A Systematic Review and Meta-analysis of the Timing of Early Intraventricular Hemorrhage in Preterm Neonates: Clinical and Research Implications

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ABSTRACT

A considerable number of intraventricular hemorrhages (IVH) occur within the first hours of life (HOL). Temporality between IVH and its antecedents as well as a consistent definition of "early IVH" is lacking in a large and growing body of literature. We performed a systematic review of prospective studies that reported onset of IVH in preterm neonates within the first HOL and afterwards. The English literature was searched using three databases up to March 2013. Four timing periods of IVH can be compared in 16 identified studies: 0-6; 7-12; 13-24; after 24 HOL. The 0-6 and after 24 HOL were the major modes of IVH timing. Pooled IVH proportions were estimated through a meta-analysis of studies that were conducted after antenatal steroid and surfactant era. In neonates weighing ≤1500 g at birth: 48% of IVH (95% CI: 42-58%, 5 studies, 279 IVH cases) occurred during 0-6 HOL and 38% (95% CI: 19-57%, 4 studies, 241 IVH cases) after 24 HOL. The 0-6 HOL is the shortest, most vulnerable period for IVH, thus, an early IVH is an IVH occurs in it. Such early IVH had prognostic, etiological/preventive and medicolegal implications. Accordingly, preterm neonates at risk of IVH should have their first routine screening head ultrasound at about 6 HOL. Future research exploring the antecedents of IVH should guaranty the temporality between these antecedents and IVH. Additional research will be required to determine whether the long term neurological outcomes of early and late IVH are the same.

Key words:
Early intraventricular hemorrhage, head ultrasound, intraventricular hemorrhage, preterm neonates, timing of intraventricular hemorrhage, very low birth weight

INTRODUCTION

Intraventricular hemorrhage (IVH) in preterm neonates is a devastating consequence of prematurity that has both perinatal and postnatal antecedents.[1] Knowing the timing of IVH is a prerequisite for identifying its antecedents and subsequently applying preventive measures.[2,3] Studies before and after the widespread use of antenatal steroid and surfactant therapy have shown that IVH may occur as early as the 1st min.[4-8] This observation suggests that IVH may occur in utero, intrapartum or during the early postnatal period.[4-8] A large body of evidence has shown that a considerable number of IVH cases occur during the first hours of life (HOL).[3,5-7,9-24] Reports in the literature from the 1980s and 1990s established that IVH occurring within the first HOL and later-occurring IVH must be analyzed separately as their antecedents may be different.[25-27] However, a more recent large and growing body of literature has considered early and late IVH as a single entity and has neglected the fact that a significant number of IVH cases may have occurred prior to the investigator's study intervention or antecedents of IVH. Underrepresentation of the studies that have carefully reported the timing of IVH and inconsistency in defining the term "early IVH" may have contributed to this negligence. Therefore, the aim of this article is to systematically review and analyze numerous previous studies that evaluated or reported onset of IVH within the first HOL and afterwards. Based on this analysis, we will propose a definition for early IVH as well as present clinical and research implications. We hope this review will increase the mindfulness of early IVH in clinical practice and research.

BIBLIOGRAPHIC SEARCH

The bibliographic search of English-language literature was performed electronically using PubMed and EMBASE databases. The search was limited to prospective studies

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Access this article online

Quick Response Code:

Website: www.jcnonweb.com

DOI: 10.4103/2249-4847.134674

published until March 2013. The following text words were used: "early [title]", "timing [title]", "intraventricular", "periventricular", "peri-intraventricular", "subependymal", "germinal matrix", "intracranial", "cerebral", "cerebroventricular", "cranial" and "brain". The following Mesh terms were used for Pubmed: "hemorrhage", "ultrasonography" and "infant, newborn". The following Emtree terms were used for EMBASE: "brain hemorrhage", "ultrasound", "echoencephalography" and "newborn". Google scholar database and reference lists of the selected articles were searched to find other relevant articles.

DESCRIPTION OF STUDIES

We abstracted 16 prospective studies in which the time interval of IVH occurrence within the first HOL was reported or could be inferred. Nine of these 16 studies included low birth weight (LBW, ≤2000 g) preterm neonates.[5,7,12,14-17,19,22,28] All these nine studies were conducted before widespread of antenatal steroid and surfactant era. One of them had two reports; a primary report on all study neonates and a secondary report on the subgroup of neonates delivered by cesarean section only.[5,13] The study of Paneth *et al*. has the largest number of neonates and the narrowest intervals of censored times to IVH.[7] The other seven of the abstracted 16 studies included very low birth weight (VLBW, ≤1500 g) preterm neonates.[3,6,11,18,20,21] Five of them were conducted after widespread of antenatal steroid and surfactant era.[6,15,17,20,21] Table 1 depicts a summary of LBW studies and Table 2 depicts a summary of VLBW studies. The studies in both tables are ordered by the earliest reported time of head ultrasound (HUS).

Another 16 studies reported IVH timing were abstracted but were excluded from this review as they did not report exact timing of IVH within the first HOL [Appendix].

