ORIGINAL ARTICLE

A Follow-up Study of Infants with Intracranial Hemorrhage at Full-Term

Balraj S. Jhawar, Adrianna Ranger, David A. Steven, Rolando F. Del Maestro

ABSTRACT: ***Objective:*** To determine physical and cognitive outcomes of full-term infants who suffered intracranial hemorrhage (ICH) at birth. ***Methods:*** A retrospective hospital-based, follow-up study of infants treated in London, Ontario between 1985 and 1996. Follow-up was conducted by telephone interviews and clinic visits. Outcome was measured according to physical and cognitive scales. Perinatal risk factors and hemorrhage characteristics were correlated with final outcome. ***Results:*** For this study 66 infants with ICH were identified, of which seven died during the first week of life. We obtained follow-up in all but ten cases (median = 3-years; range 1.0 to 10.9 years). Overall, 57% of infants had no physical or cognitive deficits at follow-up. Death occurred most frequently among those with primarily subarachnoid hemorrhage (19%) and the most favorable outcomes occurred among those with subdural hemorrhage (80% had no disability). In univariate models, thrombocytopenia (platelet count $\leq$ 70 x 10^9/L), increasing overall hemorrhage severity, frontal location and spontaneous vaginal delivery as opposed to forceps-assisted delivery increased risk for poor outcome. In multivariate models, all these factors tended towards increased risk, but only thrombocytopenia remained significant for physical disability (OR = 7.6; 95% CI = 1.02 – 56.6); thrombocytopenia was borderline significant in similar models for cognitive disability (OR = 4.6; 95% CI = 0.9 – 23.9). ***Conclusion:*** Although forceps-assisted delivery may contribute to ICH occurrence, our study found better outcomes among these infants than those who had ICH following a spontaneous vaginal delivery. Hemorrhage in the frontal lobe was the most disabling hemorrhage location and if multiple compartments were involved, disability was also more likely to occur. However, in this report we found that the factor that was most likely to contribute to poor outcome was thrombocytopenia and this remained important in multivariate analysis.

RÉSUMÉ: Suivi de nourrissons à terme présentant une hémorragie intracrânienne. ***Objectif:*** Déterminer l'issue physique et cognitive chez des nourrissons nés à terme qui ont subi une hémorragie intracrânienne (HIC) à la naissance. ***Méthodes:*** Il s'agit d'une étude rétrospective de suivi hospitalier de nourrissons traités à London, Ontario, entre 1985 et 1996. Le suivi a été fait au moyen d'entrevues téléphoniques et de visites à la clinique. L'issue était évaluée au moyen d'échelles physiques et cognitives. Les facteurs de risque périnataux et les caractéristiques de l'hémorragie ont été corrélés à l'issue finale. ***Résultats:*** Soixante-six nourrissons ayant subi une HIC ont été identifiés, dont sept sont morts dans la première semaine de vie. Nous avons obtenu des informations sur cinquante-six enfants (âge médian de 3 ans; écart de 1,0 à 10,9 ans). Au moment du suivi, 57% des enfants n'avaient pas de déficit physique ou cognitif. 19% des enfants ayant subi une hémorragie sous-arachnoïdienne sont morts. L'issue la plus favorable a été observée chez ceux qui avaient subi une hémorragie sous-durale (80% n'avaient pas de déficit). À l'analyse univariée, la thrombocytopénie (décompte plaquettaire $\leq$ 70 x 10^9/L), la sévérité de l'hémorragie, la localisation frontale et un accouchement vaginal spontané plutôt qu'avec forceps augmentaient le risque d'une issue défavorable. À l'analyse multivariée, tous ces facteurs indiquaient un risque accru, mais seulement la thrombocytopénie demeurait un facteur significatif de l'invalidité physique (rapport de cotes 7,6 ; IC à 95% de 1,2 à 56,6) et était limite pour le déficit cognitif (rapport de cotes 4,6; IC à 95% de 0,9 à 23,9). ***Conclusion:*** Bien que l'accouchement avec forceps puisse contribuer à l'HIC, l'issue était meilleure chez ces nourrissons que chez ceux qui avaient subi une HIC à la suite d'un accouchement vaginal spontané. L'HIC au lobe frontal était la plus invalidante et, si plusieurs compartiments étaient touchés, une invalidité était plus probable. Cependant, dans cette étude, le facteur qui contribuait le plus à une issue défavorable était la thrombocytopénie et ceci demeurait important à l'analyse multivariée.

