PEDIATRIC SCIENCES JOURNAL
The Official Journal of the Pediatric Department, Faculty of Medicine, Cairo University, Egypt

Original Article

Care Bundle Application Decreases The Frequency and Severity of Intraventricular Hemorrhage in Preterm Neonates: Single Center Study

Sarah S. El Tatawy[1]*, Amira M. Gad[1], Tamer S. Eissa[2], Salma Z. El Houchi[1], Amira M. Sabry[1]

[1] Department of Pediatrics, Faculty of Medicine, Cairo University, Egypt; amiragad930@gmail.com, salma.elhouchi@kasralainy.edu.eg, amirasabryelshafie@kasralainy.edu.eg
[2] Department of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, Egypt; tamereissa@live.com
***** Correspondence: statawy@cu.edu.eg
Received: 4/6/2022; Accepted: 16/6/2022; Published online: 1/7/2022

Abstract:
Background: Intraventricular hemorrhage (IVH) is a severe complication in preterm babies admitted to Neonatal Intensive Care Units (NICU). Advanced stages of IVH predispose to neurological deficits such as cerebral palsy and hydrocephalus. There are numerous strategies and policies implemented in NICUs around the world to decrease the incidence of IVH in preterm babies and prevent its ensuing neurodevelopmental complications.
Aim of the Work: To study the effect of implementing a bundle of care on incidence and severity of IVH among preterm neonates.
Materials and Methods: Retrospective analysis of patient records for incidence and severity of IVH between May and August 2018 was done. This was followed by an educational interim period where NICU staff received training of pre-natal, natal, and postnatal care bundle guidelines to reduce IVH. The guidelines were then implemented on all preterm babies (28-34 weeks gestational age (GA)) born and admitted to Kasr Al Ainy Teaching Hospital NICU, Cairo University between October 2018 and January 2019 (n=58). Cranial ultrasonography was performed at week 1 and week 2-3 of life. Frequency and severity of IVH were compared among studied groups. Risk factors for IVH were analyzed and recorded.
Results: The frequency of IVH was significantly lower in the post-bundle group (44-46% pre-bundle, and 27% post-bundle) especially evidenced by the ultrasonography in week two of life. Severity of IVH also improved post bundle since there were no grade III IVH patients in that group. Exposure to hypocapnia, blood pressure fluctuations, IV fluid boluses and administration of sodium bicarbonate were significantly correlated with development of IVH in preterm babies ($p = 0.001$).
Conclusion: Implementation of an IVH care bundle that includes perinatal measures can positively affect the neurological outcome by decreasing incidence and severity of IVH in preterm babies.

Level of Evidence of Study: IIA. (*1*)
Keywords: Care bundle; cranial ultrasonography; IVH; intraventricular hemorrhage, preterm.
Abbreviations: CBF: cerebral blood flow; CBV: cerebral blood volume; CO_2: carbon dioxide; CPP: cerebral perfusion pressure; GA: gestational age; IVH: intraventricular hemorrhage; $NaHCO_3$: sodium bicarbonate; NICU: Neonatal Intensive Care Unit; PVL: periventricular leukomalacia; US: ultrasonography.

Introduction

Intraventricular hemorrhage (IVH) is a common and severe sequalae of preterm babies admitted to the Neonatal ICU (NICU). The incidence of IVH reported in developed countries ranges between 21-23% (*2*). This number is magnified in developing countries due to lack of resources and appropriate brain protective measures. One study in Uganda puts IVH incidence

at 34% (*3*), while another in Addis Ababa, Ethiopia found a 36% incidence of IVH in preterm babies(*4*). Generally, IVH is a grave condition as a large number of patients develop neurologic sequelae. Many preterm survivors with IVH develop cerebral palsy, mental retardation, and/or hydrocephalus (*5*). In the majority of cases involving mild bleeding (classified as grade I and grade II), no clinical effects are observed, and usually resolve themselves and cause no long-term problems (*6*). The evidence-based quality improvement approach suggests that some potentially better practices can be developed and implemented to decrease brain injury. The practices include antenatal measures such as giving antenatal corticosteroids to mothers for neuroprotection; perinatal measures such as delayed cord clamping and prevention of hypothermia in the delivery room, as well as minimal handling and stimulation; and postnatal measures such as early resuscitation, maintaining the body's temperature at ≥36°C, minimizing pain and stress via developmental care, and maintenance of neutral head position (*7*, *8*). Our study aimed to assess the effect of implementation of similar perinatal measures in an effort to decrease incidence and severity of IVH in our unit at Kasr Al Ainy University Hospital NICU, Cairo University.

