patient asynchrony, maintain acid- base balance, avoid rapid infusion of fluid, stabilize blood pressure, avoid extremes of CO<sub>2</sub> variation, management of seizures and minimize handling [15,30]. A systematic review on timing of umbilical cord clamping demonstrated that delayed cord clamping lowers in incidence of IVH (RR 0.59; 95% CI, 0.41 - 0.85) [33]. But the most recent randomized controlled trial, involving 1634 preterm infants, did not show any significant difference in incidence of severe grades of IVH [34]. A recent systematic review on the effect of neutral head positioning and tilting on the incidence of IVH did not show any benefits [35]. Recently published systematic review and meta-analysis on volume target ventilation in preterm infants has shown a reduction in intraventricular hemorrhage grade 3 and 4 (RR 0.65, 95% CI 0.42 to 0.99) in comparison with pressure limited ventilation [36].

Indomethacin: A multi-center randomized controlled trial by Ment., *et al.* demonstrated that indomethacin reduces the incidence of IVH in premature infants [37]. The dose of the indomethacin is 0.1 mg/kg/day for 3 days [12]. The IVH reduced from 18% to 12% and grade 4 IVH from 4.5% to 0.5%. The proposed mechanism includes reduction in cerebral blood flow, stabilization of the germinal matrix blood vessels and reduction in the free radical production. Indomethacin could reduce the retinal, renal, mesenteric blood flow and also impair platelet aggregation [22,30]. By reducing the incidence of IVH, indomethacin should improve the neurodevelopmental outcome of the premature infants. But a large, multicentered trial (TIPP-trial), failed to show a decrease in the neurodevelopmental abnormalities [37]. This resulted in decrease in usage of prophylactic indomethacin even though Ment., *et al.* demonstrated that early administration of low dose indomethacin is not associated with adverse neurodevelopmental outcome [38].

Ethamsilate is another drug shown to be effective for prevention of IVH. Ethamsilate stabilizes the capillary basement membrane, promote platelet aggregation and has no effect of cerebral blood flow [22]. The routine use is not recommended as there is lack of data on long term morbidity.

### Treatment of symptomatic IVH and Post hemorrhagic hydrocephalus

Hemorrhages of lower grade resolve spontaneously over several days to weeks. Ventricular dilatation could be from the hydrocephalus or from hydrocephalus ex vacuo. Clinical signs and serial ultrasonogram help to guide the management of hydrocephalus [2]. Approximately 20% of grade 3 hemorrhage and 40% of PVHI require shunting [39]. Intervention is done either early if the ventricular index (VI) by Levene is > 97<sup>th</sup> centile or late if the VI is > 97<sup>th</sup> centile+ 4 mm [8].

**Lumbar puncture (LP):** Early removal of CSF up to 10 ml by serial LPs reduced the need for surgical intervention in retrospective studies [2]. Randomized controlled trial by ventriculomegaly trial group showed that early serial LPs did not reduce the need for subsequent shunt requirement compared to the control and it increased the rate of infection by 9%. Subsequent follow up of these infants did not show any neurodevelopmental advantage over the control group [40].

**Diuretics:** Randomized controlled trial of drug therapy (acetazolamide 100 mg/kg/day in combination with furosemide 1 mg/kg/day) plus standard therapy versus standard therapy by the International PHVD Drug Trial Group showed that use of the drug therapy was ineffective in reducing the need for shunt and was associated with increased neurological morbidity [41].

**Drainage, irrigation, and fibrinolytic therapy (DRIFT):** The blood in the ventricle may obstruct the flow of CSF or more commonly cause inflammatory destruction of arachnoid villi resulting in communicating hydrocephalus. Early ventriculoperitoneal shunt is impossible because of the high CSF protein and small size of the infant. A multicenter randomized controlled trial compared DRIFT versus tapping of CSF by reservoir, did not find any significant difference in need for shunt procedure. 35% of infants who underwent DRIFT procedure had secondary IVH compared with 8% in the standard treatment group [42]. However, when the neurodevelopment was assessed at 2 years, severe cognitive disability was less in the DRIFT group (31%) compared to standard therapy group (59%) [43].