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Although it is well-known that about 15% of very-low birth weight infants (less than 1500 grams) suffer intracranial hemorrhage (ICH) around the time of birth,[1,2] it is less well-recognized that ICH also occurs to infants born at term. In one study where ultrasonography was performed in 505 healthy term infants, 4.6% demonstrated sonographic abnormalities consistent with hemorrhage.[3] In a larger study of 1,000 infants,[4] in addition to 34 cases of ICH, 21 infants demonstrated abnormalities that may have been the result of previous hemorrhage (such as subependymal and choroid plexus pseudocysts). When more sensitive imaging such as computed tomogram (CT) or magnetic resonance imaging (MRI) is used, the prevalence of hemorrhage

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appears to rise.[5,6] The issue is further complicated by the influence of mode of delivery on the occurrence of hemorrhage, as a number of studies now suggest that the use of forceps,[7,8] cesarean section during labor,[8] and vacuum extraction[8] increases the risk of ICH by several-fold[8] relative to spontaneous vaginal delivery. In one study of ten infants that had vacuum extraction to assist delivery, CT scanning demonstrated evidence of hemorrhage in the area of the tentorium in every case.[6]

If ICH in full-term infants is a fairly common occurrence, then the central question that arises is which types of hemorrhage are clinically significant. In the premature group, current evidence suggests that these infants grow to attain smaller stature, suffer more chronic illnesses, have lower IQ scores and are less likely to complete high school than age matched controls.[9] Furthermore, neurological sequelae such as seizures, hydrocephalus, blindness, and developmental delay may also occur at higher rates than would normally be expected.[10-12] Corresponding data for full-term infants that have suffered intracranial hemorrhage (ICH) remains largely unavailable and the long-term outcome of this group of infants is poorly documented.

In this report, we set out to determine the outcome of infants who were born at term and who were diagnosed with ICH within the first week of life. We utilized data that were available to us from Southwestern Ontario between 1985 and 1996. Our goal was to systematically categorize infants according to functional status at the most recent available follow-up. We also wanted to determine whether extent and location of hemorrhage affected prognosis and whether thrombocytopenia, indicators of hypoxia (Apgar scores and the requirement for resuscitation) and the use of forceps instrumentation also influenced prognosis.

Participants and Methods

Study Population

In our previous report we studied a series of full-term infants for risk factors related to ICH and compared this group to matched controls.[13] In this report we utilized the same cases, but followed them over time to determine standardized outcomes.

Our cases consisted of full-term infants (gestational age greater than or equal to 37 weeks) born in London, Ontario and its referral hospitals during the period January 1, 1985 to December 31, 1996 who suffered ICH. Our centre includes two major delivery units (St Joseph's Health Sciences Centre and London Health Sciences Centre, Victoria Campus), with separate neonatal and pediatric intensive care units.

Defining Cases

Cases of intracranial hemorrhage were identified retrospectively based on ICD-9 classification codes. We separately searched the codes for subarachnoid (SAH), subdural (SDH), epidural (EDH), intraventricular (IVH), and intraparenchymal hemorrhage (IPH) and confined our query to those cases diagnosed prior to the first year of life. After reviewing records, we excluded infants born prior to 37 weeks of gestational age and those diagnosed after one week of age. Two investigators then confirmed and corroborated the diagnosis of each case by reviewing all original imaging studies and autopsy reports prior to the collection of information about risk factors (hypoxia, coagulopathy, delivery mode, etc). Our final case definition required that cases have their diagnosis confirmed by imaging (CT, MRI, or ultrasound) or autopsy within seven days of birth.

Hemorrhage Type and Severity

We reviewed all available imaging studies directly and classified each hemorrhage according to location (frontal lobe, parietal lobe, temporal lobe, occipital lobe, and posterior fossa), and compartment (SAH, subdural, epidural, intraventricular and intraparenchymal) for each newborn. Since there was only one epidural hematoma it was added to the subdural hematoma category for the purposes of analysis.

As in our previous report[13] we classified hemorrhage severity in two ways; Overall Hemorrhage Severity and Severest

TABLE 1-A: Most Severe Hemorrhage Type

HEMORRHAGE TYPE		DEFINITION
1	Subarachnoid	Hemorrhage beneath the subarachnoid space
2	Epidural	Hemorrhage between the dura and inner table of the cranium
3	Subdural	Hemorrhage between the brain and dura
4	Intraventricular	Hemorrhage in either the lateral, third, or forth ventricles
5	Intraparenchymal	Hemorrhage within the brain substance

Intraventricular hemorrhage was given high priority as it is thought to arise from important deep parenchymal structures (eg. basal ganglia).
Any patient with multiple types of hemorrhage was classified according to the severest type for this measurement.