TIMING OF IVH OCCURRENCE

The distribution of IVH occurrence in four different time intervals (0-6 HOL, 7-12 HOL, 13-24 HOL and after 24 HOL) can be compared in the included 17 reports listed in Tables 1 and 2.[3,5-7,10-22] Figures 1 and 2 depict the percentage of IVH cases in each report that occurred during these 4 time intervals in LBW and VLBW, respectively. These plots show that timing of IVH is bimodal in both LBW and VLBW neonates. These two modes are 0-6 and after 24 HOL intervals. The 0-6 HOL interval is the major mode in half of both LBW [Figure 1] and VLBW studies [Figure 2]. The 0-6 HOL interval includes ≥50% of the IVH cases in half of both LBW[5,12,14,15,22] and VLBE studies.[11,20,21] The "after 24" HOL interval includes ≥50% of the IVH cases in only two LBW[13,16] and one VLBW studies.[6]

The discrepancies between some of these studies regarding the time period during which most IVH cases occur could be attributed to the methodological heterogeneity across these studies in terms of the exact timing of HUS and the study population. One of the LBW studies that reported ≥50% of the IVH cases occurring after 24 HOL was a secondary report on cesarean section deliveries.[13] The primary report, which included both vaginal and cesarean section deliveries, indicated that at least 54% of the IVH cases occurred within the first 6 HOL, whereas the secondary report indicated that only 31% of the IVH cases occurred within the first 6 HOL.[5,13] It appears that the timing of IVH is related to the maturation of neonates. Perlman and Volpe have demonstrated that the first 18 HOL include 62%, 18% and 11% of the IVH cases reported among neonates with birth weights of 500-700 g, 701-1000 g and 1001-1500 g, respectively.[32] It has been reported that neonates who developed IVH before 12 HOL were born on average 2 weeks earlier than those who developed IVH after 48 HOL (27.5 vs. 29.5 weeks).[33]

A meta-analysis of proportions was performed to estimate pooled IVH proportions through Open Meta-Analyst software, Tufts University, USA.[34] We included studies that were conducted after antenatal steroid and surfactant era pursuing methodological homogeneity across the studies and harmony with the present practice. Thus, only the five VLBW studies that were conducted after antenatal steroid and surfactant era were included in the meta-analysis.[6,15,17,20,21] Pooled IVH proportion occurred during 0-6 HOL interval was calculated using a fixed-effect model with inverse variance weighting [Figure 3]. Pooled IVH proportion in 0-6 HOL interval is 48% (95% confidence interval 42-53%). Insignificant heterogeneity was observed: Q test with 4 degrees of freedom = 6.48, I^2 = 38%, $P = 0.17$, 5 studies, 279 IVH cases).[35] Pooled IVH proportion occurred after 24 HOL was calculated using a DerSimonian and Laird random-effect model [Figure 4]. Osborn *et al*. study was excluded from the meta-analysis as the IVH proportion after 24 HOL cannot be abstracted [Table 2].[15] Pooled IVH proportion after 24 HOL was 38% (95% confidence interval 19-57%). Significant heterogeneity was observed: Tau^2 = 0.03, Q test with 3 degrees of freedom = 29.25, I^2 = 90%, $P < 0.01$, 4 studies, 241 IVH cases).[35] These observations suggest that the first 6 HOL is the shortest, most vulnerable period of time for a neonate with respect to IVH.

WHY DOES DOCUMENTATION OF THE IVH STATUS WITHIN THE FIRST HOLMATTER?

Documentation of the IVH status within the first HOL is important due to its prognostic, etiological/preventive and medicolegal implications.[36]

Table 1: Prospective studies evaluating or reporting onset of IVH during the interval censored in low birth weight neonates

Study (country)	Study characteristics	Result		
Van de Bor *et al.* (Netherlands)	Study period: 1984	IVH incidence: 20 (41%)		
	N=49	HUS age	Number (%) IVH	Papile grade
	GA<34 weeks	At birth	6 (30)	6 grade 1-2
		Birth-24 HOL	5 (25)	Not reported
		24-96	9 (45)	
de Crespigny *et al.* (Australia)	Publication year: 1982	IVH incidence: 47 (27%); of which 24/34 (71%) IVH occurred within 6 HOL		
	N=174	Number of IVH at first HUS: 36		
	GA<33 weeks	HUS age	Number (%) IVH	
		1 HOL	10 (28)	
		1 to<2	4 (11)	
		2 to<3	3 (8)	
		3 to<4	4 (11)	
		4 to<6	3 (8)	
		6 to<24	8 (23)	
		24-36	4 (11)	
Anderson *et al.* (USA)	Study period: 1986	IVH incidence: 43 (48%)		
	N=89	HUS age	Number (%) IVH	Papile grade
	BW≤1750g	≤1 HOL	28 (65) (defined as early IVH)	26 grade 1-2 2 grade 3-4
		>1	15 (35)	Not reported
Shaver *et al.* (USA)	Study period: 1986-1988	IVH incidence: 96 (42%)		
	N=230	HUS age	Number (%) IVH	Papile grade
	GA: 29±3 weeks	≤1 HOL	47 (49) (defined as early IVH)	27 grade 1 16 grade 2 4 grade 3
	BW: ≤1750 g (1255±388)	>1	49 (51)	15 grade 1 29 grade 2 2 grade 3 3 grade 4
Anderson *et al.* (USA)	Secondary report of Shaver (USA)[5] on neonates delivered by cesarean section only	IVH incidence: 45 (42%)		
	N=106	HUS age	Number (%) IVH	
	GA: 29.5±2.7 weeks	≤1 HOL	9 (20)	
	BW: ≤1750 g (1210±351)	1 to>72	36 (80)	
Paneth *et al.* (USA)	Study period: 1984-1987	IVH incidence: 244 (25%)		
	N=976	HUS age	Number (%) IVH	
	GA: 30.9±3.6 weeks	0-3 HOL	25 (10)	
	BW: 501-2000 g (1393±406)	4	28 (11)	
		5-6	13 (5)	
		7-8	19 (8)	
		9-12	23 (9)	
		13-21	18 (7)	
		22-23	12 (5)	
		24-240	106 (45)	
Meidell *et al.* (USA)	Study period: 1981-1982	IVH incidence: 17 (43%)		
	N=40	HUS age	Number (%) IVH	Papile grade
	GA<35 weeks	At mean 1.9±0.2 HOL	15 (88)	12 grade 1
		3 DOL	2 (12)	1 grade 1
		Early IVH defined as IVH occurring within 1 DOL		

