Review

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Novel and Debatable Preventive Strategies for Intraventricular Hemorrhage in Preterm Neonates

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Abstract

Intraventricular hemorrhage (IVH) is a common complication of prematurity and continues to represent a considerable threat due to its association with significant short- and long-term morbidity and mortality. Despite the advances in neonatal care, the prevalence of IVH, particularly in the extremely preterm neonates, remains high. Therefore, it is imperative to recognize and implement in clinical practice preventive strategies, non-pharmacological or pharmacological, to reduce IVH effectively. The aim of this narrative review is to provide an overview of novel and debatable preventive measures for IVH that could be implemented in daily practice to potentially improve outcomes for very preterm neonates. IVH prevention bundles (IVHPBs) consist of strategies that aim to minimize hemodynamic and cerebral perfusion fluctuations, which are a crucial component of IVH pathogenesis. Early postnatal prophylactic indomethacin, erythropoietin, and insulin growth factor-1 administration have shown encouraging results on IVH prevention; however, the literature is still inconclusive. Stem cell-based interventions represent novel and promising techniques with the potential to contribute to the prevention of IVH. The prevention of IVH remains a field of investigation, and there is a requirement for conclusive evidence and recommendations. The necessity for further large-scale prospective studies is therefore evident.

Keywords: intraventricular hemorrhage; preterm neonates; prevention; prevention bundles; indomethacin; erythropoietin; insulin-growth factor 1; stem cells

1. Introduction

Despite the significant advances in perinatal care, prematurity remains a leading cause of neonatal morbidity and mortality [1,2]. Intraventricular hemorrhage (IVH) is a major contributor to preterm brain injury and is associated with adverse neurodevelopmental outcomes. It is an early complication of prematurity that typically occurs within the first three postnatal days, mainly affecting neonates with a gestational age (GA) of less than 32 weeks. The incidence of IVH is inversely correlated with GA, and differs among centers and geographic regions [3]. Reported rates are up to 45% in neonates with a GA of less than 23 weeks, and 2% in neonates born at 30–32 weeks of gestation [2,4,5]. Despite the considerable improvement in survival rates of preterm neonates that has been achieved, there is an inconsistency in the trend of IVH rates over time among the different studies. The extant literature on the subject is inconclusive, with some studies reporting a decline and others reporting no difference compared to previous decades [2,6-8]. An Australian study compared the incidence of IVH rates in a large cohort of preterm neonates with a GA < 32 weeks in 17 years and observed a significant decline in both IVH of any grade (23.6% vs. 21.4%,$p<0.01$) and severe IVH (4% vs. 2.8%, $p<0.01$) [6]. However, a recent systematic review and meta-analysis compared the incidence of IVH in studies conducted prior to and following 2007, and reported no significant difference [2].

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IVH typically originates from the periventricular germinal matrix (GM) located within the caudothalamic groove, underneath the ventricular ependyma. The GM is a highly cellular, vascularized, and metabolically active region. It is characterized by an irregular, immature capillary network that lacks sufficient structural support. GM begins to involute after 24 weeks of gestation and is typically absent in neonates born at term [9,10]. Moreover, this fragile network is located at the border between the small cerebral arteries and the deep cerebral vein system, rendering it vulnerable to hemodynamic fluctuations [11].

The pathogenesis of IVH is multifactorial and is mainly attributed to the fragility of the GM and fluctuations in cerebral blood flow. Impaired cerebral autoregulation in preterm neonates, particularly those who are clinically unstable, leads to pressure-passive cerebral blood flow, which is the inability to maintain constant blood flow in response to fluctuations in arterial pressure. Hypercarbia, acidemia, anemia, and hypoglycemia have also been associated with cerebral blood flow fluctuations. Cerebral blood flow fluctuations increase the likelihood of vascular rupture in the GM. The subsequent hemorrhage may be contained within the GM or extend to the lateral ventricle [10,11].

The severity of IVH is graded based on the extent and presence of dilatation of the lateral ventricle, primarily using the Papile or Volpe grading systems [12]. Severe intraventricular hemorrhage (sIVH) refers to grades III and IV hemorrhages, which are characterised by ventricular dilatation and/or extension into the parenchyma [10].

Severe IVH is associated with increased mortality and adverse neurodevelopmental outcomes in survivors, such as intellectual disability, motor deficits, hearing and visual impairment, and cerebral palsy [14,15]. A recent prospective cohort study reported mortality rates of 55.2% and neurodevelopmental impairment at the corrected age of 18-24 months in 43.3% of infants with sIVH [15]. Moreover, a recent meta-analysis has reported a 3- to 4-fold increased risk of moderate to severe neurodevelopmental impairment at the age of three years in neonates with sIVH [16]. Conversely, data on the neurodevelopmental outcomes of infants with low-grade IVH are still inconclusive and remain a topic of debate [15,17-19,20-22]. Several studies have observed a comparable neurodevelopmental outcome between infants with low-grade IVH and those with no IVH [15,17-19]. However, two recent meta-analyses concluded that infants with low-grade IVH are at an increased risk of neurodevelopmental impairment compared to infants without IVH [14,16].