TABLE 1-B: Overall Hemorrhage Severity

HEMORRHAGE SEVERITY	DEFINITION
Mild	Hemorrhage involving only one lobe and one compartment[a], with minimal or no mass effect[b]
	Intraventricular hemorrhage in only one ventricle, with no hydrocephalus
Moderate	Hemorrhage involving only one lobe and one compartment, with mass effect
	Intraventricular hemorrhage in more than one ventricle, but no hydrocephalus
Severe	Hemorrhage involving more than one lobe or more than one compartment
	Intraventricular hemorrhage with hydrocephalus

[a] Each compartment is defined as in Table 1-A. [b] Midline shift of 0.5 cm or ventricular effacement.

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TABLE 2-A: PHYSICAL DISABILITY SCALE

Category[C]	Infants and Toddlers (< 4 years)	Children (>= 4 years)
No disability	Normal motor examination	Normal motor examination
Minor disability	Delays in achieving motor developmental milestones, but proceeding well	Changes in motor examination (power, bulk, tone), but ability to ambulate independently without assistance
Major disability	Major or permanent delays in motor developmental milestones	Require assisted ambulation[a]

TABLE 2-B: COGNITIVE DISABILITY SCALE

Category[C]	Infants and Toddlers (< 4 years)	Children (>= 4 years)
No disability	No delay in language developmental milestones	Adequate performance in a school with a mainstream curriculum[b]
Minor disability	Delays in language developmental milestones	Visual or auditory impairments or had limited learning disabilities
Major disability	Major or permanent setbacks in language developmental milestones	Institutionalization, "special" schooling

[a] Wheelchair, braces, assistance from other individuals.
[b] Although individual school records were not obtained, detailed information about particular schools and their various special education programs was requested when necessary.
[c] The four-year point was used as a guideline to distinguish younger from older children.

Hemorrhage Type. Overall Hemorrhage Severity was based on the anatomical extent of intracranial compartment involvement and was an attempt to measure volume of hemorrhage and associated mass effect, while Most Severe Hemorrhage Type attempted to estimate the degree to which brain destruction occurred. The radiological definitions are provided in Tables 1-A and 1-B.

Risk Factor Information

We collected information on a number of risk factors for intracranial hemorrhage based on the review of the literature we carried out in our first report;[13] the details of the data collection methods are provided in that publication. We abstracted information from the medical charts on year-of-birth, head circumference, birth weight, associated skull fracture, platelet counts, international normalized ratio (INR), partial thromboplastin time (PTT), the requirement for resuscitation (no resuscitation, supplementary oxygen or bag-masked ventilation, or intubation), Apgar scores at one and five minutes, mode of delivery (cesarean section, spontaneous vaginal delivery, or forceps-assisted delivery), delivery hospital, and attending obstetrician.

Determination of Outcome

Based on the information obtained from medical records we attempted to contact all infants and their caregivers directly by telephone or through a clinic visit. For those infants that continued to be followed by one of our pediatric neurosurgeons (RFD or AR), we requested a clinic visit to determine outcome. For infants that were no longer followed in our clinic, we contacted caregivers for permission to obtain medical records from their primary care physicians. We also spoke with all caregivers to confirm our final assessment of outcome.

Outcome Scales

We measured the outcomes of infants on physical and cognitive scales because these constructs appear to be the most relevant to patients, caregivers and society. Furthermore, because physical and cognitive impairments often occur independently, reflecting varying levels of injury to the central nervous system, we felt that separate measures would more accurately capture the full extent of functional impairment. Although a number of sophisticated instruments have been developed to determine outcome along these axes, most of these tools are limited to older age groups or request lengthy personal interviews and extensive examination of developmental milestones. In our study, we were limited in our ability to contact patients and families primarily because of large geographical distances.

For this study we wanted all children to be evaluated by the same instruments regardless of age. Consequently we constructed our own measures that utilized broad and reproducible definitions of physical and cognitive impairment that posed questions that were easy to understand for non-healthcare professionals (caregivers and older children). In order to minimize missing information and to avoid misclassification we elected to categorize disability according to a four-tiered system (no disability, minor disability, major disability, and death). The criteria for each category of these physical and cognitive disability scales are provided in Table 2-A and 2-B and all outcomes were determined by one physician (BSJ).

Statistical Analysis

Apgar scores at one- and five-minutes were dichotomized at the median value. We dichotomized platelet count at 70 x 10^9 /L because this cut-off is clinically meaningful (below this level the American Red Cross suggests that neurosurgical procedures require platelet transfusion).