Contd...

Table 1: Contd...

Study (country)	Study characteristics	Result	
McDonald *et al.* (USA)	Study period: 1980-1981	IVH incidence: 24 (48%)	
	N=50	HUS age	Number (%) IVH
	GA<33 weeks	4 HOL	7 (29)
		5-8	2 (9)
		9-16	1 (4)
		17-24	1 (4)
		25-192	13 (54)
Weindling *et al.* (UK)	Study period: 1982-1983	IVH incidence: 34 (40%); of which 13 IVH among 25 neonates who had HUS scan every 6 h for the first 48 HOL	
	N=86	HUS age	Number (%) IVH
	Median GA: 29 weeks (23-38)	<6 HOL	4 (30)
	Median BW: 1150 (460-2000)	6-12	3 (23)
		12-18	2 (15)
		24-48	4 (32)
Beverley *et al.* (Canada)	Publication year: 1984	IVH incidence: 40 (27%)	
	N=150	HUS age	Number (%) IVH
	GA≤34 weeks	0-8 HOL	20 (50)
		8-16	5 (13)
		16-24	4 (10)
		24 to>48	11 (27)

IVH – Intraventricular hemorrhage; GA – Gestational age; HUS – Head ultrasound; HOL – Hours of life; BW – Birth weight; DOL – Day of life

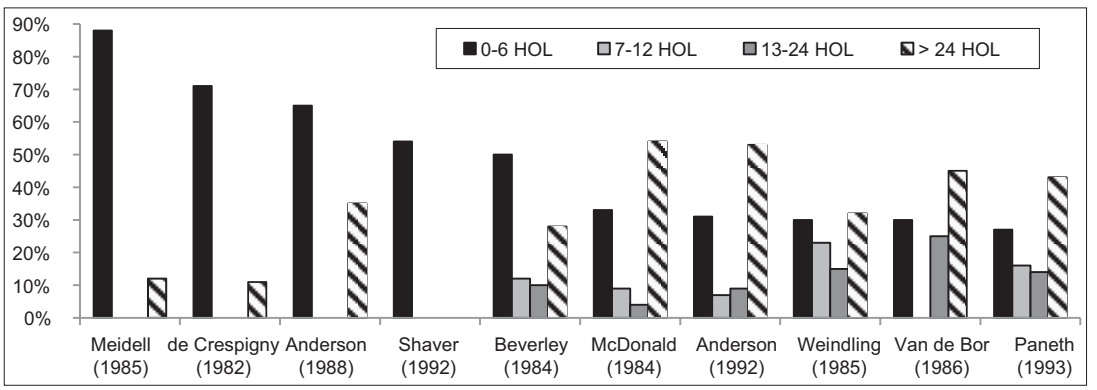

Figure 1: The percent of intraventricular hemorrhage cases that occurred during different hours of life periods in low birth weight neonates

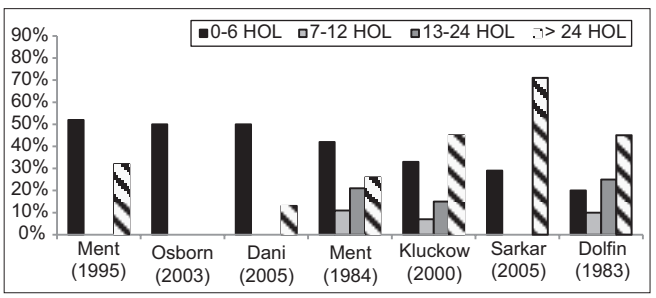

Figure 2: The percent of intraventricular hemorrhage cases that occurred during different hours of life periods in very low birth weight neonates

The prognostic implications

The severity

The available evidence is inconclusive regarding whether the IVHs occurring within the first HOL are more severe initially than the later-occurring IVHs. According to some LBW [Table 1][5] and VLBW studies [Table 2],[3,6,18] both the IVHs occurring within the first HOL and the later-occurring IVHs had the same proportion of IVH grade 3-4 IVH cases. On the contrary, in other studies, the IVHs occurring within the first HOL had a significant less proportion of grade 3-4 IVH cases than the later-occurring IVHs in both LBW [Table 1][15,17] and VLBW population [Table 2].[20,21]

