

RPA Newborn Care Guidelines

Royal Prince Alfred Hospital

Intraventricular Haemorrhage

Introduction

Throughout this guideline the term "intraventricular haemorrhage" is intended to include those lesions which may be described as germinal matrix haemorrhage \ intraventricular haemorrhage or periventricular haemorrhage elsewhere in the literature.

Intraventricular haemorrhage (IVH) is the most common type of intracranial haemorrhage in the neonate. It occurs primarily in preterm infants but is occasionally seen in near term and term infants.

Incidence

The incidence of IVH in the neonatal population has declined steadily in recent years.

- In the 1970s the incidence of IVH for infants <1500 g was 40%¹.
- In the 1980s the incidence of IVH was <20%².
- In the 1990s the incidence of IVH in the John Spence Nursery for infants born at <32 weeks gestation was <13%³ and for infants of <30 weeks gestation was 15% (JSN 1995-1997).

Pathogenesis

Most IVH is secondary to **hypoxic ischaemic reperfusion injury of the germinal matrix**^{4,5}. The factors that make the preterm infant particularly prone to this type of injury are outlined below.

1. Intrinsic vascular fragility of the germinal matrix:
 - The immature germinal matrix is richly perfused with fragile vessels which lack muscular and collagen support. These vessels may be particularly vulnerable to insult⁶.
2. Increased risk of the germinal matrix to hypoperfusion injury.
 - The resting aortic pressure of the preterm infant lies dangerously close to the lower limits of the cerebrovascular autoregulatory plateau⁷
 - Cerebrovascular autoregulation may be absent in sick preterm infants⁸.
 - PDA "steal" of blood from the cerebral circulation.
3. Exposure to biochemical disturbances (respiratory or metabolic) resulting in:
 - Fluctuations in cerebrovascular blood flow⁹

- Impaired autoregulation⁹
- 4. Iatrogenic disturbances in intravascular volume:
 - Rapid boluses of intravenous volume are frequently administered to preterm neonates and have been associated with IVH^{10, 11, 12}.
- 5. Intrinsic disturbances in coagulation:
 - Disturbances of coagulation common to the preterm infant may be associated with an increase in minor grades of IVH but they do not appear to be associated with more extensive haemorrhage¹³.

Classification of intraventricular haemorrhage

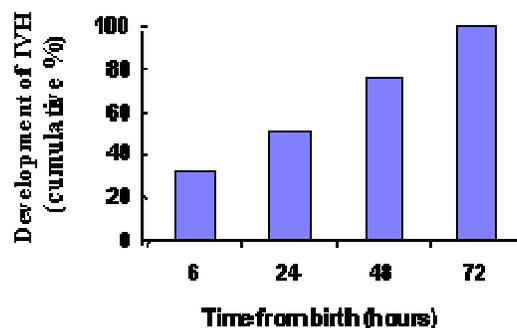
The extent of the haemorrhage, associated ventricular distension and parenchymal involvement is the basis of the classification system of Papile¹. This classification system is routinely used to describe intraventricular haemorrhage (IVH) in infants in the John Spence Nursery:

Grade	Description
I	Isolated germinal matrix haemorrhage
II	Intraventricular haemorrhage with normal ventricle size
III	Intraventricular haemorrhage of sufficient severity to dilate the ventricles with blood
IV	Intraparenchymal haemorrhage

Grade IV haemorrhage

This is usually associated with extensive intraventricular haemorrhage. It is postulated that large blood clots in the germinal matrix and ventricles impair the flow of blood from the medullary veins, which drain the cerebral white matter, into the terminal vein⁸. This impairment of blood flow may lead to venous infarction and, like other venous infarctions, this infarction may be haemorrhagic.

Timing of IVH



Nearly all intraventricular haemorrhages occur within 72 hours of birth,⁸ and the vast majority occur within the 1st 48 hours of life⁵. Many occur on the first day^{14, 15, 16} and about 30% occur within the first six hours of life. These very early onset haemorrhages probably have their origins in antenatal/intrapartum events.^{5, 17}

Risk factors

The incidence of IVH is inversely related to gestation and birth weight. This is because the germinal matrix starts to undergo spontaneous involution in the second trimester. The process is virtually complete by 32 weeks gestation when the risk of haemorrhage is almost abolished. However, many other significant associated risk factors have been identified. These can be divided into early and late risk factors

Early Risk Factors

Lack of antenatal corticosteroids	★★★★★ ¹⁸
Delivery outside a tertiary neonatal centre	★★★ ^{11, 19}
Chorioamnionitis	★★★ ^{12, 20, 21}
Low 1 minute Apgar	★★★ ²²
Bruising at delivery	★★★ ^{16, 17}
Mode of delivery: caesarean section appears to be protective	★★★ ^{5, 17}
Low umbilical artery pH (Grade III/IV IVH)	★★★ ²²

Late Risk Factors

Hyaline membrane disease	★★★ ^{16, 23}
Patent Ductus Arteriosus	★★★ ²⁴
Pneumothorax	★★★ ¹⁶

Diagnosis of IVH

Diagnosis is by clinical assessment and ultrasound evaluation.

