

Neonatal Intra-Ventricular-Hemorrhage prevention in premature at < 30 weeks gestational Age

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Abstract

Introduction: Intraventricular Hemorrhage (IVH) is a devastating condition mostly in preterm infants at < 30 weeks GA with large morbidities and mortality usually in the first 72 hours after birth. Prevention seems to be the only way to completely deal with this problem.

Material and method: We design a before and after observational study and measured the incidence of IVH when a minimum manipulation protocol was implemented at the Clínica del Country (CDC) unit. We also compare these findings to those of other units in the EpicLatino network. All patients born <30 weeks GA with less than 2 days of age, who survived at least 3 days, and had a neuroimaging taken were included.

Results: We collected data from 46 cases before, 40 after implementation, and 203 cases from the EpicLatino registry. Demographic characteristics were very similar in the post-intervention with few statistically significant differences in antenatal steroid use, prolonged rupture of membranes, vaginal deliveries, suspended chorioamnionitis. We found a significant reduction in IVH after the protocol was

implemented with only 5 (7.5%) cases post-intervention compared to 19 (29.4%) case before, and when compared to the 81 (39.1%) cases in the registry, $p < 0.001$. Most of the cases that occurred in the post-intervention occurred before admission to the unit due to obstetric trauma.

Discussion: If a well-controlled delivery minimizing obstetric trauma is achieved, a minimal manipulation protocol appears to significantly decrease the incidence of HIV. Controlled, multicenter studies are still required to confirm these findings.

Key words:

Intraventricular Hemorrhage, Very preterm infants, Epicaltino registry, Obstetric trauma, Minimal manipulation protocol.

Main manuscript

Introduction

Intra-Ventricular-Hemorrhage (IVH) is a devastating condition mostly in preterm infants < 30 weeks gestational age (GA) at birth, with large morbidities and mortality.¹⁻³ The timing of the IVH appears to occur in the first 6 hours of life^{4,5} but it can continue to develop and most cases are found in the first 72 hours after birth.⁶

Hemorrhage at delivery due to obstetric complications probably accounts for many of these cases. Observational studies show that elective cesarean section reduces the risk of IVH in preterm infants < 30 weeks GA when they present with preterm labor.⁷ Other risk factors such as germinal matrix immaturity and fluctuations in the cerebral blood flow are described.^{8,9} Clinically, low birth weight or low gestational age, lack of antenatal corticosteroids, maternal chorioamnionitis, low Apgar score (< 5) at 5 min, respiratory distress syndrome, early onset sepsis, hypercapnia or PCO_2 fluctuations, inotropes or boluses, metabolic disorders, opioids infusions, and bicarbonate therapy are also associated with IVH.^{6,7,10}

Prevention seems to be the only way to reduce this phenomenon. The prevention of IVH in this age group is focuses on strategies such as prenatal corticosteroids,¹¹ cesarean delivery,⁷ careful extraction and other nurse practices,¹² but it still has an unacceptably high incidence in this population.

A new strategy for neuroprotection was developed years ago under the name “Drive to Zero IVH Prevention Project”¹³ and was presented in one of the EpicLatino conferences. Our unit decided to adapt this project as a quality improvement practice. In this study we measured the results of this project by comparing cases before and after the intervention and we also used the EpicLatino registry as a concurrent cohort.

Material and method

Study design

Observational nonconcurrent cohort study querying a prospectively collected registry (EpicLatino).

Setting

Epiclatino is a registry of neonatal intensive care units in Latin America, based on the CNN (Canadian Neonatal Network) collection instrument for quality improvement.¹⁴ Clínica del Country (CDC) is a third level private general hospital located in Bogota, Colombia with a third level neonatal unit with a high incidence of high-risk deliveries. In October 2017, we designed and adapted a strategy for minimum manipulation to the existing prevention strategies in place. At the end we came up with this approach (Table 1).

Subjects

All patients <30 weeks of GA less than 2 days old were included in the new strategy at CDC, for this study we included patients who survived at least 3 days and had a neuroimaging taken (November 2017 to discharge by August 31 2021). For comparison, other cases from the other EpicLatino units from 2018 and 2019 and cases at the CDC from previous years (January 2016- October 2017) also born with <30 weeks GA and surviving 3 days and had a neuroimage were selected for analysis.

Variables

We define IVH grade 1 and 2 as hemorrhage in the germinal matrix and/or ventricles, without intraventricular dilation or periventricular hemorrhage. Grades 3 and 4 were defined as bleeding with ventricular dilatation or bleeding outside the ventricles. We also capture birthweight, gestational age (GA), sex, inborn/outborn, temperature at admission, prenatal corticosteroids, prolonged (>24h) rupture of membranes (ROM), delivery (vaginal or cesarian), suspected chorioamnionitis, Apgar score at 5 minutes, deaths after day 3 and treated patent ductus arteriosus (PDA).