The progression to a higher grade

The risk of IVH progression is inversely related to the timing of the IVH occurrence in both LBW and VLBW preterm neonates. It has been demonstrated that a significant portion of the grade 1 or grade 2 IVH cases occurring within the first HOL progress to a higher grade.[5,8,14,15,17,18,21,22,24,37] This may account for the greater observed mortality risk associated with IVH that occurs within the first HOL.[18,22,37]

Table 2: Prospective studies evaluating or reporting onset of IVH during the interval censored in very low birth weight neonates

Study (country)	Study characteristics	Result		
Sarkar *et al.* (USA)	Publication year: 2005	IVH incidence: 17 (27%)		
	N=62	HUS age	Number (%) IVH	Volpe grade
	GA: 23.4-28.6 weeks (26.2±1.6)	15-30 min	5 (29)	2 bilateral grade 1
	BW: 386-1405 g (884±271)			1 bilateral grade 2
				2 bilateral grade 3
		24 to>72 HOL	12 (71)	2 bilateral grade 2
				1 unilateral grade 4
				1 bilateral grade 4
				8 not reported
		Early IVH defined as IVH occurring within 72 HOL		
Osborn *et al.* (Australia)	1998-1999 cohort	IVH incidence: 38 (30%)		
	N=128	HUS age	Number (%) IVH	Papile grade
	Mean GA: 26.8 weeks	3 HOL	19 (50) (defined as early IVH)	13 grade 1
	Mean BW: 988 g			4 grade 2
				1 grade 3
				1 grade 4
		>3	19 (50)	6 grade 1
				3 grade 2
				1 grade 3
				9 grade 4
Kluckow (Australia)	1995-1996 cohort	IVH incidence: 27 (21%)		
	N=126	HUS age	Number (%) IVH	Papile grade
	Mean GA: 27 weeks (23-29)	5 HOL	9 (33) (defined as early IVH)	7 grade 1
	Mean BW: 991 g (420-1630)			1 grade 2
				1 grade 4
		6-12	2 (7)	4 grade 1
				3 grade 2
				4 grade 3
				7 grade 4
		13-24	4 (15)	
		25-48	12 (45)	
Ment *et al.* (USA)	Study period: 1982-1983	IVH incidence: 19 (61%)		
	N=31	HUS age	Number (%) IVH	Papile grade
	Mean GA: 28.3 weeks (25-33)	<6 HOL	8 (42) (defined as early IVH)	2 grade 1
	Mean BW: 981 g (600-1250)			5 grade 2
				1 grade 3
		7-18	2 (11)	Not reported
		19-30	4 (21)	
		31 to>120	5 (26)	
		No significant relation between the time of the first IVH and its initial severity		
Dolfin (Canada)	Study period: 1981-1982	IVH incidence: 20 (31%)		
	N=64	HUS age	Number (%) IVH	Papile grade
	GA<32 weeks	6 HOL	4 (20)	No significant relation between the time of IVH and its severity
	BW<1500 g			
		7-12	2 (10)	
		13-24	5 (25)	
		25-27	9 (45)	

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Table 2: Contd....

Study (country)	Study characteristics	Result		
Ment *et al.* (USA)	Multicenter trial of indomethacin prophylaxis for IVH Study period: 1989-1992 *N*=505 GA: 27.8±1.8 weeks Mean BW: 940 (600-1250)	IVH incidence: 138 (27.3%)		
		HUS age	Number (%) IVH	Papile grade
		<6 HOL	72 (52)	33 grade 1 31 grade 2 3 grade 3 5 grade 4
		6-24	22 (16)	Placebo group 13 grade 1 16 grade 2 1 grade 3 10 grade 4
		24 to>96	44 (32)	
		Early IVH defied as IVH occurring within 11 HOL		
Dani *et al.* (Italy)	Publication year: 2005 A multicenter trial of ibuprofen prophylaxis for IVH *N*=175 GA<28 weeks	IVH incidence: 59 (34%)		
		HUS age	Number (%) IVH	Papile grade
		≤6 HOL	29 (50)	9 grade 1 20 grade 2
		7-24	22 (37)	Placebo group 5 grade 2 5 grade 3 3 grade 4
		25-168	8 (13)	

IVH – Intraventricular hemorrhage; GA – Gestational age; HUS – Head ultrasound; HOL – Hours of life; BW – Birth weight