Subjects and Methods

This cohort study involved preterm infants (28-34 weeks of gestation) admitted to the inborn NICU at Kasr Al Ainy Maternal Hospital, Cairo University. The study was divided into 3 chronological phases. The first phase was a retrospective analysis of patient records over a 4-month period between May and August 2018, which included preterm babies (28-34 weeks GA) born and admitted to the Kasr Al Ainy NICU (n=50). The frequency and severity of ultrasound-proven Intraventricular hemorrhage (IVH) in these preterm babies was documented. The second phase was a one-month long educational interim spanning the month of September 2018, during which nurses and residents of the NICU received a training course on the adverse outcomes of IVH in preterm infants and how to limit its occurrence using an IVH-care bundle which included prenatal, delivery room, and post-natal guidelines. This educational interim included interactive lectures, posters, and checklists on the included incubators to ensure proper implementation. The third and final phase of the study was the practical application of the IVH-care bundle on all preterm babies (28-34 weeks GA) born and admitted to Kasr Al Ainy NICU between October 2018 and January 2019 (n=58) upon whom inclusion criteria were applied. The study was approved by the ethical committee of Cairo University Pediatric Department. An informed consent was obtained from the patients' parents.

Participants

Inclusion criteria included newborns born between 28-34 weeks of gestation whose mothers had received antenatal steroids. Babies delivered outside Kasr Al Ainy Teaching Hospital, those with multiple congenital anomalies, and those whose mothers did not receive antenatal steroids due to lack of antenatal follow up were excluded from the study.

Methods

- The IVH care bundle consisted of:

A. Prenatal practices: A course of antenatal corticosteroids (betamethasone 12 mg intramuscularly in two doses 24 hours apart) was given to women who were at risk of preterm delivery (*9*).

B. Delivery Room practices

1. Delayed cord clamping 30-60 seconds (*10*)**.** The preterm neonates were held in a position level with the bed or raised to the level of the mother's abdomen (vaginal births) or anterior thigh (caesarean births) (*11*).

2. Maintenance of normothermia: Preterm neonates were placed under radiant warmers with skin probes to monitor and maintain body temperature at 36.5°-37.5° Celsius (*12*).

C. NICU practices

The head of the incubator bed was elevated to 15-30 degrees. The baby was kept in a midline head and body position; traditional positioning aids such as bed sheet boundaries were placed around the bodies of the babies to facilitate and maintain flexion and midline orientation (*13*). Rapid flush of IV fluid boluses were avoided and instead were infused over a minimum period of

30 minutes. Blood pressure was monitored every 3 hours to avoid fluctuations. Hypocapnia was avoided by keeping $PaCO_2$ concentration in the range of 35 to 45 mmHg (*14*). The use of sodium bicarbonate was limited. Routine suctioning was avoided. Minimal handling was assured to avoid pain and stress; minimal handling signs were put on the incubators which were covered whenever possible to reduce light and noise stimulation.

- Clinical and Laboratory Data Collection:

Data collected at birth included mode of delivery, Apgar score, body temperature at delivery, birth weight, and gestational age assessment using the Ballard Score (*15*) (since many mothers who came in for delivery had inadequate prenatal care and no proper documentation of gestational age). Upon admission to the NICU, neonates were observed to measure vital signs including heart rate, blood pressure, respiratory rate and temperature every 3 hours. Blood gases were serially recorded to detect CO_2 abnormalities. Type and speed of infusions were noted and documented in patient files.

- Ultrasonography Data:

Transcranial ultrasonography (US) was done using a Toshiba apparatus (Niemo XG, USS-GYN16-009KO, Canada) equipped with multifrequency linear and microconvex transducer. Examination was performed twice; the first within the first 7 days of life to detect IVH and the second between week 2 and 3 of life for follow up. High-quality images were obtained by holding the transducer firmly between the thumb and index finger and resting the lateral aspect of the hand on the infant's head to ensure stability. Cranial sonographic examinations were performed through the anterior fontanelle. Coronal and sagittal planes were visualized and IVH was recorded according to its grade. Based on the classification mentioned by McCrea and Ment (*16*), we categorized IVH into four grades. Grade I includes germinal or subependymal matrix hemorrhage where the bleeding is restricted to the germinal matrix. Grade II involves intraventricular hemorrhage without ventricular dilatation. Grade III hemorrhage involves bleeding within the ventricles leading to their enlargement, and in Grade IV there is parenchymal hemorrhage with ischemic changes.