The potential detrimental effects of IVH on the survival and neurodevelopment of preterm neonates underscore the necessity for the implementation of effective preventative strategies to reduce the incidence of IVH in this vulnerable population. The primary antenatal preventive measures for IVH consist of antenatal corticosteroids and magnesium sulfate administration, antenatal transfer and delivery at centers with expertise in neonatal care, and the still debatable caesarean section in periviable births [23-28]. Delayed cord clamping and advances in neonatal care, including non-invasive respiratory support, surfactant administration, and circulatory management, are some of the perinatal strategies that contribute to the prevention of IVH [6,11,29-31].

Although several antenatal and perinatal strategies have been proven to be effective in the prevention of IVH and have been widely implemented, the incidence of IVH among preterm neonates remains high. Therefore, in view of the increasing survival of the most vulnerable extremely preterm neonates, there is a necessity for more effective strategies to achieve a decline in IVH rates and to improve both survival and long-term prognosis of these neonates. This narrative review aims to provide clinicians with an overview of the current literature on novel and debatable preventive measures for IVH that could be implemented in daily practice and potentially improve outcomes for very preterm neonates.

2. Methods

A comprehensive search of the PubMed and Google Scholar databases up to June 2025 was conducted based on the following keywords: *intraventricular hemorrhage; preterm neonates; prevention; prevention bundles; indomethacin; erythropoietin; insulin-growth factor 1; stem cells.* Additionally, the

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reference lists of all retrieved articles were screened to identify any further relevant studies that may not have been identified in the initial search. Randomized control trials (RCTs), systematic reviews, narrative reviews, and observational studies were included.

3. Results

3.1. IVH Prevention Bundles (IVHPB)

IVH prevention bundles (IVHPB) aim to minimize hemodynamic and cerebral perfusion fluctuations during the critical period of the first postnatal days. Despite the existence of several strategies incorporating IVHPB in different centers, these involve minimal handling, head positioning, blood pressure management, thermoregulation, appropriate respiratory support, avoidance of rapid intravenous fluid administration or rapid blood draws, and avoidance of stress and pain [32-34]. However, inconsistent results regarding the efficacy of IVHBP as a preventive measure to decrease sIVH incidence in preterm neonates have been reported among different studies.

A significant reduction in the incidence of IVH of any grade in preterm neonates with a GA <30 weeks was reported by de Bijl-Marcus et al. following the implementation of a series of nursing interventions, including the following: the maintenance of a tilted midline head position; the avoidance of elevation of the legs; and the avoidance of rapid fluid flushing or blood withdrawal during the first 72 postnatal hours. The preventive efficacy of these interventions was more notable in the group of neonates with lower gestational ages (GA <27 weeks). This is probably due to the greater impact of these preventive strategies on the most immature and vulnerable populations [35]. Wong et al. observed a significant reduction in IVH rates following the implementation of neuroprotective strategies, including positioning and minimal handling, in a population of preterm neonates with a GA of less than 26 weeks [36]. A recent study also reported a significant reduction in the incidence of IVH (24.4% vs. 9.3%) after the introduction of strategies to minimize cerebral blood flow fluctuations in the routine care of preterm neonates (GA < 30 weeks) during the first three days of life [34].

Nevertheless, a number of other studies have reported failure of the IVHPB to reduce the rate of IVH in preterm populations [37,38]. In addition to differences in study populations, poor adherence to IVHPB may explain the conflicting observations regarding the efficacy in preventing IVH among different studies. This was demonstrated by Kolnik et al., who reported a significant reduction in the rates of IVH with improved adherence to clinical protocols. The incidence of sIVH in preterm neonates was compared between two epochs, when adherence to IVHPB increased from 24% (preintervention period) to 88% (intervention period), and a 76% reduction of sIVH was observed (9.8% vs. 2.4%) [32]. Tang et al. also observed a significant decrease in sIVH rates following the introduction of a bedside assessment tool that provided medical staff with real-time assessments of care bundle implementation and immediate feedback [33]. However, a recent, large, systematic review concludes that the reasons for the inconsistency of the efficacy of clinical strategies implemented to prevent IVH in different settings are not known [39].

3.2. Head Position

Fluctuations in cerebral blood flow, in association with impaired autoregulation, contribute to the pathogenesis of IVH in preterm neonates. It has been proposed that the position of the head can affect cerebral hemodynamics and potentially impact the development of IVH during the critical first days of life in the most vulnerable population [40]. The optimal posture for preterm neonates to avoid cerebral blood flow fluctuations has been the subject of investigation for many years. Although elevated midline head positioning (MHP) is widely adopted during the early transitional period in clinical practice and is a core part of IVHPB, there is still a lack of conclusive evidence on its effectiveness in preventing IVH [41].