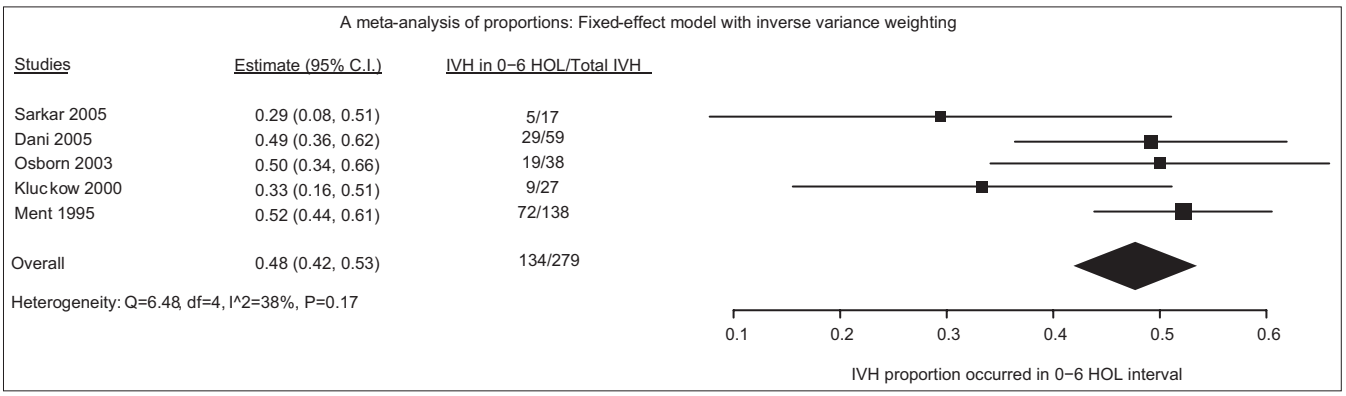

Figure 3: Forest plot of intraventricular hemorrhage proportion occurred during 0-6 h of life interval in very low birth weight neonates

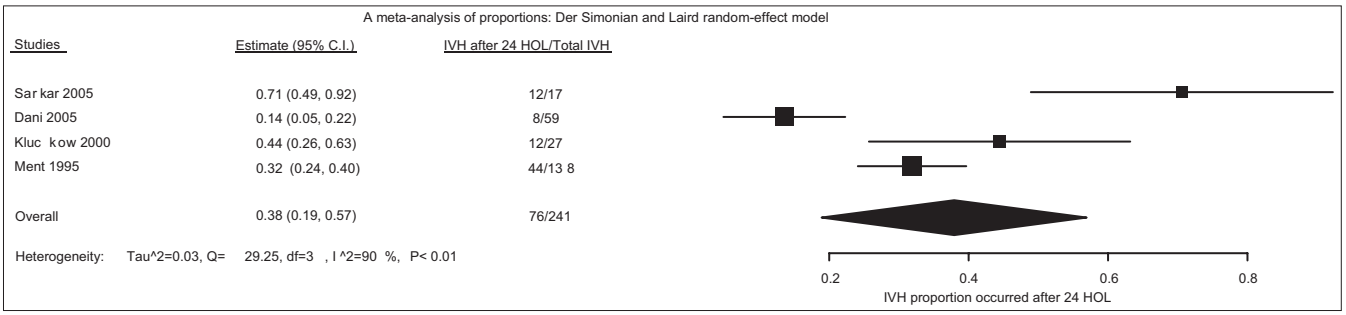

Figure 4: Forest plot of intraventricular hemorrhage proportion occurred after 24 h of life interval in very low birth weight neonates

A small study on LBW preterm neonates from 1984 reported that progressed cases of IVH occurred at an earlier median HOL compared with non-progressed cases of IVH (35 vs. 48 HOL).[38] Another old report on LBW preterm neonates concluded that the majority of 20 IVH cases that were identified within the first 8 HOL progressed to

a higher grade.[22] The exact number of IVH cases that progressed was not provided in this report. Meidell *et al*. found that in LBW preterm neonates 60% (9/15) of the IVH grade 1 cases identified at a mean of 2 HOL progressed to a higher grade by 3 DOL.[14] Shaver *et al*. found that in LBW preterm neonates 48% (13/27) of the IVH grade 1 identified at ≤1 HOL progressed to grade 2-3 versus 20% (3/15) of the same IVH grade identified at >1 HOL progressed to grade 2-3 ($P = 0.07$).[5] They found that 75% (12/16) of the IVH grade 2 identified at ≤1 HOL progressed to a higher grade, whereas only 31% (9/29) of the same IVH grade identified at >1 HOL progressed ($P = 0.005$).[5]