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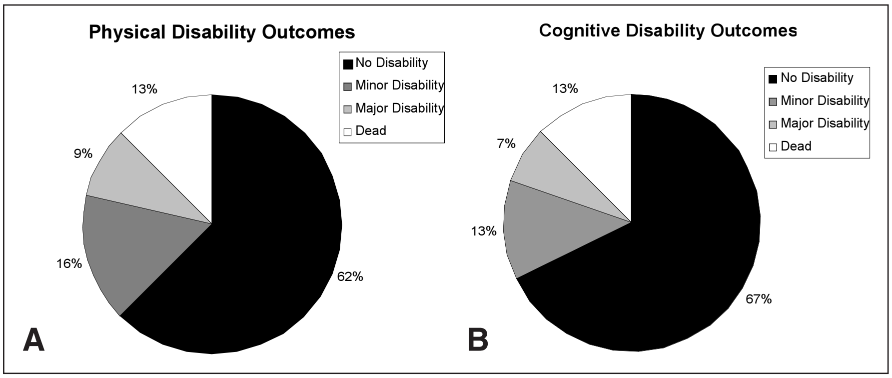

Figure 1A: *Physical Disability Outcomes* ***Figure 1B:*** *Cognitive Disability Outcomes*

Dichotomous risk factors were compared with disability outcomes using Fisher's Exact test. Continuous outcomes were compared between groups using Student's t-test. Cognitive and physical disability, *Overall Hemorrhage Severity*, and *Severest Hemorrhage Type* were modeled as ordinal categorical variables. To estimate the association between risk factors and the polytomous outcomes (cognitive and physical disability) we used multinomial ordinal logistic regression assuming proportional odds. All tests of significance were two-sided and at the 5% level. Stata version 6.0 was used for statistical analysis.

Results

Study Population

From 1985 to 1996, sixty-six infants were diagnosed with intracranial hemorrhage at the London Health Sciences Centre

TABLE 3: Distribution of Physical and Cognitive Outcomes according to Risk Factors

RISK FACTOR	(n)	COG / PHYS Norm / Norm	COGNITIVE OUTCOME Normal	Minor	Major	PHYSICAL OUTCOME Normal	Minor	Major	MORTALITY Death
Primary Hemorrhage Type[a,e]									
IPH	17	47%	65%	12%	12%	47%	24%	18%	12%
SAH	16	56%	63%	13%	6%	63%	19%	0%	19%
IVH	13	54%	69%	15%	8%	69%	15%	8%	8%
EDH / SDH	10	80%	80%	10%	0%	80%	0%	10%	10%
Platelets[b]									
≤ 70 x 10^9 /L	15	33%	47%	20%	7%	40%	20%	13%	27%
> 70 x 10^9 /L	28	71%	75%	11%	7%	79%	4%	11%	7%
One-Minute Apgar[c]									
1 - 6	38	61%	66%	13%	8%	66%	11%	11%	13%
7 - 10	18	24%	72%	11%	6%	56%	28%	6%	11%
Five-Minute Apgar[c]									
1 - 8	29	55%	62%	14%	7%	62%	10%	10%	17%
9 - 10	27	59%	74%	11%	11%	63%	22%	7%	7%
Resuscitation									
Required Resuscitation	29	52%	59%	10%	14%	55%	14%	14%	17%
Intubation	17	53%	65%	12%	12%	59%	12%	18%	12%
Bag mask / oxygen	12	50%	50%	8%	17%	50%	17%	8%	25%
No resuscitation	27	63%	78%	15%	0%	70%	19%	4%	7%
			p=0.22			p=0.52			p=0.43
Delivery									
SVD	28	43%	57%	14%	14%	46%	25%	14%	14%
Cesarean Section	2	0%	50%	0%	0%	0%	50%	0%	50%
Forceps	26	77%	81%	12%	0%	85%	4%	4%	8%
Primary Hemorrhage Location[d]									
Frontal	12	25%	42%	25%	8%	33%	33%	8%	25%
Parietal	11	45%	64%	0%	18%	45%	9%	27%	18%
Temporal	9	78%	78%	0%	11%	78%	0%	11%	11%
Occipital	17	53%	59%	18%	6%	59%	18%	6%	18%
Posterior Fossa	7	100%	100%	0%	0%	100%	0%	0%	0%
All Cases	56	57%	68%	13%	7%	63%	16%	9%	13%

[a] - Hemorrhage Type: IPH = Intra-parenchymal; SAH=Subarachnoid; IVH=Intraventricular; SDH= Subdural Hemorrhage.; EDH=Epidural Hemorrhage
[b] - Platelet count was dichotomized at 70 x 10(9) / L. [c] - Apgar Scores were dichotomized at the median value. [d] - Primary hemorrhage location was the single location most affected by brain hemorrhage. [e] - Primary Hemorrhage Type was the single most dominant type of hemorrhage.