As the two internal jugular veins represent the main outflow path for cerebral blood, it has been suggested that the lateral position of the head is associated with compression of the homolateral

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jugular vein, which can compromise venous return and lead to venous congestion and increased intracranial pressure and cerebral blood flow [42-44]. Conversely, it has been demonstrated that an elevated head position is associated with reduced central venous pressure and facilitates cerebral venous drainage [45].

A discrepancy exists among studies investigating the effect of different head positions on cerebral hemodynamics and oxygenation in neonates [46]. Ancora et al. evaluated brain hemodynamics in 24 clinically stable, very preterm neonates at six different positions using near-infrared spectroscopy (NIRS) and concluded that the effects depend on GA. No significant differences were observed in tissue oxygenation or tissue hemoglobin index. However, a decrease in cerebral blood volume was noted following head rotation in the subgroup of neonates with a GA of less than 26 weeks, as indicated by a decrease in the tissue hemoglobin index. The tissue oxygenation index remained stable [47]. Pellicer et al. conducted a study on a cohort comprising both preterm and term neonates, reporting a significant increase in cerebral blood volume with lateral head position [48]. A subsequent study by Liao et al. evaluated the effect of short-term head position changes on regional cerebral saturations in a cohort of 20 relatively stable preterm neonates with a mean GA of 26^{+5} weeks during the first three postnatal days. Although a significant decrease in regional cerebral saturation on the ipsilateral side when the head was turned to the left lateral was noted, this was determined as probably clinically insignificant. The authors concluded that brief postural changes of the head did not affect cerebral oxygenation in stable preterm neonates [46]. In a more recent study, stable very preterm neonates did not have altered cerebral blood flow velocities or regional cerebral oxygenation when the posture changed from supine MHP to prone with a lateral head position [49]. A systematic review concluded that data regarding the effects of head posturing on cerebral hemodynamics and oxygenation in preterm neonates are inconclusive [40].

In an RCT involving 48 preterm neonates with a GA of less than 30 weeks, Al-Abdi et al. randomised the subjects to be cared in either the MHP or lateral head position (both groups in 0° tilt) for the first postnatal week, and reported no difference in the incidence of IVH [50]. A multicenter RCT from the same group of authors was terminated early due to a low recruitment rate. However, no difference in the incidence of IVH was observed between the MHP and lateral head position groups in the 72 neonates enrolled [51]. Kochan et al. randomized 180 ELBW infants to be placed in either an elevated MHP (30° tilt) or a flat supine position for the first four postnatal days. The overall incidence of IVH was similar in the two groups; however, the incidence of IVH grade IV was significantly lower in the MHP group. Interestingly, although no difference in the incidence of common neonatal morbidities related to preterm birth was observed between the two groups, the in-hospital survival rate was significantly higher for neonates in the MHP group (88% vs 76%) [52]. However, in a large multicenter study involving 2021 VLBW neonates, the incidence of IVH was comparable between the elevated MHP and routine posture groups, but the risk for developing sIVH was higher in the MHP group. The authors hypothesized that this increased risk may be attributable to agitation in the neonates when maintained in a fixed position for a protracted period [53]. A recent meta-analysis concluded that, according to low-quality data, there is no impact of MHP on the incidence of IVH [54].

In conclusion, although elevated MHP is incorporated in prevention bundles for IVH and is a part of routine clinical practice on the care of preterm neonates during the first postnatal days in many NICUs based on physiological rationale, definite evidence of the effectiveness of this practice is lacking. High-quality evidence from well-designed, large RCTs is needed [41].

3.3. Indomethacin

Indomethacin, a cyclooxygenase inhibitor that has been used in NICUs since the 1970s primarily for ductal closure, remains a common medication for preterm neonates and has been ranked as the tenth most commonly used drug for ELBW neonates [55,56]. Indomethacin inhibits prostaglandin synthesis through inhibition of cyclooxygenase pathways. Moreover, it suppresses the hyperemic responses of the cerebral vascular network in situations of hypercapnia and hypoxia, and prevents

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cerebral ischemia due to impaired perfusion [57-59]. Indomethacin has also been demonstrated to promote basement membrane deposition in germinal matrix microvessels [60].

Several studies conducted in the 1990s, including two large RCTs, suggested that the early postnatal administration of a low dose of indomethacin as prophylaxis is associated with a reduced risk of IVH development [61-63] (Table 1). Several recent studies have also demonstrated the benefits of indomethacin in IVH prevention [64-67]. Indomethacin prophylaxis was associated with a significant reduction, compared to no prophylaxis, of IVH of any grade (32.7% vs. 36.9%, p=0.04), sIVH (9.7% vs. 16%, p=0.02), and mortality (15.9% vs. 23.2%, p=0.01) in a large cohort of preterm neonates with a GA <26 weeks born in the context of amniotic infection syndrome [64]. A meta-analysis of 15 trials demonstrated, with moderate certainty, a moderate reduction in sIVH with indomethacin prophylaxis [68]. The recently updated Cochrane meta-analysis on this topic concluded with moderate certainty that prophylactic indomethacin is associated with a small reduction in sIVH and a moderate reduction in mortality [69].

