

## Association between Intracerebral Hemorrhage and Cerebral Palsy in Preterm Infant: A Systematic Review Article

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### Abstract

**Background:** Intracerebral hemorrhage (ICH) is a type of intracranial bleed that occurs within the brain tissue or ventricles. The present study aimed to review the association between ICH and cerebral palsy (CP) in the preterm infants.

**Materials and Methods:** In the systematic review, the electronic databases of Medline, Web of Science, Cochrane, EMBASE, and Scopus were systematically searched to find the relevant studies using the main keywords of (Premature OR Preterm OR Premature Infant OR Premature Birth) AND (Cerebral Palsy) AND (Brain Hemorrhage OR Intracranial Hemorrhages OR Cerebral Hemorrhage OR Putaminal Hemorrhage) up to October 26, 2019.

**Results:** Finally, three studies with 1,730 participants were enrolled in this study. In the first study, results showed no strong association between early brain lesions with subsequent neurological consequences; in addition, the association between chorioamnionitis in intrauterine life was not substantiated with the incidence of brain lesions. In the second study, results showed progression of brain lesions and neurodevelopmental disorders like other previous studies in the follow-up of very preterm (VPT) infants up to the age of two; overall, the preterm infants are at greater risk of brain damage and neurodevelopmental disorders than term infants, independent of risk factors. In the third study, a neurological assessment was performed in the fourth, 8th, 12th, and 18th months to detect the function of the neuromotor system and CP, with higher degrees of cerebral hemorrhage associated with a higher prevalence of neurodevelopmental defects.

**Conclusion:** Cerebral hemorrhage is considered a very important pathologic factor in preterm and low birth weight infants, which is associated with irreversible consequences of neurocognitive development.

**Key Words:** Cerebral Palsy, Intracerebral Hemorrhage, Preterm Infant.

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## 1- INTRODUCTION

Intracranial hemorrhage (ICH) is the most common intracranial disorder in preterm infants. Preterm infant survival has increased today with the rapid diagnosis and care of infants, and the ICH remains a major problem in preterm infants (1). The ICH is associated with severe neurological complications and high mortality, with a prevalence of 15% in infants weighing less than 1500 g and gestational age less than 32 weeks. The highest risk is for infants born at less than 28 weeks' gestation and weighing less than 1000 g, with a prevalence of 30% reported (2). The ICH is divided into five groups according to the site of occurrence and complications, two of which are common in preterm infants: cerebellar hemorrhage that is caused by hypoxia and traumatic events and is dangerous, and intraventricular hemorrhage (IVH) that can occur only in preterm infants and is inversely correlated with gestational age, so that infants younger than 28 weeks are three times more likely to have hemorrhage and infants less than 28-31 weeks are twice as likely to have hemorrhage. It often occurs in the first two days and mainly in the first week of life and is clinically dangerous (3).

The IVH as one of the most common complications of preterm infants occurs in the germinal matrix, which is the highly vascular region of the prenatal and premature brain and is prone to hemorrhage, and can cause post-hemorrhagic hydrocephalus (PHH), long-term disability, cerebral palsy (CP), mental retardation, seizures, cognitive and behavioral disabilities and death in patients. Preventing IVH in neonatal period can improve neurological outcomes in these children (4). Apart from preterm birth, which is the most important predisposing factor for IVH, factors such as respiratory distress, hypoxia, ischemia, hypotension or hypertension, elevated

central venous pressure, pneumothorax and hypovolemia increase the risk of IVH (5). The preterm infants with PHHs who require ventriculoperitoneal (VP) shunt placement are at significant risk for neurodevelopmental complications. Reportedly, 75% to 90% of these infants show a wide range of common disabilities, such as CP, mental health disorders and epilepsy, as well as neurobehavioral disorders, such as attention deficit hyperactivity disorder (ADHD), and emotional/behavior disorder (E/BD).