Analysis

We gathered all available cases in a convenience sample with no sample size calculation. All the parameters were compared within the two time periods and the EpicLatino registry using Chi-square test by Fischer's exact method or Kruskal-Wallis rank test, depending on the type of variable. A p value less than 0.05 was considered significant.

Ethics

EpicLatino registry is an approved registry by the local institutional review board at each center with a waiver of informed consent as it gathers non identifiable data for research and quality improvement programs. This manuscript has been also approved by an ethic committee as a minimal risk and waived the informed consent.

Results

We collected a total of 46 cases at CDC before and 40 post-implementations, and we gathered 203 cases from the EpicLatino registry (2018-2019). Anthropometric and demographic characteristics are shown in table 2. Of note, temperature at admission and prolonged ROM were statistically different due in the before intervention group. On the other hand, prenatal corticosteroids, and suspected chorioamnionitis were statistically different in EpicLatino group. Vaginal deliveries and treated PDA were statistically different in both pre-intervention and EpicLatino groups.

Regarding IVH, distribution was statistically significant among the groups (Figure 1). There were one grade 1-2 hemorrhage and 2 grade 3-4 during the post-intervention period. Both grade 3-4 happened during very traumatic deliveries with multiple hematomas around the head, body, and extremities.

Discussion

We found a statistically significant reduction in the incidence of IVH in the post-intervention group when compared to the historical cohort (before) and the EpicLatino registry, and both severe cases were related to delivery trauma. The hemorrhage during delivery is well described¹⁵ and must be prevented by the obstetric team.

We found some factors that could explain some of the difference in the intraventricular hemorrhagic results. Temperature at admission as a marker of moderate/severe acute transitional hypothermia has been associated with increased risk of intraventricular hemorrhage (from 6.8% in

normal temperature to 13% with moderate/severe hypothermia),¹⁶ but not in all studies.¹⁷ Prolonged ROM has been associated with increased risk of IVH¹⁸ but it is difficult to separate it from the risk of prematurity, so it is not easy to evaluate how much ROM > 24 hours can increase the risk of IVH. Lack of prenatal corticosteroids increases the risk of IVH,¹¹ and can explain in part the increased risk of IVH in the EpicLatino group. On the other hand, suspected chorioamnionitis also increases the risk of IVH¹¹ in the EpicLatino group but decreases the risk in the historical cohort since it is lower than the post-intervention group. The relation between vaginal delivery and C-section may also favor the post-intervention group, especially compared to EpicLatino⁷ but more PDA treatment in both control groups could favor IVH prevention since in the post-intervention group only 10% were treated even if some studies question its significance.¹⁹ We believe that this large difference in IVH incidence is not explained by the difference in these factors described above but in the protocol applied. Our study has limitations as is not a randomized control study, the variables affecting the incidence of IVH could not be properly controlled and this could explain at least part of the results. Large randomized clinical trials are needed to confirm our findings.

Conclusion

We believe that the gentle handling described with minimal manipulation and unnecessary laboratories and therapies is linked to reducing the incidence of IVH in this population. Modification of a single parameter, as observed in randomized control studies, will probably not change the incidence of IVH significantly, but a set of modifications in many as observed in this quality improvement protocol may decrease the incidence of IVH. Large multicenter clinical trials are needed to confirm these findings.

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Conflict of Interest: We have no conflict of interest and nothing to declare.

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Table 1 Minimal manipulation protocol

Old strategies

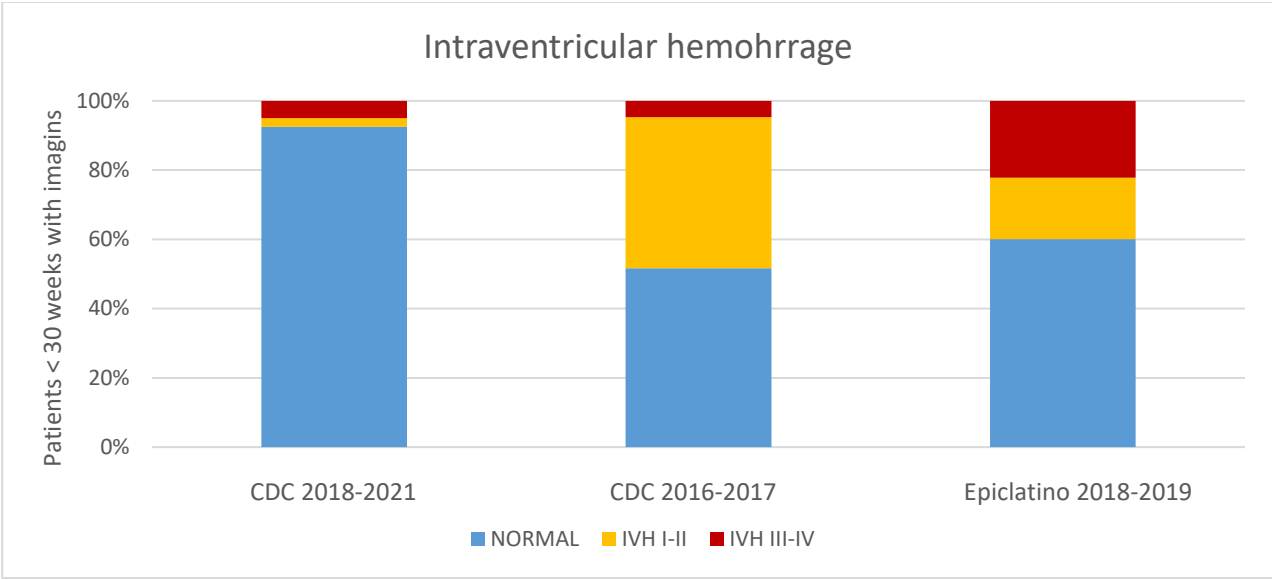
- Regulated temperature and high humidity (80%)
- Umbilical catheters when possible
- No PDA therapy or Echo if possible
- Routine therapy:
 - Hydrocortisone 0.5 mg/kg/day in less than 27 weeks GA
 - Erythropoietin 1200 U/Kg/week
 - Caffeine
 - Parenteral nutrition with fluids 70cc/K/d
 - Glucose 4mg/K/min
 - Protein 4 g/k/d
 - Lipids 3 g/K/d
- Trophic feeding (1-3 mL q. 3 hours)
- Probiotics