TABLE 4: Multinomial Logistic Regression Models for Risk Factors versus Physical and Cognitive Disability Outcomes

		Cognitive Disability[g]				Physical Disability[g]			
		Univariate		Multivariate		Univariate		Multivariate	
RISK FACTOR	**n**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Primary Hemorrhage Type[a]									
IPH	17	2.2	(0.3 - 13.8)	0.7	(0.02 - 22.2)	4.5	(0.7 - 27.8)	0.6	(0.01 - 75.0)
SAH	16	2.4	(0.4 - 15.3)	2.3	(0.2 - 31.4)	2.4	(0.4 - 15.3)	0.97	(0.04 - 23.6)
IVH	13	1.8	(0.3 - 12.4)	1.4	(0.1 - 29.3)	1.8	(0.3 - 12.4)	0.3	(0.004 - 20.5)
EPD / SDH	10	ref	-	ref	-	ref	-	ref	-
Platelet Count[af]									
≤ 70 x 10^9 /L	15	3.4	(0.9 - 12.9)	4.6	(0.9 - 23.9)	5.5	(1.4 - 21.7)	7.6	(1.02 - 56.6)
> 70 x 10^9 /L	28	ref	-	ref	-	ref	-	ref	-
Resuscitation Category[a]									
Required Resuscitation	29	2.5	(0.8 - 8.0)	2.6	(0.5 - 14.2)	1.9	(0.6 - 5.8)	5.6	(0.5 - 64.9)
Intubation	17	1.9	(0.5 - 7.3)	2.7	(0.5 - 15.2)	1.7	(0.5 - 5.9)	5.6	(0.5 - 69.1)
Bag mask / oxygen	12	3.5	(0.8 - 14.9)	2.1	(0.2 - 28.1)	2.4	(0.6 - 9.6)	5.9	(0.1 - 424)
No resuscitation	27	ref	-	ref	-	ref	-	ref	-
One-Minute Apgar[ae]									
1 - 6		0.9	(0.3 - 2.8)	0.7	(0.1 - 6.0)	0.6	(0.2 - 1.7)	0.3	(0.02 - 5.9)
7 - 10		ref	-	ref	-	ref	-	ref	-
Five-Minute Apgar[ae]									
1 - 8	29	1.7	(0.6 - 5.5)	2.7	(0.4 - 20.2)	1.03	(0.4 - 3.1)	3.4	(0.3 - 35.3)
9 - 10	27	ref	-	ref	-	ref	-	ref	-
Delivery[a]									
Cesarean Section	2	1.3	(0.1 - 23.5)	1.9	(0.1 - 62.0)	***	-	***	-
Forceps	26	0.3	(0.1 - 1.1)	0.3	(0.03 - 303)	0.2	(0.04 - 0.6)	0.1	(0.004 - 3.0)
Spontaneous Vaginal	28	ref	-	ref	-	ref	-	ref	-
Overall Hemorrhage Severity[b c]	-	1.5	(0.7 - 2.9)	2.0	(0.5 - 7.8)	2.1	(1.0 - 4.1)	5.9	(0.6 - 53.7)
Severest Hemorrhage Type[b d]	-	1.2	(0.7 - 1.9)	0.5	(0.1 - 2.0)	1.5	(0.9 - 2.6)	0.8	(0.1 - 4.9)
Primary Hemorrhage Location[bh]									
Frontal	12	7.3	(1.5 - 34.4)	5.7	(0.5 - 60.2)	8.8	(1.7 - 45.0)	1.6	(0.02 - 95.6)
Parietal	11	1.6	(0.3 - 7.5)	1.2	(0.2 - 9.2)	3.4	(0.8 - 15.3)	1.9	(0.1 - 29.7)
Temporal	9	0.4	(0.1 - 3.0)	0.1	(0.01 - 2.4)	0.3	(0.03 - 1.9)	0.03	(0.0002 - 3.7)
Occipital	17	2.9	(0.7 - 11.9)	1.7	(0.2 - 17.4)	2.0	(0.5 - 8.2)	0.3	(0.01 - 14.6)
Posterior Fossa	7	ref	-	ref	-	ref	-	ref	-