The preterm infants, behind PHH, have significantly lower quality of life compared to the preterm peers (6). The CP as one of the most common static encephalopathies of the movement and posture with non-progressive course in childhood occurs due to brain injury in development, in approximately 2 to 2.5 births per 1000 live births. Such infants may experience a wide range of developmental motor, postural, coordination, sensory and intelligence disorders (7). Various statistics have been reported on CP etiology, some of which include perinatal asphyxia, intrauterine factors, preterm labor, jaundice and trauma (8). Survival rates in low birth weight, very low birth weight and preterm infants have increased significantly in recent years owing to advances in prenatal care and setting up of neonatal intensive care units.

The survived infants are more susceptible to disorders such as severe disabilities, mental retardation, CP, and vision/hearing impairments. Another report indicates a prevalence of CP up to two per 1000 live births in the United States. Although the prevalence of CP is now significantly reduced due to prenatal infections and Kernicterus, preterm birth and low birth weight have increased the prevalence of this disorder, leading to a new generation of CP, especially in developed countries. The reason may be attributed to brain injury in preterm infants with

Intraparenchymal hemorrhage (IPH), and IVH as well as white matter injury, which are different in full-term birth (2). The literature review revealed three studies examining the association between ICH and CP. The first study reported the association of IVH with CP (3). In the second study, the preterm infants with ICH had greater incidence of CP compared to controls without ICH (9). In the third study, the CP in low-grade IVH with manifestations of neurologic deficits could occur in the infants older than two years (10). Due to the absence of a study evaluating the association between ICH and CP, the present study aimed to review the association between ICH in the preterm infants and CP.

## 2- MATERIALS AND METHODS

### 2-1. Search strategy

Systemic research of electronic databases: Medline (via PubMed), Web of Science, EMBASE, Cochrane and Scopus were systematically searched to find the relevant studies using the main keywords of (Premature OR Preterm OR Premature Infant OR Premature Birth) AND (Cerebral Palsy) AND (Brain Hemorrhage OR Intracranial Hemorrhages OR Cerebral Hemorrhage OR Putaminal Hemorrhage) from the inception to October 26, 2019 in the context of Article title/ Abstract/ and Key words.

### 2-2. Eligibility criteria

Participants, interventions, comparators, and outcomes (PICO) was used to formulate the review objective and inclusion criteria (11). All studies assessed the association between intracerebral hemorrhage and cerebral palsy in preterm infants up to October 26, 2019.

### 2-3. Selection process of relevant articles

Two independent reviewers selected the related studies in two steps. The first step

(screening) involved reviewing the title or abstracts of the searched articles so that all items that appeared to meet the inclusion and exclusion criteria, as well as those that were suspicious and needed to be studied in their full text, were directed into the second step. In the second step, the full text of the remaining articles was carefully reviewed and articles that met the inclusion and exclusion criteria were systematically reviewed; the third reviewer resolved any disagreement. In addition, the reference section of the entered articles and review articles on the study subject were also carefully reviewed for a more comprehensive search.

### 2-4. Screening step and data extraction

Two independent researchers were responsible for the data extraction, and a consensus or a third party resolved any discrepancy. The required data were the name of first author, year of study, country of study, method of measurement, scales, key findings and primary outcome. The primary outcome was association between intracerebral hemorrhage and cerebral palsy in preterm infants.

### 2-5. Quality assessment of included articles

STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) statement for observational (non-randomized) studies was used to assess quality of studies (12).

This included 22 items. Some items are study design, objectives, key results, setting, bias, statistical, limitations, interpretation and generalizability (**Table.1**). Two reviewers carried out the assessment independently and in duplication, and the third reviewer resolved any discrepancies.