However, several recent studies have not proven that early indomethacin administration reduces the incidence of IVH, possibly due to significant changes in antenatal and perinatal medical practice since the two large RCTs [70-72]. Recently, Clyman et al. reported no significant difference in the rate of IVH and other neonatal morbidities among neonates with a GA of less than 25 weeks when different epochs at which indomethacin prophylaxis was routinely administered were compared with an epoch at which it was not administered [71]. Szakmar et al. also reported no reduction in the incidence of sIVH in extremely preterm neonates in the period following the implementation of a prophylactic indomethacin protocol [72]. In a combined meta-analysis of RCTs and retrospective cohort studies, Al-Matary et al. reported no significant difference in the incidence of sIVH between neonates who received prophylactic indomethacin and those who did not [73].

Several researchers have hypothesized that the benefits of prophylactic indomethacin may be more significant for preterm neonates at high risk of sIVH, and have investigated the effectiveness of risk assessment and targeted prophylaxis [65,74-76]. Luque et al. demonstrated that indomethacin prophylaxis is associated with a lower risk of IVH in a cohort of preterm neonates with a birthweight of less than 1250 g. The benefit was found to be more substantial among neonates at a higher risk of sIVH [65]. A recent multicenter retrospective study by Chawla et al. investigated the potential benefits of targeted prophylactic indomethacin administration to a group of extremely preterm neonates who were at a higher risk of IVH according to a risk prediction model based on clinical variables. The study demonstrated no reduction in the incidence of sIVH [76]. The study conducted by Foglia et al. suggests that the relative treatment effect on the risk of sIVH development showed no significant variation across the different groups, regardless of their baseline risk of IVH development. However, the absolute treatment effect was found to be dependent on the baseline risk of sIVH in the population, corresponding to a number needed to treat (NNT) of 71 in the low-risk group and 11 in the high-risk group to prevent sIVH [77].

The proposed dosing regimen based on the two early RCTs was 0.1mg/kg/day intravenously for three days, starting 6-12 hours after birth [61-62]. However, a recent retrospective study demonstrated that a single dose of indomethacin (0.2 mg/kg) within the first six hours was non-inferior to the standard regimen in terms of rates of brain injury [78]. Gillam-Krakauer et al. retrospectively compared neonates with a GA of less than 29 weeks who received a single dose of indomethacin at birth with those who did not. The GA-adjusted incidence of IVH was lower in the treated group [66]. In two retrospective studies, Mizra et al. compared the efficacy of prophylactic indomethacin initiated prior to 6 hours of age and between 6-12 hours, reporting similar efficacy in both groups [79,80].

Despite the potential for a reduced rate of sIVH in preterm neonates, a number of longitudinal studies have not demonstrated a benefit of prophylactic indomethacin at birth in terms of survival and neurodevelopmental outcome. Ment et al. compared the long-term neurodevelopmental outcomes at 36 months and 4.5 years of age in preterm neonates with a birth weight of less than 1,250 g who received prophylactic indomethacin within 12 hours of birth, and in neonates who received a

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placebo. They reported no significant difference in the rates of cerebral palsy or neurosensory impairment. A lower incidence of intellectual disability was observed among children who received prophylactic indomethacin at birth at the age of 4.5 years, which was not sustained at the age of 12 years [81,82]. A large multicenter RCT (Trial of Indomethacin Prophylaxis in Preterm-TIPP) by Schmidt et al., involving 1202 ELBW neonates, reported a significant reduction in the incidence of sIVH among neonates treated with prophylactic indomethacin compared to placebo. However, no benefit of the composite outcome of death or severe neurodevelopmental impairment at the age of 18 months was demonstrated [61]. In a post-hoc analysis of the TIPP trial, Foglia et al. recently investigated the long-term effects of targeted indomethacin prophylaxis on ELBW neonates at a higher risk of sIVH and concluded that selective prophylaxis did not offer an advantage in terms of survival or neurodevelopmental outcome [77].

The lack of an established long-term benefit of early indomethacin prophylaxis, coupled with concerns regarding potential adverse effects, has resulted in a diversity of practices among NICUs [76]. Indomethacin has vasoconstrictive properties, which may consequently alter blood flow in the central nervous, renal and gastrointestinal systems [83]. Although a number of retrospective studies have reported an increased risk of spontaneous intestinal perforation or necrotizing enterocolitis, a recent Cochrane review provides more reassurance, reporting no significant difference in rates of gastrointestinal pathologies or cerebral palsy [68,76,84].

Table 1. Studies investigating the efficacy of indomethacin prophylaxis for preventing IVH compared with routine care.