[a] - Multivariate odds ratios in these models controlled for primary hemorrhage type, platelet count, resuscitation category, one- and five-minute Apgar scores and mode of delivery (each defined according to the categories in this table). [b] - Multivariate odds ratios in these models controlled for platelet count, resuscitation category, one- and five-minute Apgar scores, Overall Hemorrhage Severity, Severest Hemorrhage Type and primary hemorrhage location each defined according to the categories in this table. [c] - The Overall Hemorrhage Severity category assumed proportional odds between intervals (mild, moderate and severe). [d] - The Severest Hemorrhage Type assumed proportional odds between each increasing hemorrhage severity category. See Table 1-A. [e] - Apgar scores were dichotomized at the median value. [f] - Platelet count was dichotomized at 70 x 10(9)/L. [g] - Proportional odds were assumed between each increasing outcome category of Physical and Cognitive Disability (normal, minor, major and death). [h] - Primary hemorrhage location was the single location most affected by brain hemorrhage. *** model did not converge

and Saint Joseph's Health Centre (61% male). One third of these cases were referred after delivery from outside of London. Computed tomography or magnetic resonance imaging confirmed hemorrhage in 56 cases and in six others only ultrasound was used to establish diagnosis. Reviewing autopsy reports identified four additional cases.

Follow-Up Study

Ten children were lost to follow-up, and all seven deaths occurred within the first week of life. Among survivors, we achieved follow-up at a median age of three years (range 1.0 to 10.9 years). There were no significant differences between cases lost to follow-up and those with complete data with regard to *Overall Hemorrhage Severity* (p=0.69), *Severest Hemorrhage Type* (p=0.88), sex (p=0.97), platelet count (p=0.70) or use of forceps instrumentation (p=0.10).

Descriptive Statistics

Figures 1-A and 1-B graphically depict the distribution of physical and cognitive outcomes of the 56 children at final follow-up. The Pearson correlation coefficient (r=0.89) and the weighted Kappa statistic (Î=0.78) were high between physical and cognitive disability scores, but 18% of infants had dissimilar outcomes suggesting some degree of independence.

In Table 3, physical and cognitive outcomes are depicted according to primary hemorrhage type, platelet counts dichotomized at 70 x 10^9/L, Apgar scores at one- and five-minutes, resuscitation category, mode of delivery and primary hemorrhage location.

The data demonstrate that death occurred most frequently among those infants that suffered primarily subarachnoid hemorrhage (19%), but 56% of the survivors from this group had no evidence of disability. The most favorable outcomes were observed among those infants that had subdural hemorrhage,

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with 80% having no reported disability. The primary hemorrhage type with the greatest proportion of major disability was intra-parenchymal (12% major cognitive and 18% major physical disability).

There was a 20% excess mortality observed among those infants with platelet counts less than 70 x 10^9 /L compared to those with higher counts (p=0.09). Physical and cognitive outcomes were also improved among those with higher platelet counts, but this was only statistically significant for physical disability (p=0.04) with almost twice as many infants being categorized as having “normal” physical function.

Our data on infants born by cesarean section were limited as there were only two cases (one died, while the other suffers from a minor physical disability). When we excluded these infants and compared infants born by spontaneous vaginal delivery to those born with forceps-assistance, we noted better cognitive (p=0.15) and physical (p=0.02) outcomes in the forceps group. Although mortality was less frequent in the forceps group (8%) than the spontaneous vaginally delivered group (14%), this did not reach statistical significance (p=0.67).

There was no statistically significant difference between physical and cognitive outcomes based on Apgar scores dichotomized at the median value at either one- or five-minutes (Table 3). The mortality was 2% higher among those infants with lower one-minute Apgar scores (p=0.43) than those with higher scores, and 10% higher among those with lower five-minute Apgar scores (p=0.43); but neither of these analyses reached statistical significance.

When we compared those infants that required some form of resuscitation to those that did not, we noted a greater likelihood of death (required resuscitation, 17% mortality; did not require resuscitation, 7% mortality; p=0.43). Physical and cognitive outcomes were not statistically different between these groups.

With regard to primary hemorrhage location, suprisingly we observed the most favorable outcomes and no deaths among the seven infants that had posterior fossa hemorrhage. Hemorrhage in the frontal location was most likely to be lethal and least likely to have normal physical and cognitive outcome. The highest frequencies of major physical and major cognitive disability were seen in the parietal location.

Multivariate Analysis

The univariate and multivariate multinomial logistic regression relationships between risk factors and disability outcome are shown in Table 4. The risk factors year-of-birth, head circumference, birth-weight, attending obstetrician, hospital, associated skull fracture, and surgical management are not reported as no significant relationships were noted.

