IVH in Term Neonates with HIE: A Comparison Study between Neonates Treated with and without Hypothermia

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Hypoxic-ischemic encephalopathy (HIE) is a serious neonatal condition resulting from a lack of oxygenation of the brain that manifests itself as central nervous system dysfunction. Moderate or severe HIE affects 0.5-1 per 1000 live births in the Western world and causes significant mortality and morbidity with over 25% of children experiencing long-term neurodevelopmental disability (1). The only neuroprotective treatment currently known to improve the outcome in HIE is therapeutic hypothermia. This therapy consists of whole body or selective head cooling to a basal ganglia temperature of about 32-34 degrees Celsius for three days to prevent reperfusion injury.

A meta-analysis of several major studies including the CoolCap study, the National Institute of Child Health and Human Development study, and the TOBY trial, has demonstrated a reduction in death and neurological impairment at 18 months following hypothermia (2). A Cochrane Collaboration review on the safety of this therapeutic approach has shown thrombocytopenia and hypotension to be its major side-effects (1). Nevertheless, some authors have also raised concerns that hypothermia might increase the risk of intracranial hemorrhage (3,4).

Intraventricular hemorrhage (IVH) and HIE were long believed to be pathologically interrelated. Yet, the incidence of IVH in term neonates with HIE is not well documented. In a study of factors affecting outcome in HIE in term infants in 1983, 4 cases of IVH were reported in 43 infants with HIE who had undergone computed tomographic scans (5). To the best of our knowledge, no previous radiological study resorted to MRI and US to establish the frequency of IVH in term encephalopathic neonates. We believe that our report is also the first one to compare the incidence of IVH in term babies with HIE treated by therapeutic hypothermia versus those managed conventionally.

The purpose of our work is to retrospectively determine the overall prevalence of IVH in full-term neonates with HIE using head ultrasound (HUS) and MRI, and whether there is an association between hypothermia and an increase in IVH.
Methods and Materials

A total of 61 term neonates from two institutions were diagnosed with HIE shortly after birth. Thirty infants were treated with whole body hypothermia and 31 neonates received conventional care. All the neonates underwent HUS in their first 23 days of life. The majority (54 survivors) also underwent MRI. The imaging studies were all reviewed for IVH.

From November 2008 to November 2010, 30 term newborns with HIE were treated with therapeutic hypothermia at the Montreal Children's Hospital. These infants had to satisfy the entry criteria for neonatal hypothermia protocol of the institution. According to these standards, the administration of whole body hypothermia therapy is based on physiologic indications of hypoxia (criteria A) and neurologic signs (criteria B), both of which must be met. According to criteria A, if a cord or postnatal blood gas is available, there must be a pH $\leq 7.0$ or a base deficit $\leq 16.0$ mEq/L. If no blood gas is available, the pH is 7.01 to 7.15, or the base deficit is 10 to 15.9 mEq/L, there must be a documented acute perinatal event as well as an Apgar score $\leq 5$ at 10 minutes or a continued need for ventilation initiated at birth and continued for at least 10 minutes. In keeping with criteria B, the child must exhibit signs of moderate to severe encephalopathy defined as seizures or presence of one or more signs in three of the following six categories: level of consciousness, spontaneous activity, posture, tone, primitive reflexes, and autonomic system. Babies in whom hypothermia could not be initiated within the first 6 hours of life, or infants with a severely abnormal aEEG tracing, a known chromosomal abnormality, a major congenital abnormality, a weight $<1800$ g, a gestational age $<36$ weeks, evidence of severe injury, or multi-organ system failure were not eligible candidates for hypothermia.

The 31 babies who underwent conventional treatment were selected from December 2001 to April 2004 at the Hospital for Sick Children in Toronto. At that time, hypothermia was not yet a standard of care at that institution. Neonates with severe congenital abnormalities, metabolic abnormalities, or infectious disease that would have made them ineligible for hypothermia were excluded from the study.
Results

Four of the 61 infants (6.6%) were diagnosed with IVH on HUS. Amongst the 30 babies who received whole body hypothermia, there were 18 males and 12 females, the mean birth weight was 3.5 kg (2.5 kg to 5.2 kg), and the HUS study was performed within 14.8 to 41 hours of life (Table 1). The group of 31 infants treated conventionally was comprised of 12 boys and 19 girls, the infants had an average birth weight of 3.3 kg (2.3 to 4.2 kg), and they underwent HUS 1 to 23 days after birth, with only five children being older than 1 week at the time of the imaging studies.