Author	Type of study	Population	Dosage	IVH (IP vs. control)	sIVH (IP vs. control)	Main Conclusions
Ment, 1994 [62]	RCT	431 neonates, BW 600-1250g (209 IP-222 placebo)	0.1 mg/kg at 6-12 hours, followed by 0.1 mg/kg/day for 2 days	14% vs. 18%, p=0.03)	0.5% vs. 4.5%, p=0.01 (grade IV IVH)	IP was associated with reduced rate of IVH and particularly grade IV IVH
Smidt, 2001 [61]	RCT	1202 neonates, BW 500-999g (601 IP-601 placebo)	0.1 mg/kg/day for 3 days	ND	9% vs. 13%, p=0.02	IP reduced the rate of sIVH and PDA IP did not improve survival without neurosensory impairment at 18 months
Yanowitz, 2003 [67]	Retrospective cohort	160 neonates, GA < 29 weeks ,BW < 1350g (102 IP-158 (evaluated for PDA at 26 hours) of who 117 received indomethacin)	0.1mg/kg/day at <24h hours for 3 days (IP) 0.2 mg/kg at 36h flowed by 2 doses, every 12 hours 0.1-0.2mg/kg (PDA)	ND	6% vs. 14%, p=0.041	Reduced incidence of sIVH with IP compared to early echocardiographic strategy
Nelin, 2017 [70]	Retrospective cohort	671 outborn neonates, GA <28 weeks (530 IP-141 controls)	ND	55% vs. 53%, p=0.63	21% vs. 23%, p=0.64	IP was not associated with lower IVH rates IP was associated with improved survival rates
Gillam-Krakauer, 2021 [66]	Retrospective cohort	384 neonates, GA< 29 weeks (299 IP-85 control)	0.2 mg/kg at 12 hours (single dose)	38% vs. 45%	12% vs. 14%	Decreased IVH rates with IP, in the gestation-adjusted but not in the propensity-adjusted model IP was associated with decreased mortality No increased risk of acute kidney injury
Clyman, 2022 [71]	Intention-to-treat, Cohort-controlled	106 neonates, GA<25 weeks (68 IP-38 controls)	0.2 mg/kg at <24 hours, followed by 2-4 doses 0.1 mg/kg	ND	27% vs. 35%	IP was not associated with a significant reduction in IVH or other prematurity-related morbidities IP was associated with a lower risk of PDA associated morbidities
Hanke, 2023 [64]	Observational multicenter cohort	1767 neonates, GA<26 weeks with amniotic infection syndrome (195 IP-1572 controls)	0.1 mg/kg/day for up to 3 days	32.7% vs. 36.9%, p=0.04	9.7% vs. 16%, p=0.02	Singificant reduced IVH rates in preterm neonates with amniotic infection syndrome

RCT: randomized controlled trial; GA: gestational age; BW: birthweight; IP: indomethacin prophylaxis; IVH: intraventricular hemorrhage; PDA: patent ductus arteriosus; ND: no data.

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3.4. Erythropoietin (EPO)

Human erythropoietin (EPO) is a glycoprotein that is primarily known for its role in erythropoiesis, and recombinant EPO (rhEPO) is widely used in preterm neonates to address the issue of anemia of prematurity [85]. Apart from its role as an erythropoietic agent, EPO exerts neuroprotective effects due to its anti-apoptotic, anti-inflammatory, and anti-oxidative properties [86]. Moreover, EPO has been shown to promote cerebral vascular stability through the inhibition of apoptosis and the promotion of angiogenesis in brain capillaries, thereby contributing to the maintenance of cerebral vascular integrity [86-88]. A number of studies have investigated the potential neuroprotective effects of rhEPO in neonates at risk of brain injury, including preterm neonates and those with hypoxic-ischemic injury; however, the results regarding its benefit to long-term neurodevelopmental outcomes have been inconsistent [85]. The potential benefits of administering EPO early postnatally, at different dosing regimens with high or low doses, to prevent IVH in preterm neonates have been investigated; however, the data remain inconclusive [85,89] (Table 2).

As less than 2% of EPO crosses the blood-brain barrier, it has been suggested that high doses are necessary to achieve neuroprotective effects [90]. Moreover, studies on experimental animals have shown that the neuroprotective effect of rhEPO is dose-dependent, with high doses being required to improve both short- and long-term outcomes [91,92]. Several studies have been conducted to assess the efficacy and safety of high-dose rhEPO in preterm neonates, based on this evidence. Juul et al. in a multicenter RCT involving 941 preterm neonates with a GA < 28 weeks, compared the rate of short-term morbidities and the neurodevelopmental outcome at the age of two years in neonates that received high-dose rhEPO (1000 U/kg intravenously every 48 hours for 6 doses, followed by 400 U/kg subcutaneously three times per week until 32 weeks corrected age) and placebo. The rates of IVH of any grade and sIVH were comparable in both groups, as were the rates of other prematurity complications and neurodevelopmental outcomes [93]. Similar findings regarding IVH and other complications of prematurity were reported by Fauchère et al. in an RCT, in which preterm neonates with a GA of 26–32 weeks were given three intravenous doses of rhEPO or a placebo at 3, 12–18, and 36–42 hours postnatally [94]. Neither of these two large-scale studies identified any safety concerns associated with the administration of high-dose rhEPO, such as an increased risk of premature complications or adverse events, such as arterial hypertension or thromboembolic events, that have been reported in adult populations [93,94]. However, according to the preliminary report of the Erythropoietin for the Repair of Cerebral Injury in Very Preterm Infants (EpoRepair) trial, in which 121 preterm neonates with GA < 32 weeks and moderate or severe IVH were enrolled to investigate the efficacy of high-dose rhEPO (2000 U/kg/day intravenously every 24 hours for three days and two further doses at days 10 and 17 after the initial dose), a statistically insignificant increase in the mortality rate was observed in the rhEPO group compared to the placebo group (16.7% vs. 8.2%, p=0.15) [95].