We observed nonsignificant associations between various primary hemorrhage types (IPH, SAH, and IVH compared to the EPD/SDH group) and physical and cognitive outcomes in univariate analyses, but after controlling for other risk factors (platelet count, resuscitation category, one- and five-minute Apgar scores and mode of delivery) no statistically significant relationships were observed.

When we compared those infants that had a platelet count of less than 70 x 10^9 /L with those that had higher counts, a poorer physical outcome was observed over five-times more frequently in the thrombocytopenia group (OR = 5.5, 95% CI = 1.4 – 21.7) and in multivariate analysis, this result was stronger (OR = 7.6, 95% CI = 1.02 – 56.6). With regard to cognitive outcome, having a low platelet count also appeared to be important, but the magnitude of effect was not as intense and the results were only borderline significant (multivariate OR = 4.6; 95% CI = 0.9 – 23.9).

When we compared infants that required intubation or bag mask ventilation / oxygen with those that did not, we found a greater odds of disability in univariate models (cognitive disability, OR = 2.5, 95% CI = 0.8 – 8.0; physical disability, OR=1.9, 95% CI = 0.6 – 5.8). In multivariate models the magnitude of effect between the need for resuscitation and outcome remained unchanged for cognitive disability (OR = 2.6, 95% CI = 0.5 – 14.2) and stronger for physical disability (OR = 5.6, 95% CI = 0.5 – 64.9), but in neither case did the results reach statistical significance. The prediction of poor outcome was less impressive for low Apgar scores at either one or five-minutes, and our results were not statistically significant (Table 4).

With regard to mode of delivery, no meaningful observations could be made about cesarean section. For forceps-assisted delivery compared with spontaneous vaginal delivery, we found a lower likelihood of physical (OR = 0.2, 95% CI = 0.04 – 0.6) and cognitive disability (OR = 0.3, 95% CI = 0.1 – 1.1) in univariate analysis and in multivariate analysis these relationships had a similar magnitude of effect but with wider confidence intervals (cognitive disability, OR = 0.3, 95% CI = 0.03 – 303; physical disability, OR = 0.1, 95% CI = 0.004 – 3.0).

A more severe category according to our *Overall Hemorrhage Severity scale* was a more powerful predictor of disability than our *Severest Hemorrhage Type* scale. In multivariate models that controlled for other risk factors seen in Table 4, including primary hemorrhage location, we found that the predictive ability of Severest Hemorrhage Type was lost, but Overall Hemorrhage Severity remained important, but due to limited power was not statistically significant.

The affect of primary hemorrhage location on disability also become attenuated in multivariate analyses. Only the frontal location compared to the posterior fossa was a statistically significant predictor of cognitive and physical disability in univariate models (OR = 7.3, 95% CI = 1.5 – 34.4; physical disability, OR = 8.8, 95% CI = 1.7 – 45.0), but after controlling for other risk factors and Overall Hemorrhage Severity, this relationship became weaker and failed to reach statistical significance (OR = 5.7, 95% CI = 0.5 – 60.2; physical disability, OR = 1.6, 95% CI = 0.02 – 95.6).

Discussion

In this report we retrospectively identified full-term infants from Southwestern Ontario who suffered intracranial hemorrhage over a twelve-year period. At follow-up, we were able to determine outcome in 85% of infants according to functional measures of physical and cognitive disability. We found that of those infants who died, death tended to occur early, and for those who survived nearly 60% showed no evidence of disabilities according to our measures. However, significant impairment did occur as 25% of infants had physical limitations and 20% had deficits in cognitive function. When we attempted to determine factors that may have contributed to death and poor outcome, we found that infants born with platelet counts below

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70 x 10^9 /L were more likely to do poorly than those with higher counts. We also observed less favorable outcomes among those infants who had a spontaneous vaginal delivery when compared to those who had a forceps-assisted delivery and those who had hemorrhage in the frontal location. In multivariate analyses, only having a low platelet count remained significant.

In our review of the literature we were able to identify eight studies that reported clinical outcome on at least ten patients.[14-22] These studies together identified 235 infants who suffered ICH in a manner similar to our patients. There were 27 deaths in this group for a mortality fraction (11.5%) that was similar to our own observation (12.5%). These deaths all occurred within the neonatal period and in our series, all deaths occurred within the first week of life.

Other studies have also attempted to determine outcome in such patients but have generally suffered from non-uniform and poorly defined definitions of outcome. If the term "normal" is taken at face-value from the literature, among seven previous studies where follow-up data was available, only 40 infants were described in this manner among 124 cases. Our group of infants showed a more favorable outcome and this may either represent our failure to identify deficits, or a lower threshold to include cases in this study.