A report on VLBW neonates from 1984 concluded that cases of grade 1 IVH identified at a median of 12 HOL were more likely to progress than those identified at a median of 42 HOL.[24] The exact number of IVH cases that progressed was not provided in this report. One trial involving the use of indomethacin prophylaxis as an IVH prevention in VLBW neonates found that 63% (10/16) of the grade 1 IVH cases in the placebo group that were identified at 6 HOL progressed to grade 2 in five, grade 3 in four and grade 4 in one case.[8] Another trial involving the use of ibuprofen prophylaxis as an IVH prevention in VLBW neonates found that 44% (4/9) of the grade 1 IVH cases identified within 6 HOL progressed to a higher grade; three progressed to grade 2 and one case to grade 3.[21] Another study demonstrated that 5 of 6 (83%) IVH cases identified within the first 6 HOL in VLBW neonates and had repeated HUS progressed, in which three of them progressed to IVH grade 4, whereas none of the 11 IVH cases identified after 6 HOL progressed.[18] This study showed that IVH cases identified within the first 6 HOL had a significantly higher mortality rate than IVH cases identified after 6 HOL (6/8 [75%] vs. 2/11 [18%], $P = 0.04$).[18] A considerable number of IVH that were identified among two different cohorts of Australian VLBW preterm neonates at 5 (1995-1996 cohort) and 3 (1998-1999 cohort) HOL progressed to higher grades.[15,17] The total rate of IVH progression was 30% (3/9) among the 1995-1996 cohorts. Two of the seven (28%) of IVH grade1 progressed to grade 2 and the IVH grade 2 case progressed to grade 3 among the 1995-1996 cohorts.[17] The total rate of IVH progression was 37% (7/19) among the 1998-1999 cohorts.[15] Thirty eight percent (5/13) of IVH grade 1 progressed to a higher grade among the 1998-1999 cohorts. The proportion of IVH grade 3-4 among the IVH cases identified at 3 HOL was 11% (2/19) then subsequently increased to 37% (7/19).[15] Cerebral hypoperfusion may have contributed to the observed IVH progression as the superior vena cava flow was low in all three progressed IVH cases and normal in all the 6 non-progressed IVH cases in the 1995-1996 cohort.[17] The superior vena cava flow was low in 4 of the 7 progressed IVH cases in the 1998-1999 cohort.[15] Ment *et al*. in their study have reported that the proportion of IVH grade 3-4 among IVH cases identified during the first 5-11 HOL increased from 9% (4/43) to 28% (12/43) at 21 DOL in a preliminary report on 229 of 505 neonates enrolled in a multicenter trial investigated the use of indomethacin prophylaxis to prevent IVH.[37]

The neurological outcomes

A secondary report from the above-mentioned trial of Ment *et al*. is the only report that we are aware of that has addressed the long-term neurological outcomes of IVH occurring within the first 5-11 HOL.[39] The study included 29 neonates with IVH identified at 5-11 HOL and the controls were a combination of 32 neonates with IVH identified after 11 HOL and 217 neonates with no IVH. The report demonstrated that the neurological outcomes at 3 years corrected for age for patients with IVH were worse than those observed in the controls. This result is axiomatic as 87% (217/249) of controls had no IVH at any time. Unfortunately, the small numbers of early and late IVH cases preclude a meaningful comparison of the neurological outcomes of these IVH cases.

Nevertheless, the comparisons between the severity, progression and the short- and long-term outcomes of the IVH cases that were identified within the first HOL and those that were identified later were not the primary objective of the above cited studies.

The etiological/preventive implications

Early and late IVH may have both common and different antecedents.[15,17,18,25,27,40,41] A growing body of literature has shown that certain perinatal antecedents are related to IVH occurring within the first HOL but not to IVH occurring later on.[15,18,22,28,42-44] Several reports suggest that early IVH is associated with a longer duration of the active phase and total labor compared with late IVH.[5,12,14,26] A study by Meidell *et al*. found that a total labor duration of more than 12 h is inevitably associated with IVH identified at a mean of 2 HOL.[14] Other researchers have shown that grade 1 IVH identified within the first 12 HOL is associated with active labor.[26] Similarly, another group of researchers found that the occurrence of IVH during the first 1 HOL was increased in neonates of women who went through the active phase of labor.[5,12] Unexpectedly, these same investigators did not observe this association in a secondary report that included neonates delivered by caesarian section only; however, they did observe that the active phase of labor is associated with the progression of the hemorrhage.[13] Based on a multivariable analysis this group of researchers proposed that cesarian section or forceps delivery may attenuate the effect of active-phase labor.[5]

Similarly, four additional reports suggested that cesarean section is protective against IVH identified in the

first 1-11 HOL.[12,15,17,20] Using a multivariable analysis, three of these reports concluded that cesarean section was independently associated with a lower risk of such IVH.[15,17,20] One of these reports included two different cohorts of Australian preterm neonates and found no association between the mode of delivery and IVH occurring after 5 HOL in either cohort.[15] Two small studies found no association between the mode of delivery and IVH occurring in the first HOL.[14,41] Together, these observations support the notion that the protective effect of a cesarean section may be strongest for IVH occurring within the first HOL rather than later on.[45]

Medicolegal implications

The IVH occurring within the first 12 HOL is more strongly associated with perinatal hypoxic-ischemic events than the later onset IVH.[1,25,26,41] Perhaps documentation of the IVH status within the first HOL is a surrogate for perinatal hypoxic-ischemic events in preterm labors as these events are difficult to diagnosis based on intrapartum fetal monitoring, cord pH, Apgar score, or clinical findings.[46-49]

PROPOSED DEFINITION OF EARLY-ONSET IVH

There has been inconsistency in defining the term "early IVH" in the literature [Tables 1 and 2]. The term "early IVH" has been used to refer to IVH occurring as early as the first HOL and as late as the first 10 DOL.[4,50-52] We propose that early IVH is an IVH that occurs within the first 6 HOL for three reasons. First, this period is the earliest mode of the bimodal distribution of IVH timing. Second, it is the shortest, most vulnerable period of time for IVH because it includes about 50% of the IVH cases [Figures 1-3]. Third, it is less vulnerable to postnatal intervention bias.[53,54]

GUIDELINES FOR CLINICAL PRACTICE

A high percentage of IVH is clinically silent.[1,3,23] Thus, there is universal consensus that all preterm neonates born at <30 weeks gestation or a birth weight of <1500 g should have a routine screening HUS. However, the timing of the first routine screening HUS varies widely ranging from the first 6-12 HOL[36,55,56] to the 2nd week of life.[50,57-64] Given the important prognostic and medicolegal aspect of early IVH and the fact that about 50% of IVH cases occur within the first 6 HOL, we recommend that the first routine screening HUS to be performed at about 6 HOL. A portable user-friendly ultrasound machine that can be operated by physicians is affordable and has been proven to be reliable.[6,65] Japanese researchers were able to perform continuous HUS monitoring 25 years ago.[2,66] Continuous HUS monitoring can be accomplished by using a hands-free ultrasound system, including ultrasound probe holders.