Statistical Analysis

Comparisons were made regarding incidence and severity of IVH between the pre-bundle group (n=50) and the post- bundle group (n=58). We then took the whole number of included neonates of both pre-and post-bundle groups (n=108) and re-assigned them based on the results of their cranial ultrasound into IVH (n=39) and Normal-scan (n-69) groups and compared each group to various risk factors for occurrence of IVH. Results were expressed as mean ± standard deviation or number (%). Comparison between categorical data was performed using Chi-square test or Fisher exact test. Test of normality, Kolmogorov-Smirnov test, was used to measure the distribution of data. Accordingly, comparison between normally distributed variables in the two groups was performed using t-test. Statistical Package for Social Sciences (SPSS) computer program (version 21 windows) was used for data analysis. P value ≤ 0.05 was considered significant.

Results

This study involved 108 preterm neonates (28-34 GA) divided into two groups; pre-bundle group (n=50), and post-bundle group (n=58). The two groups were comparable in gestational age, gender, mode of delivery and birth weight (Table 1). The frequency of IVH in the first week of life was apparently lower in the post-bundle than in the pre-bundle group (27.6% vs 44%), however, the difference was not statistically significant ($p = 0.075$). During the follow up cranial ultrasound (2nd /3rd week) however, the frequency of IVH was significantly lower in the post-bundle group ($p = 0.047$). Also, notably in the post-bundle group, no cases of grade III IVH were detected in any of the transcranial examinations denoting a positive effect regarding severity of IVH (Table 2). In the second wave of data collection, after pooling our patients and reassigning them to two different groups according to presence or absence of IVH, we found no statistical differences in any of the demographic data between both groups (Table 3).

Table 1. Demographic Characteristics of Studied Preterm Neonates Before and After Implementation of Bundle of Care.

	Pre-implementation of Bundle of Care group (n=50)	Post-implementation of Bundle of Care group (n=50)	*P* value
Gestational age (in weeks)*	31.1±2.0	31.7±1.6	0.076
Birth weight (in grams) *	1406±349	1336±195	0.211
Gender (male/female)	30/20	29/29	0.298
Mode of delivery (vaginal/cesarian)	21/29	16/42	0.116

*Data are expressed as mean ± SD.

Table 2. Frequency and Severity of IVH by Cranial Ultrasonography of Studied Preterm Neonates Before and After Implementation of Bundle of Care.

	Pre-implementation of Bundle of Care group Number=50(%)	Post-implementation of Bundle of Care group Number=50(%)	*P* value
Week 1	22 (44.0)	16 (27.6)	0.075
Grade I	9 (18.0)	8 (13.8)	0.138
Grade II	10 (20.0)	8 (13.8)	
Grade III	3 (6.0)	0 (0.0)	
Week 2/3	23 (46.0)	16 (27.6)	0.047
Grade I	8 (16.0)	5 (8.6)	
Grade II	11 (22.0)	11 (19.0)	0.060
Grade III	4 (8.0)	0 (0.0)	

*Data are expressed as actual number and percentage.

Table 3. Demographic Characteristics of Studied Preterm Neonates with normal Ultrasound Scan and those with detected IVH.

	Normal Scan (n= 69)	IVH (n= 39)	P value
Gestational age (in weeks)*	31.7±1.7	31.0±2.0	0.057
Birth weight (in grams) *	1407±242	1301±326	0.057
Gender (male/female)	40/29	19/20	0.354
Mode of delivery (vaginal/cesarian)	20/49	17/22	0.125

*Data are expressed as mean ± SD; IVH: intraventricular hemorrhage.

We did however find significant correlations between presence of IVH and various risk factors. Exposure to hypocapnia, blood pressure fluctuations, IV fluid boluses and administration of sodium bicarbonate were significantly more common in preterm neonates who developed IVH (p = 0.001). (Table 4).

Table 4. Comparison of Risk factors for IVH among Studied Preterm Neonates with normal Ultrasound Scan and those with detected IVH.