New strategies added

- Ventilatory parameters as needed and volume ventilation when possible.
- Only one routine fiscal exam a day. No routine measurements or weight
- Maintain neutral head position²⁰ and bed elevated 30 degrees.
- Only 1 blood pressure measurement per shift.
- No keel prick measurements (glucose measurement once a day within blood gases).
- Continuous dim light less than 20 Lux when possible and noise level less than 45 dB.
- Minimal touching except to clean perinatal area and change dippers when needed.
- No vasoactive medication or boluses except in extreme cases.

Table 2. Anthropometric and demographic characteristics

At Birth	Nov 2017- 2021CDC	2016-2017 Oct CDC	Epiclarino 2018-2019 without CDC	p*
	n (%)	n (%)	n (%)	
n	40	46	203	
Weight (gr)				
< 500	2 (5.0)	0 (0)	0 (0)	0.179
500-750	6 (15.0)	2 (4.4)	31 (15.3)	
751-1000	12 (30.0)	22 (47.8)	69 (34.0)	
1001-1250	13 (32.5)	11 (23.9)	69 (34.0)	
1251-1500	7 (17.5)	9 (19.6)	31 (15.3)	
1500-1750	0 (0)	2 (4.4)	3 (1.5)	
Gestational age (w)				
23	0 (0)	0 (0)	1 (0.5)	0.180
24	0 (0)	1 (2.2)	9 (5.0)	
25	5 (12.5)	6 (13.0)	16 (12.8)	
26	3 (7.5)	2 (4.4)	38 (31.5)	
27	6 (15.0)	13 (28.3)	44 (21.7)	
28	11 (27.5)	10 (21.7)	47 (23.2)	
29	15 (37.5)	14 (30.4)	48 (23.7)	
Sex				
Male	24 (60.0)	28 (60.9)	96 (48.3)	0.226
Female	16 (40.0)	18 (39.1)	105 (51.7)	
Inborn	39 (97.5)	45 (96)	194 (95.6)	1.000
T° at admission(med, IQR)	36.4 (0.85)	35.8 (0.9)	36.0 (1.4)	0.0165**
Prenatal corticosteroids	39 (97.5)	44 (96)	161 (79.3)	0.016
ROM (>24h)	6 (15.0)	2 (4)	31 (15.25)	<0.0001
Vaginal delivery	3 (7.5)	5 (10.9)	49 (24.1)	0.011
Cesarean section	37 (92.5)	41 (88)	154 (75.9)	
Suspected Chorio	5 (12.5)	3 (6)	41 (20.2)	<0.0001
Apgar 5´ (mean ±SD)	8 (1.0)¥	8.0 (0.9)¥	8 (1.5)¥	0.055¥
Deaths ≥ 3 days	5 (12.8)	11 (24)	34 (16.75)	0.202
PDA (treated)	4 (10%)	88 (40%)	13 (28%)	0.01
ROM: rupture of membranes, Chorio: chorioamnionitis, PDA (treated): Patent ductus arteriosus treated; *Chi-square test by Fischer's exact method; **Kruskal-Wallis equality-of-populations rank test; ¥ t-test mean difference				



IVH	2018-2021 CDC	2016-2017 CDC	Epiclarino 2018-2019 without CDC	p*
	n (%)	n (%)	n (%)	
NORMAL	37 (92.5)	27 (69.6)	122 (60.1)	<0.001
IVH I-II	1 (2.5)	15 (58.7)	36 (17.7)	0.014
IVH III-IV	2 (5.0)	4 (6.3)	45 (22.2)	0.009

*Chi-square test by Fischer's exact method

Figure 1. IVH Results. CDC: Clinica del Country, IVH: Intraventricular Hemorrhage