Despite the evidence that high doses of rhEPO are required to exert its neuroprotective activity, studies have shown that the administration of repeated low doses of rhEPO to prevent anemia of prematurity in preterm neonates resulted in beneficial neurodevelopmental outcomes. Furthermore, the cumulative dose of rhEPO was associated with long-term outcomes [96,97]. Song et al. randomised 743 very preterm neonates to receive either 500U/kg of rhEPO intravenously within the first three days of life and subsequently every other day for two weeks, or a placebo. They reported a significantly lower incidence of sIVH in the EPO-treated group compared to the placebo-treated group (6.6% vs. 15.9%, p<0.001, respectively) and significantly lower rates of neurological disability at 18 months (p<0.001) [98]. A significantly decreased rate of sIVH in neonates who received the same dosing regimen of rhEPO compared to placebo (3.9% vs. 7.6%, p = 0.001) was reported in an RCT reanalysis from the same group of authors, involving 1898 very preterm neonates [99]. Moreover, a recent pilot study demonstrated a 97% decrease in the odds of IVH in preterm neonates who received 400 units/kg intravenously three times per week until 32 weeks of corrected age [89]. However,

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Peltoniemi et al. reported no significant difference in the rate of IVH with the administration of 250 U/kg/day rhEPO in the first 6 postnatal days [100].

The evidence regarding the efficacy of early postnatal rhEPO in the prevention of IVH remains inconclusive. Ohlsson et al., in a Cochrane systematic review, reported no significant difference in the incidence of IVH of any grade in preterm neonates with a GA of less than 32 weeks who received early postnatal rhEPO (RR:0.98, 95% CI 0.76 to 1.26). However, a significant reduction in sIVH was noted (RR:0.60, 95% CI 0.43 to 0.85) [101]. According to another meta-analysis of 12 studies, a moderate reduction in sIVH was reported with early rhEPO administration (RR: 0.68; 95% CI: 0.57–0.83) [67].

Although several studies have reported no safety concerns regarding the early postnatal administration of rhEPO in preterm neonates, further research is required before definitive conclusions can be established [93,94,100,101]. Although concerns were raised in previous versions of the Cochrane review about an increased risk of retinopathy of prematurity (ROP) in preterm neonates treated with rhEPO, a recent Cochrane systematic review concluded that there is no increased risk of ROP of any grade or severe ROP following early postnatal rhEPO administration [101].

Table 2. Studies investigating the efficacy of early prophylactic erythropoietin administration in the prevention of IVH in preterm neonates.

Author	Study	Population	Dosage	IVH (EPO vs. control)	sIVH (EPO vs. control)	Main conclusions
Ohls, 2014 [96]	RCT	99 neonates, BW 500-1250g (33 rhEPO-33 darbepoetin-33 placebo)	400 U/kg rhEPO sc three times per week until 35 weeks PMA	ND	9.4% vs. 23%	There was no statistically significant difference in the rate of sIVH and other prematurity complications between groups. EPO and darbepoetin administration were associated with fewer transfusions and exposure to fewer donors.
Fauchere, 2015 [94]	RCT	443 neonates, GA 26-32 weeks (229 rhEPO- 214 placebo)	3000 U/kg iv rhEPO at the age of <3 hours, 12-18 hours and 36-42 hours	21.1% vs. 18.8%	ND	Early high-dose of rhEPO was not associated with adverse effects, and no significant differences in prematurity complications were observed.
Song, 2016 [98]	RCT	743 neonates, GA < 32 weeks (336 rhEPO-377 placebo)	500 U/kg iv rhEPO, initial dose <72 h postnatally, every other day for 2 weeks	ND	6.6% vs. 15.9% (p<0.001)	Repeated low doses of rhEPO significantly reduced the incidence of sIVH and the neurodevelopmental disability at 18 months.
Peltoniemi, 2017 [100]	RCT	39 neonates, BW 700-1500g, GA < 30 weeks (21 rhEPO-18 placebo)	250 U/kg/day iv rhEPO during the first 6 postanatal days	14% vs. 17% (p=1.000)	10% vs. 0% (p=0.490)	Early postnatal administration of rhEPO without iron supplementation reduced the iron load. No benefit on IVH incidence or neurodevelopmental outcome at 2 years. No significant difference in the rate of prematurity complications (IVH, ROP, NEC)
Juul, 2020 [93]	RCT	941 neonates, GA 24-28 weeks (376 rhEPO-365 placebo),	1000 U/kg iv every 48 hours for 6 doses, followed by 400 U/kg sc three times per week until 32 weeks PMA	35% vs. 39%	12% vs. 14%	No benefit of high doses of rhEPO on neurodevelopmental outcome at 2 years No significant difference in the rate of prematurity complications (IVH, ROP, NEC)
Sun, 2020 [99]	RCTs reanalysis	1898 neonates, GA 24-32 weeks	500 U/kg iv rhEPO, initial dose <72 h postnatally, every other day for 2 weeks	ND	3.9% vs. 7.6% (p=0.001)	Repeated low doses of rhEPO had no significant impact on the incidence of ROP Significantly lower rates of IVH,NEC and mortality in the rhEPO group
Fernandez, 2025 [89]	Pilot study	40 neonates, GA < 32 weeks (33 rhEPO, 7 placebo)	400 U/kg iv three times per week until 32 weeks PMA	CA 3 days: 6.5% vs. 71.4% CA 10 days: 6% vs. 28.6%	ND	Low and sustained doses of EPO significantly reduced the rate of IVH.