	Normal Scan (n= 69)	IVH (n= 39)	P value
Hypocapnia> 3 times	4 (5.8%)	24 (61.5%)	0.001
BP fluctuations > 3 readings	1 (1.4%)	23 (59.0%)	0.001
IV fluid boluses given			
Given < 3 times	17 (24.6%)	9 (23.1%)	0.001
Given > 3 times	0 (0.0%)	23 (59.0%)	
IV Sodium bicarbonate given	2 (2.9%)	15 (38.5%)	0.001

Data are expressed as actual number and (percentage).
IVH: intraventricular hemorrhage.
Hypocapnia was defined as $PaCO_2$ concentration below 35 mmHg (*14*).
Blood Pressure fluctuations were defined as variations in blood pressure measurements between normal and abnormal ranges.

Discussion

Intraventricular hemorrhage (IVH) is one of the major complications in premature infants and continues to pose challenges in NICUs worldwide (*17*, *18*). Nevertheless, the incidence of IVH has decreased significantly over the last decade due to worldwide improvements in neonatal care attributable to improved practices like use of antenatal corticosteroids, better infrastructure, effective resuscitation skills, appropriate handling of infants, and judicious use of ventilation (*2*, *19*).

The aim of our study was to improve our perinatal care protocols and consider brain protection by incorporating an IVH care bundle into our NICU care. Our care bundle included prenatal, natal, and postnatal measures that have been shown in other studies to decrease the incidence of IVH. One such study drafted a charter using the Model for Improvement which included prolongation of infusion rates of saline and blood products, minimizing bicarbonate infusions, using an IVH risk calculator, implementing delayed cord clamping, midline head positioning, bed head elevation, and minimal handling of babies(*20*). Another study by Schmid et al. applied a bundle of preventive measures including preference of caesarean section as a method of delivery, delayed clamping of the umbilical cord, and additional dose of betamethasone during pregnancy which resulted in decreased incidence and severity of IVH (*21*, *22*).

Our primary aim was to show whether application of the care bundle would decrease incidence and severity of IVH in preterm neonates. Although not statistically significant, our data showed a decrease in IVH cases in the week 1 cranial ultrasounds in the post bundle group. Furthermore, results of the week 2 and/or week 3 cranial ultrasounds showed a statistically significant difference in the incidence of IVH between the two groups. Our data also reflected a statistically significant reduction in terms of severity of IVH cases in the post bundle group. Our study results therefore, similar to others (*20*, *21*) showed a significant decrease in the incidence and severity of IVH after implementation of a care bundle which promoted neuroprotection.

In terms of mode of delivery, the literature is ambiguous regarding its correlation to incidence of IVH, with studies showing no association(*23*) while others promoting an inclination to CS delivery as a protective measure against IVH (*24*, *25*).

In our study, similar to others (*26*), the incidence of IVH was significantly increased in neonates who received IV sodium bicarbonate for management of metabolic acidosis. The cerebral hemodynamic responses to a rapid NaHCO3 infusion may be explained by the resultant increase in cerebral blood flow (CBF) due to an increase in the concentration of CO_2 which is produced as a byproduct of the reaction of NaHCO3 with acid. Since CO_2 is a potent vasodilator, it induces an increase in CBF through local effects on cerebral vasculature thus predisposing to IVH (*27*, *28*). The combination of the inherent germinal matrix fragility in premature babies and fluctuations in CBF in preterm neonates causes the rupture of the vasculature, leading to

intraventricular hemorrhage (*29*). In neonates, as intracranial pressure (ICP) cannot be measured directly like in adults, arterial blood pressure (ABP) is often used as the surrogate for cerebral perfusion pressure (CPP) (*30*, *31*); a method we adopted. Comparable to results published by Bada et al, ours also showed a significant increase in incidence of IVH in neonates exposed to blood pressure fluctuations (*32*, *33*). Another risk factor for development of IVH is hypocapnia. Hypocapnia in premature infants is associated with poor neurodevelopmental outcome, including periventricular leukomalacia (PVL), IVH, and cerebral palsy possibly due to cerebral vasoconstriction, decreased CBF, and decreased cerebral oxygen delivery to infants (*34*–*36*). Our study, comparable to another (*37*) showed significant increase in incidence of IVH in neonates exposed to hypocapnia.

There are other simple and easily applicable measures included in our IVH bundle to minimize IVH in preterm babies such as reducing pain and stress, proper positioning of the newborn and alterations of the NICU environment (*38*). Pain and stress may impede venous return, increasing cerebral blood volume (CBV); thus swaddling, boundaries, preemie hugs, minimal stimulation, quiet and dark environment are recommended (*39*). Midline head positioning has been included in recent germinal matrix-IVH prevention bundles at many institution (*7*) as an increase in intracranial pressure and CBV after head rotation, caused by obstruction of the homolateral jugular veins, has been reported to predispose to IVH (*40*–*42*).