The finding that subarachnoid hemorrhage occurred frequently among those who did not survive has been described.[14] The mechanism has been attributed to hypoxic-ischemic encephalopathy where small vessels rupture under metabolic stresses and venous stasis (related to low oxygen tension).[23] This is consistent with our other observations of increased mortality among those who required resuscitation and had low five-minute Apgar scores. There was a lack of association between low one-minute Apgar scores and outcome, but this may be due to the insensitivity of this measure towards arterial hypoxemia.[24, 25]

Many of the infants who suffered subarachnoid hemorrhage did not have a poor outcome. For infants who did well with primarily subarachnoid hemorrhage, the mechanism may not be due to hypoxic-ischemic encephalopathy, but rather direct trauma to the superficial cortical vessels. We observed this frequently among infants that had forceps-assisted delivery and these children as a group did relatively well.

We observed the greatest disability among those infants who suffered intracerebral hemorrhage and relative to extra-axial types of hemorrhage the probability of disability in univariate analyses was several-fold. Such hemorrhages by definition destroy brain parenchyma. However, 47% of infants from this group did not have disability and when we simultaneously controlled for other risk factors we found that intracerebral hemorrhage became a less important predictor of disability. In contrast, we observed the best outcomes among those infants who had primarily subdural hemorrhage. This type of hemorrhage has been found to be common among healthy normal newborns.[5,6] In most cases, but not all, subdural hemorrhage may be incidental and a natural consequence of birthing. In a minority of cases it may be related to a difficult delivery.

Thrombocytopenia (platelet count ≤ 70 x 10^9 /L) is a frequent occurrence among full-term infants with intracranial hemorrhage (31% infants in our series). In our previous report we found that intra-parenchymal hemorrhage was the most frequent type of hemorrhage that occurred when the platelet count was low, and the probability of such hemorrhage increased with increasing severity of thrombocytopenia.[13] We also observed that with lower platelet counts, more compartments (subarachnoid, subdural, intracerebral and intraventricular) were likely to be involved. In this study, we found that thrombocytopenia and increasing category of *Overall Hemorrhage Severity* also contributed towards subsequent disability, but in multivariate analysis only low platelet count remained significant. Because coagulopathy appears to be an important determinant of intracranial hemorrhage and poor outcome, it seems reasonable to assume that early correction of such abnormalities has the potential to limit injury.

A number of studies have implicated instrumented delivery with either forceps[7, 8, 16, 26-29] or vacuum extraction[8, 30, 31] as being potentially causative in the occurrence of intracranial hemorrhage. In London, only forceps are used to assist delivery and when we compared infants who had this type of delivery with those who had spontaneous vaginal delivery, we also found increased risk of ICH.[13] In addition, we also observed that hemorrhage tended to occur in the location where these devices are applied to the scalp. However, when we looked at hemorrhage severity comparing these two modes of delivery, we found that forceps-associated hemorrhage tended to be less severe in terms of *Overall Hemorrhage Severity* and *Severest Hemorrhage* Type than spontaneous vaginal delivery. In this report we found that full-term infants with ICH who had forceps used to assist delivery were less likely to die and the most likely (among all the risk factors we studied) to have a favorable outcome. These results were only significant in univariate analysis as our study had insufficient statistical power to confirm this observation in multivariate models.

Our study is small and has limited follow-up and yet it is one of the largest series to report on delayed outcomes in this group of neonates. We used telephone interviews and clinic assessments to evaluate outcomes but the scales we used are not validated. However, our definitions were relatively simple, with few categories and this limited misclassification. Nevertheless, it remains difficult to classify a child who is four-years-old on the same scale as that of a ten-year-old. This is why our category definitions are as liberal as possible while still attempting to capture important disability in a manner that is not affected by developmental milestones. If a more comprehensive instrument was used to assess functional status or a longer period of follow-up was available, more subtle deficits may have been detected.

In our study, we looked at full-term infants who suffered a wide-spectrum of intracranial hemorrhages and we found that serious disability was not the rule. Nearly 60% of the infants we followed lacked evidence of physical or cognitive impairment, but the sensitivity of our assessment tools may have been limited. We previously found that forceps-assisted delivery was associated with ICH, but in this report we observed that most of these infants had favorable outcomes. Similarly the indicators of perinatal hypoxia that we studied were also previously noted to be strongly associated with ICH occurrence. In models that attempted to predict outcomes, this was not an important factor, but were unable to predict outcome. Our most important observation was that thrombocytopenia associated hemorrhage was more likely to be associated with more severe hemorrhage and poorer outcomes, even after controlling for other risk factors.

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