Clinical Signs

IVH is often asymptomatic but the likelihood of signs increase with the severity of haemorrhage. Possible clinical signs are:

- tense anterior fontanelle
 - pallor and associated drop in haematocrit
 - limp, unresponsive infant
 - tonic fits with decerebrate posturing
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Ultrasound Screening

Formal diagnosis is by cranial ultrasound.

All infants <30 weeks gestation in the John Spence Nursery should have at least **two** examinations performed by an ultrasonographer.

1st Ultrasound

The first formal ultrasound should routinely be performed between **days 5 and 7 of life**. This is the optimal time for a single ultrasound examination as all cases of IVH and >90% of associated parenchymal haemorrhages will be evident⁸. However, as many haemorrhages occur on the first day of life and the vast majority by 48 hours earlier ultrasound examination may be performed on the basis of clinical concerns or as part of the ongoing research of the unit.

2nd Ultrasound

The second cranial ultrasound should routinely be performed around **day 28 of life**. By this stage parenchymal abnormalities and/or ventriculomegaly will be evident, providing important prognostic information and guidelines for further management.²⁵

Additional ultrasound scans are indicated in the following circumstances:

- Infants >29 weeks gestation in whom there are clinical concerns or who are considered to be at significant risk (see risk factors). There is no justification for routine screening in this population.³
- Head circumference growth deviating from the normal intrauterine growth curves. This situation is most common after Grade III-IV IVH and is indicative of progressive hydrocephalus.
- Ventriculomegaly on the routine day 28 scan:

If this is associated with a late increase in the rate of growth of the head circumference, further ultrasound scans should be performed at regular intervals to assess the need for intervention in case of developing hydrocephalus.

Note: Cranial ultrasound scans which are reported as abnormal and/or ultrasound scans of infants thought to have clinical signs of evolving hydrocephalus should be viewed by senior medical staff.

Complications

IVH may be asymptomatic and without long term consequence.

However potential complications are:

- Death
- Neuro-developmental handicap
- Post haemorrhagic hydrocephalus

Death

There is a strong association between early neonatal mortality and extensive IVH with the higher rates reflecting more extensive parenchymal involvement.⁸

The following table shows the association between death and grade of IVH in the John Spence Nursery.

John Spence Nursery 1995-1997

Grade of IVH	Associated Mortality
I	6 %
II	33 %
III	60 %
IV	93 %

These figures for John Spence Nursery include those infants with extensive haemorrhage in whom death followed withdrawal of care after discussion with parents and clinicians.

Neuro-developmental handicap

IVH is associated with neuro-developmental handicap. Most observers agree that the more severe grades of haemorrhage are associated with a higher incidence of neuro-developmental handicap.^{25, 26, 27, 28, 29}

Relationship between IVH and neuro-developmental outcome at 1 and 3 years for infants

1 year follow-up: Disability (CP or Griffiths DQ <70) for babies <30 weeks gestation: John Spence Nursery, 1992-1994.

Grade of IVH	Number with disability / Number reviewed (%)	Odds ratio for disability at 1 year	Significant difference from no IVH
No IVH	17/152 (11%)	1.0	
I	3/17 (18%)	1.7	Not significant
II	4/11(36%)	4.5	P<0.05
III & IV	6/8 (75%)	23.8	P<0.01

3 year follow-up: Disability (CP or Griffiths DQ <70) for babies <30 weeks gestation: John Spence Nursery, 1992-1994.

Grade of IVH	Number with disability / number reviewed	Odds ratio for disability at 3 years	Significant difference from no IVH
No IVH	28/146 (19%)	1.0	
I	5/12 (42%)	3.0	Not significant
II	7/9 (78%)	14.8	P<0.01
III & IV	6/8 (75%)	12.6	P<0.01

The numbers of cases with haemorrhage are small but these figures demonstrate the association between increasing grade of IVH and significantly abnormal developmental outcomes. They also demonstrate the need for long term follow up for all infants including those without extensive haemorrhage in this very premature population.

Prevention of Intraventricular Haemorrhage

Antenatal Interventions

The following are currently recommended in RPA Newborn Care to reduce the risk of IVH

- **Maternal transfer to a tertiary neonatal centre**
 - Despite advances in neonatal transport, significant differences persist in neonatal morbidity, including Grade III and IV IVH, between "inborn" and "outborn" populations.¹⁹ Attempts should be made to transfer all women at risk of preterm delivery in NSW to an appropriate perinatal centre. This is current practice in NSW using the regional perinatal advisory service.
- **Corticosteroids**
 - The administration of antenatal corticosteroids to the mother 48 hours prior to delivery significantly reduces the incidence of IVH¹⁸ and should be considered for all women at risk of preterm delivery.
- **Maternal magnesium sulphate**