**Table-1:** Some of characteristic of included studies and quality assessment using STROBE scale (12).

Author, Year, Country, Reference	Study design	Aim of study	Study size	Scale	Key results	STROBE score
Zayek et al., 2012, USA, (15)	Cohort	The effect of CH on mortality and ND outcome	1120	Cranial ultrasounds	CH is an important pathology in the preterm infant. CH should be specifically suspected in the most extremely immature and sick infant.	18
Kidokoro et al., 2014, New Zealand, (14)	Cohort	The relationships of injury and growth impairment to perinatal risk factors and subsequent neurodevelopmental outcome.	325	MRI scans	Severe brain injury and impaired brain growth patterns were independently associated with prenatal risk factors and delayed cognitive development.	18
Dyet et al., 2005, UK, (13)	Cohort	The range of cerebral injury and abnormalities of cerebral development in preterm infants, and to correlate those findings with eurodevelopmental outcome after birth.	119	MRI scans	Diffuse white matter abnormalities and post-hemorrhagic ventricular dilation are common at term and seem to correlate with reduced developmental quotients.	17

### 3- RESULTS

Finally, three studies with 1,730 participants were enrolled in this systematic review. In a cohort study, Dyet et al. in 2006, investigated the range of cerebral injury and neurodevelopmental defects in the infants born between 23 and 30 weeks of age at Hammersmith Hospital, London, United Kingdom using serial MRI scans of the brain from birth to the second day after birth, and correlated those findings with neurodevelopmental outcome after 18 months corrected age. Although a number of neonates died, the study conditions made it possible for the research team to assess the pathological status early. Four of the 119 surviving infants born at 23 to 30 weeks of gestation showed major destructive brain lesions, and tissue loss was found at term for the two survivors. Different degrees of ICH, ventricular dilatation and white matter lesions of the brain were reported in the infants, but no strong association was found between major brain lesions and subsequent neurological outcomes. In addition, the association between chorioamnionitis in intrauterine life was not substantiated with the incidence of brain lesions in this study (13). A different cohort study was conducted by Kidokoro et al. in 2014, on 448 preterm infants aged 32 weeks and less who were collected

from three different geographic regions of New Zealand, Australia and Missouri but with the same study conditions, aimed at assessing brain injury and the change in their progress as well as the predisposing and predictive factors of brain injury in the preterm infants by MRI via the same operator. Their results showed the progression of brain lesions and neurodevelopmental disorders, as in other previous studies in the follow-up of Very preterm (VPT) infants up to the age of two years. Severe brain lesions were more common in the infants with necrotizing enterocolitis, low Apgar score and patent arterial duct. Reduced bi-parietal width (BPW) on MRI was associated with low gestational age, necrotizing enterocolitis, prolonged parenteral nutrition, decreased oxygen delivery and cognitive developmental delay. Overall, the preterm infants are at risk for brain injury and neurodevelopmental disorders more than the term neonates are, independent of risk factors (14). In a prospective study, Zayek et al. in 2012 examined 1,120 eligible infants of less than 28 weeks gestation born from 1998 to 2008 with at least one cranial ultrasound, who were routinely subjected to ultrasound of both anterior and posterior fontanelle on days 2, 7, 10 and 42 and week 36. The infants with chromosomal abnormalities and congenital

malformations were excluded. Most cases of ICH were seen in the infants weighing less than the 10th percentile and gestational age less than 25 weeks. Other factors such as Apgar score < 3, one-minute Apgar score  $\leq 3$  and intubation at birth were among the most important risk factors. In addition, more cases of sepsis, metabolic acidosis, hypertension on the fifth day of birth, and pneumothorax were reported in the infants with grade III and IV cerebral hemorrhage. The neurological assessment was performed in the fourth, eighth, twelfth, and eighteenth months to detect the function of the neuromotor system and CP, with higher degrees of cerebral hemorrhage (CH) associated with a higher prevalence of neurodevelopmental defects (15).