**Temporary Shunt:** As permanent shunt is not practical for small infants because of the high failure rates and need for shunt revision, temporary surgical procedures are done in the interim. Temporary surgical procedure helps to drain the CSF until the infants grows and CSF protein content comes down. The temporary surgical options include ventricular reservoir (VR), external ventricular drainage (EVD) and ventriculosubgaleal shunt (VSG). The ventricular reservoir is tapped under aseptic precaution on regular basis. Earlier studies have shown higher rates of infection from VR. But recent studies have shown that following tapping of the reservoir, the incidence of infections are either very low or negligible [44]. The VSG involves a tubing which direct the CSF to contralateral subgaleal pocket from where CSF slowly gets absorbed [2]. The VSG drain the CSF into an anatomical space and there is no need to remove CSF manually. This has theoretical advantage of less infection rate but probably could lead to more mechanical failure because of the buildup of blood products and debris [45]. The result of a systematic review and meta-analysis of various treatment strategies are summarized below [45] (Table 2).

Outcome	Ventriculosubgaleal Shunt	Ventricular Access Device	External Ventricular Drain
Mortality	12.1%	15.3%	19.1%
Infection	9.2%	9.5%	6.7%
Obstruction	9.6%	7.3%	6.8%
Arrest of hydrocephalus	13.9%	17.5%	31.8%
Operative revision	12.2%	10.8%	47.3%
Favorable neurodevelopmental outcome	58.7%	50.1%	56.1%

Table 2

**Permanent Shunt:** The permanent shunt is placed in those infants when the temporary surgical measures fails, infants reach at least 1500 grams, the CF protein has decreased to 1.5 g/L and there are no more risks of necrotizing enterocolitis [2,44]. Delaying the shunt procedure may reduce the risk of infection [2]. The options include ventriculoperitoneal shunt (VP shunt), ventriculoatrial shunt (VA shunt) and ventriculopleural shunt. A retrospective study has shown that VP shunts were inserted at mean gestational age of 43 week and mean weight of 2.9 kg. Almost 45% of those infants who required permanent shunt prior to 1 year of age needed revision within 9 months [2].

**Endoscopic Third Ventriculostomy:** In this procedure fenestration of 3rd ventricle and surrounding arachnoid allow communication to the CSF spaces surrounding the brainstem, thereby helping to bypass the obstruction at 3rd ventricular outlets [39]. Efficacy in preterm infants with non-communicating post hemorrhagic hydrocephalus need more studies.

### Neurodevelopmental outcome

Preterm infants with intraventricular hemorrhage can have adverse neurodevelopmental outcomes in the form of deafness, blindness, seizures, motor deficits and cognitive impairment. The extend of the impairment depends on the gestational age, severity of hemorrhage, unilateral or bilateral involvement, progressive ventriculomegaly, associated parenchymal hemorrhagic infarction, need for shunt placement or revision and shunt infection [8]. In contrast to the earlier studies, latest studies have reported adverse outcomes even for lower grades of hemorrhages (grade 1 and 2) [4]. Even after excluding the ultrasound abnormalities like PVL, porencephaly and ventricular enlargement, infants with grade 1 and 2 IVH had higher rates of moderate-severe neurosensory impairment (19%) compared to those without IVH (12%) [4]. Infants with grade 3 hemorrhage and those with PVHI, had higher rate (43%) of moderate to severe neurosensory impairment [4]. As the severity of hemorrhage increases, the impairment also increases. Bilateral involvement is associated with worse outcome than unilateral IVH [46]. Most of the studies in which outcomes were reported used ultrasound (US) as the diagnostic modality. The US is ineffective in detecting small white matter lesions which could explain the adverse outcomes reported in some of the studies.

### Conclusion

Even though overall incidence of IVH has decreased recently, the incidence of higher grades of hemorrhage continues to be a major concern for the treating physicians. Lack of consensus in assessing the severity of ventricular dilatation by ultrasound and inability to detect white matter lesions is a major drawback in assessing the outcome of infants with intracranial hemorrhage. Even with advances in treatment, infants with higher grades of hemorrhage continues to need permanent surgical procedures. As more and more premature babies are surviving, we need an optimal management strategy to improve the neurological outcomes of these infants.

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