This study may perhaps have been limited by the restricted number of cranial ultrasounds performed for each patient. A longer follow up with repeated ultrasounds may have had a bigger impact on the results of our study. Also, a developmental assessment during the infancy years of these patients may have shed some more light on the long-term morbidities of IVH as well as the developmental outcome of these babies. Finally, despite best efforts, sometimes old practices prevail and less than perfect vigilance may have led to some bundle measures being overlooked and thus produced adverse outcomes.

Conclusion

Implementation and methodical application of an IVH care bundle that encompasses perinatal measures surrounding the birth of preterm babies can positively affect their neurological outcome by decreasing IVH. These measures require training and education on behalf of the entire NICU staff in order to be thoroughly implemented. As more awareness regarding brain protection in the preterm newborn is gained, measures such as IVH care bundles will hopefully be considered in all countries around the world and become part of the routine NICU care of preterm babies.

Author Contributions: All authors searched medical literature, databases, conceptualized, conducted the case review and reviewed the final manuscript. All authors have read and agreed to the published version of the manuscript.

FUNDING

Authors declare there was no extramural funding provided for this study.

CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the reported study. Authors declare veracity of information.

References

1. S. Tenny, M. Varacallo, *Evidence Based Medicine.* (StatPearls Publishing; Treasure Island (FL), 2020; https://www.ncbi.nlm.nih.gov/books/NBK470182/).
2. K. T. Yeo, R. Thomas, S. S. Chow, S. Bolisetty, R. Haslam, W. Tarnow-Mordi, K. Lui, Improving incidence trends of severe intraventricular haemorrhages in preterm infants <32 weeks gestation: a cohort study. *Arch. Dis. Child. - Fetal Neonatal Ed.* **105**, 145–150 (2020).
3. R. MacLeod, J. N. Paulson, N. Okalany, F. Okello, L. Acom, J. Ikiror, F. M. Cowan, C. J. Tann, L. E. Dyet, C. F. Hagmann, K. Burgoine, Intraventricular haemorrhage in a Ugandan cohort of low birth weight neonates: the IVHU study. *BMC Pediatr.* **21**, 12 (2021).