IMPLICATIONS FOR RESEARCH

According to Hill, when trying to determine the cause and effect, temporality plays a key role.[67-69] Thus, temporal intervals used in a study are critical; "the shorter the temporal and spatial interval, the less room for confounders to interfere".[69] Therefore, linking perinatal antecedents such as the mode of delivery to the cases of IVH that occurred after the first 6 HOL is not sensible because multiple confounders may have interfered. Similarly, logic dictates that temporality cannot be assumed for the postnatal antecedents in studies where the first HUSs were performed after the first 6 HOL because about 50% of IVH cases occur within the first 6 HOL [Figures 1-3]. Therefore, future research using a continuous HUS monitoring or shorter temporal interval is required to explore the antecedents of IVH. Analyzing early IVH separately from late IVH will reduce the observed inconsistency and more effectively delineate additional antecedents of IVH.[15,45] Future research is required to elucidate whether the long-term neurological outcomes of early and late IVH are the same. A large-scale study is required to elucidate whether the severity of early and late IVH are the same. A more precise assessment of the severity can be accomplished by using an IVH severity score.[70]

SUMMARY

The 0-6 and after 24 HOL were the major modes of IVH timing. The first 6 HOL is the shortest, most vulnerable period of time for a neonate with respect to IVH. We propose that early IVH is an IVH that occurs within the first 6 HOL. Documentation of the early IVH status has important prognostic and medicolegal implications. Thus, we recommend that the first routine screening HUS to be performed at about 6 HOL for all preterm neonates at risk of IVH. Future research exploring the antecedents of IVH should guaranty the temporality between these antecedents and IVH. Additional research will be required to determine whether the long-term neurological outcomes of early and late IVH are the same.

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How to cite this article: Al-Abdi SY, Al-Aamri MA. A systematic review and meta-analysis of the timing of early intraventricular hemorrhage in preterm neonates: Clinical and research implications. J Clin Neonatol 2014;3:76-88.

Source of Support: Nil, **Conflict of Interest:** None declared.

APPENDIX: EXCLUDED STUDIES

Study (study country)	Study characteristics	Resulttt	
Gupta *et al.* (India)[1]	Study period: June-Sep1991	IVH incidence: 33 (22%)	
	N=150	HUS age	Number (%) IVH
	GA: 27-34 weeks (31.24±3.19)	At mean 10 HOL	17 (52)
		DOL 2	8 (24)
		3	3 (9)
		4	5 (15)
Morgan and Cooke (UK)[2]	Study period: 1981	IVH incidence 97 (33%); of which 90 was timed to a 12-h period	
	N=290	HUS age	Number (%) IVH
	BW<1500 g (*N*=181)	<12 HOL	17 (19)w
		13-24	13 (14)
		25-48	28 (31)
		>48	32 (36)

Contd...

APPENDIX: Continued

Study (study country)	Study characteristics	Resulttt		
Szymonowicz and Yu (Australia)[3]	Publication year: 1984	IVH incidence: 30 (60%)		
	N=50	HUS age	Number (%) IVH	
	GA: 24-32 weeks (27±4)	12 HOL	15 (50)	
	BW: 430-1250 g (888±204)	13-24	4 (13)	
		25-96	11 (37)	
Pagano *et al.* (USA)[4-6]	Multicenter trial of phenobarbital prophylaxis for IVH	IVH incidence: 125 (27%)		
	Study period: 1981-1984	HUS age	Number (%) IVH	Papile grade
	N=328	12 HOL	48 (38) (defined as early IVH)	27 grade 1
	BW<1750 g			21> grade 1
		≥12	77 (62)	Placebo group
				7 grade 1
				11 grade 2
				8 grade 3-4
Perlman and Volpe (USA)[7]	Study period: 1982-1985	500-700 g IVH incidence: 34 (62%)		
	BW: 500-700 g (*N*=55)			
	BW: 701-1000 g (*N*=120)	HUS age	Number (%) IVH	
	BW: 1001-1500 g (*N*=246)	18 HOL	21 (62)	
		19-72	7 (20)	
		>72	6 (18)	
		701-1000 g IVH incidence: 39 (33%)		
		HUS age	Number (%) IVH	
		18 HOL	7 (18)	
		19-72	30 (77)	
		>72	2 (5)	
		1001-1500g IVH incidence: 52 (21%)		
		HUS age	Number (%) IVH	
		18 HOL	6 (11)	
		19-72	44 (85)	
		>72	2 (4)	
Levene *et al.* (UK)[8]	Publication year: 1981	IVH incidence: 16 (32%)		
	N=50	HUS age	Number (%) IVH	
	BW: ≤1000-4000 g	<24 HOL	5 (31)	
		24-48	6 (38)	
		49-72	1 (6)	
		4-6 DOL	1 (6)	
		7-10 DOL	3 (19)	
Levene *et al.* (UK)[9]	Study period: 1979-1981	IVH incidence 52 (36%); of which 41 had accurate timing of IVH		
	N=146	HUS age	Number (%) IVH	
	GA: 27-34 weeks (median 31)	<24 HOL	10 (24)	
	BW: 705-2920 g (median 1390)	24-48	11 (27)	
		3 DOL	11 (27)	
		4	3 (7)	
		5	4 (10)	
		6	1 (2)	
		7	1 (2)	
Thorburn *et al.* (UK)[10]	Study period: 1979	IVH incidence: 36 (38%); of which only 30 IVH had satisfactory timing		
	N=95			
	GA: 23-32 weeks (median 30)			
	BW: 540-2500 g (median 1252)			
	Inborn: 42 %			