RCT: randomized controlled study; BW: birthweight; rhEPO: recombinant erythropoietin; sc: subcutaneously; iv: intravenously; PMA: postmenstrual age; IVH: intraventricular hemorrhage; GA: gestational age; ROP: retinopathy of prematurity; NEC: necrotizing enterocolitis; CA: corrected age; ND: no data.

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3.5. Insulin-like Growth Factor 1 (IGF-1)

Insulin-like growth factor 1 (IGF-1) is a mitogenic hormone involved in numerous physiological processes, including growth, angiogenesis, and differentiation [102,103]. It is an essential growth factor for central nervous system development as it contributes to the processes of myelination, neurogenesis, and the differentiation of brain cells [104]. Furthermore, it has been demonstrated that IGF-1 through the expression of structural vascular components, promotes vascular maturation and decreases vascular fragility [105,106]. Specific carrier proteins, the IGF-binding proteins (IGFBPs), have been demonstrated to regulate the bioavailability of IGF-1, with approximately 98% of the circulating IGF-1 being bound, and more than 80% of this being bound to IGFBP-3 [107].

During gestation, IGF-1 is a crucial mediator of fetal growth, with levels increasing with increasing gestational age [108]. However, in neonates born preterm, there is a rapid decline in IGF-1 levels following delivery, with levels falling below intrauterine levels, and a slower rise compared to term neonates [109,110]. Low IGF-1 levels in preterm neonates have been associated with poor extrauterine growth, various neonatal morbidities, and neurodevelopmental impairment [102].

Several studies have investigated the potential role of recombinant (rh) IGF-1/IGFBP3 supplementation, intending to achieve concentration within normal intrauterine range, in reducing the short- and long-term morbidities of preterm birth, including IVH, bronchopulmonary dysplasia (BPD), ROP, and neurodevelopmental impairment [106,110-114]. A number of studies have examined the pharmacokinetic properties of rhIGF-1/IGFBP3 in neonates, a population with unique physiological and developmental characteristics. These studies have concluded that the half-life is much shorter in neonates than in older populations, and that a continuous intravenous infusion of rhIGF-1/IGFBP3 is necessary to achieve serum concentrations comparable to those expected in utero for a specific GA [107,113-115]. Following these studies, Chung et al. developed a population pharmacokinetic model, concluding that a continuous intravenous infusion of 250 μg/kg/day would achieve and maintain serum concentrations within the target range [116]. Although adverse effects such as hypoglycemia, sepsis, and intracranial hypertension have been reported in older populations, there have been no reported safety concerns in the neonatal population [107,113,114].

Due to the role of IGF-1 in the process of vascular maturation and its contribution to the maintenance of vascular stability, it has been hypothesized that the administration of rhIGF-1/IGFBP3 could have a beneficial effect in the prevention of IVH in preterm neonates [106,117]. Gram et al. demonstrated the potential role of rhIGF-1/IGFBP3 in preventing IVH by showing that its administration led to the upregulation of gene expression of factors implicated in cerebrovascular maturation, particularly choroid plexus genes, using a preterm pup model [106].

In a phase 2 multicenter RCT, 61 preterm neonates with a GA of 23 to 27^{+6} weeks were randomized to receive rhIGF-1/IGFBP3 at a dose of 250 μg/kg/day as a continuous intravenous infusion from the first postnatal day until the corrected age of 29^{+6} weeks and 60 to standard neonatal care, to evaluate the effect of rhIGF-1/IGFBP3 on the incidence of prematurity complications. The rate of sIVH in the rhIGF-1/IGFBP3 treated population was lower, although statistically insignificant, compared to the controls (13.1% vs. 23.3%, respectively). Among the 24 neonates with >70% of serum IGF-1 concentrations in the target range, the incidence of sIVH was 8.3%. However, as the authors note, an exposure-response relationship between IGF1 levels and the severity of IVH could not be determined due to the small number of events [112]. In a post-hoc analysis of this RCT, which included only neonates without pre-existing IVH at the time of enrollment, a more pronounced decline in the rates of sIVH, was reported in neonates treated with rhIGF-1/IGFBP3 compared to standard care (25% vs. 40.5%, respectively). However, the difference was not statistically significant [118].