4. B. Worku, T. Tilahun, T. T/Mariam, J. Schneider, Occurrence of intra-ventricular hemorrhage among preterm infants admitted in Tikur Anbessa Hospital. *Ethiop. Med. J.* **42**, 109–114 (2004).
5. R. L. Sherlock, P. J. Anderson, L. W. Doyle, Neurodevelopmental sequelae of intraventricular haemorrhage at 8 years of age in a regional cohort of ELBW/very preterm infants. *Early Hum. Dev.* **81**, 909–916 (2005).
6. A. H. Payne, Neurodevelopmental Outcomes of Extremely Low-Gestational-Age Neonates With Low-Grade Periventricular-Intraventricular Hemorrhage. *JAMA Pediatr.* **167**, 451 (2013).
7. D. McLendon, J. Check, P. Carteaux, L. Michael, J. Moehring, J. W. Secrest, S. E. Clark, H. Cohen, S. A. Klein, D. Boyle, J. A. George, S. Okuno-Jones, D. S. Buchanan, P. McKinley, J. M. Whitfield, Implementation of potentially better practices for the prevention of brain hemorrhage and ischemic brain injury in very low birth weight infants. *Pediatrics.* **111**, e497-503 (2003).
8. K. de Bijl-Marcus, A. J. Brouwer, L. S. De Vries, F. Groenendaal, G. van Wezel-Meijler, Neonatal care bundles are associated with a reduction in the incidence of intraventricular haemorrhage in preterm infants: a multicentre cohort study. *Arch. Dis. Child. - Fetal Neonatal Ed.* **105**, 419–424 (2020).
9. Practice Bulletin No. 171: Management of Preterm Labor. *Obstet. Gynecol.* **128**, e155–e164 (2016).
10. H. Rabe, G. M. Gyte, J. L. Díaz-Rossello, L. Duley, Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. *Cochrane Database Syst. Rev.* (2019), doi:10.1002/14651858.CD003248.pub4.
11. N. E. Vain, D. S. Satragno, A. N. Gorenstein, J. E. Gordillo, J. P. Berazategui, M. G. Alda, L. M. Prudent, Effect of gravity on volume of placental transfusion: a multicentre, randomised, non-inferiority trial. *The Lancet.* **384**, 235–240 (2014).
12. World Health Organization, *Safe Motherhood. Thermal Protection of the Newborn: A Practical Guide* (Geneva, Switzerland, 1997).
13. S. Aucott, P. K. Donohue, E. Atkins, M. C. Allen, Neurodevelopmental care in the NICU. *Ment. Retard. Dev. Disabil. Res. Rev.* **8**, 298–308 (2002).
14. M. K. Brown, D. M. Poeltler, K. O. Hassen, D. V. Lazarus, V. K. Brown, J. J. Stout, W. D. Rich, A. C. Katheria, Incidence of Hypocapnia, Hypercapnia, and Acidosis and the Associated Risk of Adverse Events in Preterm Neonates. *Respir. Care.* **63**, 943–949 (2018).
15. J. L. Ballard, J. C. Khoury, K. Wedig, L. Wang, B. L. Eilers-Walsman, R. Lipp, New Ballard Score, expanded to include extremely premature infants. *J. Pediatr.* **119**, 417–423 (1991).
16. H. J. McCrea, L. R. Ment, The Diagnosis, Management, and Postnatal Prevention of Intraventricular Hemorrhage in the Preterm Neonate. *Clin. Perinatol.* **35**, 777–792 (2008).
17. H. Blencowe, S. Cousens, D. Chou, M. Oestergaard, L. Say, A.-B. Moller, M. Kinney, J. Lawn, the Born Too Soon Preterm Birth Action Group (see acknowledgement for full list), Born Too Soon: The global epidemiology of 15 million preterm births. *Reprod. Health.* **10**, S2 (2013).
18. M. Gladstone, C. Oliver, N. Van den Broek, Survival, Morbidity, Growth and Developmental Delay for Babies Born Preterm in Low and Middle Income Countries – A Systematic Review of Outcomes Measured. *PLOS ONE.* **10**, e0120566 (2015).
19. S. T. M. Marba, J. P. S. Caldas, L. E. F. Vinagre, M. A. Pessoto, Incidence of periventricular/intraventricular hemorrhage in very low birth weight infants: a 15-year cohort study. *J. Pediatr. (Rio J.)* (2011), doi:10.2223/JPED.2137.
20. L. Christ, J. Barber, A. Murray, M. Dunleavy, J. Stoller, D. Taha, L. Brown-Jackson, M. McElroy, M. Posencheg, REDUCING INTRAVENTRICULAR HEMORRHAGE IN A LEVEL III NEONATAL INTENSIVE CARE UNIT. *BMJ Qual. Saf.* **24**, 731–732 (2015).
21. M. B. Schmid, F. Reister, B. Mayer, R. J. Hopfner, H. Fuchs, H. D. Hummler, Prospective Risk Factor Monitoring Reduces Intracranial Hemorrhage Rates in Preterm Infants. *Dtsch. Aerzteblatt Online* (2013), doi:10.3238/arztebl.2013.0489.
22. I. Fortmann, L. Mertens, H. Boeckel, B. Grüttner, A. Humberg, M. Astiz, C. Roll, I. Rickleffs, A. Rody, C. Härtel, E. Herting, W. Göpel, V. Bossung, A Timely Administration of Antenatal Steroids Is Highly Protective Against Intraventricular Hemorrhage: An Observational Multicenter Cohort Study of Very Low Birth Weight Infants. *Front. Pediatr.* **10**, 721355 (2022).