- Observational studies have described a reduced incidence of IVH in the preterm infants of women exposed to intravenous magnesium sulphate^{30, 31} but not all studies support this.³² We are currently participating in a multicentre randomised controlled trial looking at this intervention (ACTOMgSO4 Trial).
 - **Management of preterm premature rupture of membranes (PPROM)**
 - The use of antimicrobial therapy in the expectant management of preterm premature rupture of the membranes is associated with a significant reduction in the number of women who deliver within one week and a reduction in chorioamnionitis, neonatal sepsis and IVH.³³ This is now standard obstetric practice within our unit.
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Treatment

Clearly optimal resuscitation and stabilisation of the infant are important^{11, 16} (*resuscitation guideline*)

Careful attention should be paid to the management of ventilation with particular care to avoid hypocapnia (ventilation guideline) and haemodynamic stabilisation.

Haemodynamic stabilisation requires assessment and management of cardiac output and the ductus arteriosus. In John Spence Nursery a clear association has been demonstrated between the size of the patent ductus arteriosus, measures of cardiac output (superior vena cava flow) and the development of IVH in infants of < 30 weeks gestation.²⁴ A randomised trial of systemic circulatory support for the preterm infant is currently underway in the John Spence nursery. The aim of this study is to find the optimal circulatory management of the preterm infant in the 1st 24 hours of life. Inotropic support and indomethacin will be targeted to the at risk population within the study.

Other potential management strategies

Many other interventions have been described; a brief summary of them follows:

Maternal vitamin K and phenobarbitone

The administration of these prior to preterm delivery have been reported to reduce the incidence of IVH but these findings are not supported in studies which have been adequately randomised and blinded.^{34, 35} They are not currently being administered antenatally in this hospital.

Mode of delivery

Vertex presentation, vaginal delivery and severe bruising,¹⁷ low Apgars²² and acidosis on cord blood gases³⁶ in the low birthweight population have all been associated with early onset IVH. Delivery by Caesarean section appears to be protective^{14, 15, 37} but there is insufficient randomised controlled trial data to justify any specific policy on the mode of delivery.

Fresh frozen plasma

Postnatal correction of the coagulation abnormalities present in premature infants using fresh frozen plasma has been promoted. Some reduction in the incidence of IVH has been reported^{13, 38} but not in the incidence of severe IVH. A larger more recent randomised trial failed to demonstrate any advantage from FFP infusions.³⁹ Current data does not support the use of fresh frozen plasma.

Ethamsylate

Ethamsylate has been used extensively in urological and gynaecological surgery to reduce capillary bleeding time. Animal studies have suggested that it might reduce the risk of IVH in immature infants.⁴⁰ The evidence from trials to date is conflicting although the largest and only adequately randomised and blinded study⁴¹ showed a significant reduction in the extension of haemorrhages by two or more grades in the treatment population. This intervention has not been studied in a population exposed to antenatal corticosteroids and requires further evaluation.

Vitamin E

Vitamin E is a free radical scavenger and it is speculated that it may reduce the extent of IVH following hypoxic damage to the subependymal layer.⁴² Literature reports of its benefits are conflicting although a randomised trial⁴² of Vitamin E treatment in infants < 32 weeks gestation reported a significant reduction in the rates of IVH in the treated population. This intervention requires further evaluation.

Indomethacin

Indomethacin reduces the incidence of IVH in beagle pups following haemorrhagic hypotension and reperfusion.⁴ Subsequently there have been several randomised trials of indomethacin prophylaxis for IVH in the preterm infant. A meta-analysis of these studies⁴³ showed a significant reduction in grade III-IV IVH in the treated infants. In many units consideration is being given to the routine administration of indomethacin to all preterm infants <30 weeks gestation but as of yet there is no clear evidence of long term benefit. The TIPP study is seeking to address this question by randomising all infants < 30 weeks gestation to indomethacin or placebo. In John Spence Nursery it is policy to administer indomethacin only to those infants in whom there is an echocardiographic diagnosis of a significant patent ductus arteriosus

Key Points

The incidence of IVH increases with decreasing gestational age.	★ ★ ★ ¹⁶
Risk factors for IVH are multiple and include obstetric and perinatal variables.	★ ★ ★ ^{16, 17, 21}
IVH usually occurs early in postnatal life (75% by 72 hours) but may develop in utero or intrapartum.	★ ★ ★ ^{8, 16} ★ ★ ²⁴
IVH is related to adverse neurological outcome; extent of the IVH is highly significant.	★ ★ ★ ^{25, 28, 29} ★ ⁶

The pathogenesis of IVH: hypoperfusion -reperfusion injury with venous infarction.	★ ★ 4, 5 ★ 6
Antenatal corticosteroids provide significant risk reduction.	★ ★ ★ ★ ★ 18
Delivery within a perinatal centre is desirable.	★ ★ ★ 19
Early indomethacin reduces IVH.	★ ★ ★ ★ ★ 43

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