#### 4- DISCUSSION

The current systematic review is the first study examining the association between ICH and CP in the preterm infants. The search efforts resulted in three relevant articles; in the first prospective study on 1,120 eligible neonates less than 28 weeks pregnant at birth between 1998 and 2008, the neurological assessment was performed in the fourth, eighth, twelfth, and eighteenth months to detect the function of the neuromotor system and CP, with higher degrees of cerebral hemorrhage (CH) associated with a higher prevalence of neurodevelopmental defects (15). The second study investigated the range of cerebral injury and neurodevelopmental defects in the infants born between 23 and 30 weeks of age using serial MRI scans of the brain from birth to the second day after birth, and correlated those findings with neurodevelopmental outcome after 18 months corrected age, no strong association was reported between early brain lesions with subsequent neurological consequences. In addition, the association of chorioamnionitis in intrauterine life and the incidence of brain lesions was not

substantiated in this study (13). The third study examined 448 preterm infants with gestational age of 32 weeks, the results of which showed progression of brain lesions and neurodevelopmental disorders like other previous studies in the follow-up of VPT infants up to the age of two. In conclusion, the preterm infants are at greater risk of brain damage and neurodevelopmental disorders than term infants are independent of risk factors (14). Overview studies of the developmental outcomes of the preterm infants have shown that the preterm births and very low birth weight have irreparable costs on societies worldwide, even in developed countries, from high prevalence of neonatal mortality to sustained neurological consequences in the following years after birth (16).

Developmental delays in the areas of gross motor and fine motor, hearing and visual impairments, speech problem, and in particular, neurobehavioral dysfunction following cerebral hemorrhage can be assessed with serial ultrasound followed by posthemorrhagic hydrocephalus of prematurity (5). According to previous research, most preterm infants with a gestational age of 25 to 28 weeks and weight loss at birth up to 750 g are exposed to neurodevelopmental impairments following IVH and ICH, which consequently result from CP disabilities. It has been proven that the destructive lesions following intraparenchymal hemorrhage are equated with persistent neurocognitive and behavioral problems that are associated with mental retardation in school-age children, and motor disability (13). In a recent study, Agajany et al. in 2019 examined the effect of neonatal posthemorrhagic hydrocephalus of prematurity requiring shunt placement in preterm infants less than 32 weeks of gestation on the pattern of family functioning in preschool children.

Pathological conditions, including CP with the highest brain prevalence (81.6%), visual impairment (63.2%), incidence of chronic diseases and hospital admissions in the first six months of birth (44.7%), and other hearing and nutritional problems had the highest socioeconomic burden, with enduring family defects (6). In a historic cohort study, the Neonatal Research Network in Japan investigated the effects of late-onset circulatory collapse (LCC) in response to glucocorticoid therapy in preterm infants, which caused severe and systemic hypotension, and a compensation system for increasing volume or increased level of vasoconstrictors was not responsive and resulted in postnatal complications.

The onset of late-onset outcomes, such as CP, in the infants aged 36-42 months with 22-27 weeks' gestation at birth between 2008 and 2012 showed that 666 of 3,474 infants experienced LCC and subsequently CP (9). There have been many studies on the severity of ICH and its association with persistent neurodevelopmental outcomes. However, mild IVH in the very low birth weight and preterm infants born between 23 and 28 weeks of gestation showed postpartum delayed and persistent neurological complications. Briana and Malamitsi-Puchner in 2019 investigated the neurodevelopmental and motor consequences in the infants with grades I and II IVH, using the cranial ultrasound. Although numerous challenges have been reported due to the variety of studies, data collection, demographic characteristics and diverse maternal and neonatal morbidities, differences in measurement tools and other different parameters of short- and long-term follow-up and presence or absence of neurological complications; for example, the preterm and very preterm infants with low-grade IVH may not have neurological consequences and cognitive problems in childhood, as in the infants without IVH, learning problems and cognitive/executive

dysfunction were documented in 16-year-old teens with low-grade IVH. Therefore, it is recommended that follow-up monitoring techniques of these infants using advanced MRI should be continued during the postnatal and school years compared to the cohort term infants (10).

## 5- CONCLUSION

According to these reports, cerebral hemorrhage is considered a very important pathologic factor in preterm and low birth weight infants, which is associated with irreversible consequences of neurocognitive development, and it should be given special attention by pediatric perinatologists now more than ever.

**6- CONFLICT OF INTEREST:** None.

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