23. D. Szpecht, M. Szymankiewicz, I. Nowak, J. Gadzinowski, Intraventricular hemorrhage in neonates born before 32 weeks of gestation—retrospective analysis of risk factors. *Childs Nerv. Syst.* **32**, 1399–1404 (2016).
24. N. Köksal, B. Baytan, Y. Bayram, E. Nacarküçük, Risk factors for intraventricular haemorrhage in very low birth weight infants. *Indian J. Pediatr.* **69**, 561–564 (2002).
25. I. Kolic, J. R. Nisevic, I. Prpic, High grade intraventricular hemorrhage in preterm infant – Risk factors and outcome. *Eur. J. Paediatr. Neurol.* **21**, e69 (2017).
26. K. El-Atawi, Risk Factors, Diagnosis, and Current Practices in the Management of Intraventricular Hemorrhage in Preterm Infants: A Review. *Acad. J. Pediatr. Neonatol.* **1** (2016), doi:10.19080/AJPN.2016.01.555561.
27. K. Nakashima, T. Yamashita, S. Kashiwagi, N. Nakayama, T. Kitahara, H. Ito, The effect of sodium bicarbonate on CBF and intracellular pH in man: Stable Xe-CT and ^{31} P-MRS. *Acta Neurol. Scand.* **93**, 96–98 (1996).
28. S. K. Chilakala, H. Parfenova, M. Pourcyrous, The effects of sodium bicarbonate infusion on cerebrovascular function in newborn pigs. *Pediatr. Res.* (2021), doi:10.1038/s41390-021-01876-x.
29. P. Ballabh, Intraventricular Hemorrhage in Premature Infants: Mechanism of Disease. *Pediatr. Res.* **67**, 1–8 (2010).
30. R. Aaslid, K. F. Lindegaard, W. Sorteberg, H. Nornes, Cerebral autoregulation dynamics in humans. *Stroke.* **20**, 45–52 (1989).
31. R. B. Panerai, J. S. Minhas, O. Llwyd, A. S. M. Salinet, E. Katsogridakis, P. Maggio, T. G. Robinson, The critical closing pressure contribution to dynamic cerebral autoregulation in humans: influence of arterial partial pressure of CO2. *J. Physiol.* **598**, 5673–5685 (2020).
32. H. S. Bada, S. B. Korones, E. H. Perry, K. L. Arheart, J. D. Ray, M. Pourcyrous, H. L. Magill, W. Runyan, G. W. Somes, F. C. Clark, K. V. Tullis, Mean arterial blood pressure changes in premature infants and those at risk for intraventricular hemorrhage. *J. Pediatr.* **117**, 607–614 (1990).
33. K. Javorka, K. Haskova, B. Czippelova, M. Zibolen, M. Javorka, Blood Pressure Variability and Baroreflex Sensitivity in Premature Newborns—An Effect of Postconceptional and Gestational Age. *Front. Pediatr.* **9**, 653573 (2021).
34. H. Zhou, X. Hou, R. Cheng, Y. Zhao, J. Qiu, Effects of Nasal Continuous Positive Airway Pressure on Cerebral Hemodynamics in Preterm Infants. *Front. Pediatr.* **8**, 487 (2020).
35. M. P. Collins, J. M. Lorenz, J. R. Jetton, N. Paneth, Hypocapnia and Other Ventilation-Related Risk Factors for Cerebral Palsy in Low Birth Weight Infants. *Pediatr. Res.* **50**, 712–719 (2001).
36. A. Okumura, F. Hayakawa, T. Kato, K. Itomi, K. Maruyama, N. Ishihara, T. Kubota, M. Suzuki, Y. Sato, K. Kuno, K. Watanabe, Hypocarbia in Preterm Infants With Periventricular Leukomalacia: The Relation Between Hypocarbia and Mechanical Ventilation. *PEDIATRICS.* **107**, 469–475 (2001).
37. W. Zhou, W. Liu, Hypercapnia and hypocapnia in neonates. *World J. Pediatr.* **4**, 192–196 (2008).
38. M. Slevin, N. Farrington, G. Duffy, L. Daly, J. Murphy, Altering the NICU and measuring infants' responses. *Acta Paediatr.* **89**, 577–581 (2007).
39. Carole Kenner,, Judy Wright Lott, *Comprehensive Neonatal Nursing Care* (Springer Publishing Company, LLC, New York, ed. 5th, 2014).
40. A. Pellicer, F. Gaya, R. Madero, J. Quero, F. Cabanas, Noninvasive Continuous Monitoring of the Effects of Head Position on Brain Hemodynamics in Ventilated Infants. *PEDIATRICS.* **109**, 434–440 (2002).
41. S. Malusky, A. Donze, Neutral Head Positioning in Premature Infants for Intraventricular Hemorrhage Prevention: An Evidence-Based Review. *Neonatal Netw.* **30**, 381–396 (2011).
42. O. Romantsik, M. G. Calevo, M. Bruschettini, Head midline position for preventing the occurrence or extension of germinal matrix-intraventricular haemorrhage in preterm infants. *Cochrane Database Syst. Rev.* (2020), doi:10.1002/14651858.CD012362.pub3.