In conclusion, the existing evidence regarding the potential role of IGF-1 in IVH prevention is encouraging but scarce, and further larger studies are needed to provide more conclusive results.

3.6. Stem Cells

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Stem cell-based therapies, particularly mesenchymal stem cell (MSC) therapies, are an evolving field of research that shows great promise in the treatment of various types of disease. During the perinatal period, umbilical cord blood and tissue are valuable sources of MSCs, which are characterized by reduced immunogenicity, high differentiation potential, and easy, non-invasive collection [119-121]. Research is increasingly focusing on the potential of MSCs to prevent and treat multiple neonatal conditions, with a particular attention on perinatal brain injury [122-125]. It has been demonstrated in vitro that MSCs represent a source of growth factors such as IGF-1, epidermal growth factor, and interleukin 11, which are crucial for oligodendrocyte maturation. In preclinical models of encephalopathy of prematurity, MSCs have been shown to promote myelination and oligodendrocyte maturation and to reduce inflammation [126,127]. A recent meta-analysis of preclinical studies concluded that, while further research is required, umbilical cord blood-derived cells represent a promising intervention for perinatal brain injury [125].

The hypothesis that stem cells may have a role in the prevention of IVH has been proposed based on their known angiogenic properties and the expression of growth factors such as IGF-1 and vascular endothelial growth factor. However, although several studies have investigated the role of MScs in mitigating brain injury following sIVH, to date, there is a paucity of data to support the hypothesis of their role in IVH prevention [122,128]. Kotowski et al. enrolled 20 preterm neonates with GA <32 weeks who developed anemia and received either an autologous umbilical cord blood transfusion (n = 5) within the first five postnatal days or an allogeneic red blood cell transfusion (n = 15). A significantly reduced incidence of IVH was noted in neonates who received an autologous umbilical cord blood transfusion compared to the control group (p=0.07) [129]. In a phase 2, non-randomised, placebo-controlled trial, Ren et al. administered a single intravenous dose of autologous cord blood mononuclear cells within 8 hours after birth to preterm neonates with a GA of less than 35 weeks, to assess whether a decreased rate of prematurity-related complications would be observed. No significant difference in the rate of IVH was reported between the two groups (p=0.962) [130]. A recent Cochrane meta-analysis concluded that no evidence to date supports the role of stem cell-based interventions in preventing IVH in preterm neonates, and future prospective studies are needed [128].

4. Conclusion

IVH is a common complication of prematurity, and despite recent advances in perinatal care, it remains a significant concern in terms of survival and long-term neurodevelopment. Despite the efficacy of several preventive measures that have been implemented in routine clinical practice, such as antenatal corticosteroid administration, the increasing survival of preterm neonates, and particularly of neonates at the border of viability, necessitates the recognition and application of strategies to reduce the incidence of IVH further and improve both survival and the quality of life of these neonates.

The implementation of IVHPB in routine clinical practice, to minimize hemodynamic and cerebral perfusion fluctuations, through strategies including head positioning, minimal handling, stress and pain avoidance, avoidance of blood pressure fluctuations, and rapid intravenous fluid administration and blood withdrawal, represents a promising strategy. Nevertheless, it is imperative that appropriate education is provided and that measures are implemented to ensure adherence to achieve the desired efficacy. There is significant controversy regarding optimal head positioning. Although the tilted midline head position is widely used during the first days of life in preterm neonates, further research is required before it can be recommended universally.

Despite the proposal of several pharmacological agents as potentially useful in the prevention of IVH, controversies persist, and no agent has yet been proven to be efficacious to be introduced in the routine care of preterm neonates. Indomethacin is a drug that has been used for decades to promote ductal closure in neonates. Several large RCTs and observational studies have proven its effectiveness in preventing IVH. However, its efficacy has been disputed in a number of studies, and given the absence of proven longitudinal benefit, its universal administration in neonates is not

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recommended. Recombinant erythropoietin is a drug used to treat anemia of prematurity. Although the evidence from different studies has been inconsistent, it has shown promising results in preventing IVH. There is very little data on the efficacy of administering rhIGF-1/IHFBP3 to preterm neonates to restore normal intrauterine levels and prevent IVH.

Although the potential role of indomethacin, rhEPO, and rhIGF-1/IGFBP3 in preventing IVH in preterm neonates has been investigated, and encouraging results have been reported, larger prospective studies and RCTs are needed to evaluate their efficacy and provide conclusive evidence and recommendations. Regenerative cell administration is a promising, rapidly evolving domain that has the potential to be useful in the management of preterm neonates. The efficacy of stem cell-based interventions in the prevention of IVH remains to be investigated.

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