In the group of neonates treated with hypothermia, there were 3 cases (10%) of IVH. The first child with IVH had a large, unilateral right intraventricular bleed seen on HUS (Figs. 1-4) and verified with MRI. The second case showed a bilateral hemorrhage which was not evident on HUS due to symmetry, but which was confirmed by MRI. In the third infant, HUS revealed a bilateral enlarged choroid plexus. However, IVH could not be confirmed with MRI, as the baby did not survive. The former two children were classified as having HIE of Sarnat stage II and the latter infant as Sarnat stage III.

In the group not subjected to hypothermia, IVH occurred in one infant (3.2%). The hemorrhage was bilateral and was noted both on US and MRI (Figs. 5-6).
**Fig. 1:** HUS with coronal image shows echogenic material within the right lateral ventricle.
Fig. 2: Sagittal image confirms IVH.
Fig. 3: Normal left choroid plexus.

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**Fig. 4:** Brain section of pathology specimen demonstrates blood within the right ventricle.

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**Fig. 5:** HUS with coronal image shows enlarged choroid plexus.

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Fig. 6: MRI with T2-weighted axial image confirming bilateral IVH.

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<table>
<thead>
<tr>
<th></th>
<th>Hypothermia Treatment Group (n=30)</th>
<th>Conventional Treatment Group (n=31)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>18 males; 12 females</td>
<td>12 males; 19 females</td>
<td>30 males; 31 females</td>
</tr>
<tr>
<td>Birth Weight</td>
<td>3.5 kg (2.5 to 5.2 kg)</td>
<td>3.3 kg (2.3 to 4.2 kg)</td>
<td>3.4 kg (2.3 to 5.2 kg)</td>
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<tr>
<td>Age at HUS study</td>
<td>14.8 to 41 hrs</td>
<td>1 to 23 days</td>
<td>14.8 hrs to 23 days</td>
</tr>
<tr>
<td>IVH</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>
Table 1: Gender distribution, birth weight, age at HUS, and number of diagnosed IVH in infants treated with hypothermia or conventionally.

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Conclusion

IVH is well documented in premature infants. It is far less common in term infants, although rates of 3% have been reported in healthy term babies studied with HUS (6). Unlike in pre-term children in whom IVH originates in the germinal matrix, neuropathological studies demonstrate that the site of bleeding in term neonates is usually the choroid plexus (7). Germinal matrix hemorrhage occurs only in a minority of term neonates with IVH, and usually involves the caudothalamic groove (8). The proposed reason for this difference is that the high cellularity and vascularity of the germinal matrix progressively disappear from 24 to 32 weeks of gestation as the brain matures (9-11). Moreover, there are differences in regional cerebral blood-flow: as the baby matures, the majority of the blood flow is directed to the cortex and white matter in contrast to the basal ganglia and periventricular regions that are most highly irrigated in premature infants (10). This hemodynamic change might explain the lower incidence of IVH in term infants.

The pathogenesis of IVH is multifactorial and no clear mechanism is known. An altered autoregulation, hemodynamic instability with fluctuating blood flow and arterial or venous pressure, early filling of the deep venous system, immaturity of the capillary bed, poorly supported capillaries, and coagulation disturbances may all contribute to vessel injury (8,11-14). Moreover, sinusvenous thrombosis was found to be implicated in almost a third of thalamic hemorrhage in term neonates with IVH (6).

In our study, IVH occurred at a higher rate in children who underwent hypothermia (10%) than in those treated conventionally (3.2%). This difference might not necessarily reflect a higher risk of IVH following hypothermia, but rather the selection of clinically more severe cases for the hypothermia treatment. Indeed, the inclusion criteria stipulate that only neonates presenting with Sarnat stage II or stage III (15) be considered eligible candidates for the procedure. Higher Sarnat stages indicate poorer prognosis and outcomes as well as an increased risk of complications: Term neonates with mild encephalopathy are often normal at follow-up, whereas those at a moderate stage have sequelae 20 to 35% of the time, and infants with severe brain damage almost always present some long-term complications and have a 75% risk of death in the neonatal period (16).

On the other hand, hypothermia has been associated with significantly increased thrombocytopenia, which is an independent risk factor for IVH (1,11,13). It has also been found to increase the need for inotrope support to treat hypotension, which may contribute to hemodynamic instability, a factor that might predispose to IVH.
In conclusion, our study demonstrated that IVH remains uncommon in term infants with HIE, occurring at a rate of 6.6%. However, it was more prevalent in the group treated with hypothermia (10% vs 3.2%). The higher prevalence of IVH in neonates treated with hypothermia may not necessarily be a consequence of the therapy. It might reflect the selection protocol of more clinically severe cases of HIE in the hypothermia group. It remains to be determined whether a difference in IVH incidence between the hypothermia group and the control group persists in a randomized control trial with an equal disease severity in both populations. The alternative may be to perform HUS before and during hypothermia.
References