Contd...

APPENDIX: Continued

Study (study country)	Study characteristics	Resulttt		
		HUS age	Number (%) IVH	Papile grade
		<1 DOL	12 (40)	6 grade 1 4 grade 2 2 grade 3
		1	4 (13)	3 grade 1 1 grade 2
		2	8 (27)	6 grade 1 1 grade 2 1 grade 4
		3	5 (17)	3 grade 1 2 grade 2
		4-5	Zero	Grade 1
		6	1 (3)	
		7-9	Zero	
Partridge et al. (USA)[11]	Study period: 1979-1980	IVH incidence: 35 (55%)		
	N=64	HUS age	Number (%) IVH	
	GA: 24-33 weeks (mean 29)	<1 DOL	23 (66)	
	BW:580-1480 g (mean 1113)	4	9 (26)	
	All outborns	7	2 (5)	
		14	1 (3)	
Perlman and Volpe (USA)[12]	Study period: 1980-1981	IVH grade 1-3 incidence: 36 (36%); of which timing of 4 IVHs was not reported		
	N=100	HUS age	Number (%) IVH	Volpe grade
	BW<1500 g	<24 HOL	15 (47)	1 grade 1 10 grade 2 4 grade 3
		24-48	7 (22)	1 grade 1 3 grade 2 3 grade 3
		49-72	8 (25)	1 grade 1 3 grade 2 4 grade 3
		73-96	2 (6)	1 grade 2 Grade of the second IVH was missing
Bada *et al.* (USA)[13]	Study period: 1981-1982	IVH incidence: 122 (79%)		
	N=155	HUS age	Number (%) IVH	Papile grade
	GA: 30.6±2.2 weeks	24 HOL	85 (70) (defined as early IVH)	69 grade 1-2 16 grade 3-4
	BW ≤1500 g (1077±275)	>24 HOL	37 (30)	34 grade 1-2 1 grade 3-4
Amato *et al.* (Switzerland)[14]	Study period: 1987-1988	IVH incidence: 15 (30%)		
	N=50	HUS age	Number (%) IVH	
	GA: 26-34 weeks	<24 HOL	2 (13)	
	BW: 780-1480 g	24-48	3 (20)	
		49-72	9 (60)	
		73-96	1 (7)	
Babnik *et al.* (Slovenia)[15]	Study period: 2000-2002	IVH incidence: 46 (37%)		
	N=125			
	GA: 23-29 weeks			
		HUS age	Number (%) IVH	Papile grade
		<1 DOL	25 (54) (defined as early IVH)	18 grade 1 4 grade 2 1 grade 3 2 grade 4

Contd...

APPENDIX: Continued

Study (study country)	Study characteristics	Resulttt		
		>1 DOL	21 (46)	10 grade 1-2 5 grade 3 5 grade 4
Meek *et al.* (UK)[16]	Publication year: 1999	IVH incidence: 7 (29%)		
	N=24	HUS age	Number (%) IVH	
	GA: 24-31 weeks (median 26)	1 DOL	2 (29)	
	BW: 620-1470 g (median 873)	2	4 (57)	
		3	1 (14)	
Kadri *et al.* (Syria)[17]	Study period: 2002	IVH incidence: 126 (45%)		
	N=282	HUS age	Number (%) IVH	
	GA<37 weeks (84<30 weeks)	1 DOL	15 (12)	
		2	18 (14)	
		3	16 (13)	
		4	14 (11)	
		5	17 (13)	
		6	14 (11)	
		7	13 (10)	
		1 week	11 (9)	
		2 weeks	5 (6)	
Rashid *et al.*(Pakistan)[18]	Study period: 2007-2008	IVH incidence: 15 (15%)		
	N=100	HUS age	Number (%) IVH	
	GA: 32.4±1.8 weeks	1 DOL	11 (73)	
	BW: 1600±1100 g	2	2 (13)	
		3	1 (7)	
		4	Zero	
		5	Zero	
		6	1 (7)	

GA – Gestational age; BW – Birth weight; IVH – Intraventricular haemorrhage; HUS – Head ultrasound; HOL – Hours of life; DOL – Day of life

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