Impact of Common Treatments Given in the Perinatal Period on the Developing Brain

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Key Words

Neuroprotection · Neonate · White-matter damage

Abstract

Background: Over the last decades, considerable progress has been made in the perinatal management of high-risk preterm neonates, changing the landscape of pathological conditions associated with neurological impairments. Major focal destructive lesions are now less common, and the predominant neuropathological lesion is diffuse white-matter damage in the most immature infants. Similarly, over the last few years, we have observed a trend towards a decrease in neurological impairment in the absence of treatments specifically aimed at neuroprotection. **Objectives:** We examined whether recent changes in treatment strategies in perinatal care during the perinatal period could have had an indirect beneficial impact on the occurrence of brain lesions and their consequences. **Methods:** Thus, we reviewed the effects of the most common treatments administered during the perinatal period to the mother or to very preterm infants on brain damage and neurocognitive follow-up. **Results:** Ante-

natal steroids and exogenous surfactant are the two main treatments capable of leading to neuroprotection in very preterm infants. Randomized controlled trials are currently investigating the effects of inhaled nitric oxide and erythropoietin, while antenatal magnesium sulphate and caffeine are also likely to provide some neuroprotection, but this needs to be further investigated. Finally, other common treatments against pain, haemodynamic failure and patent ductus arteriosus have conflicting or no effects on the developing brain. **Conclusion:** While specific neuroprotective drugs are still awaited, recent advances in perinatal care have been associated with an unexpected but significant decrease in the incidence of both severe brain lesions and neurological impairment.

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Introduction

Brain injury and neurodevelopmental disabilities resulting from premature birth are a major public health concern. In recent studies, 5–10% of very preterm infants

Table 1. Unexpected effects of perinatal drugs used in preterm infants: rationale in perinatal risk factors, pre-clinical and clinical evidences as well as long-term effects

Risk factors	Drugs	Preclinical evidence for neuroprotection	Beneficial effect on brain lesions	Long-term effect
Inflammation	antibiotics	0	0	0
	NSAIDs	+	+	0
	antenatal steroids	++	++	+/-
Hypoxia/haemodynamic disturbances	surfactant	?	++	+
	caffeine	++	+	++
	iNO	+	+/-	+/-
	inotropes	0	0	0
Stress (pain)	opioids	+/-	+/-	0
Growth factor deprivation	erythropoietin	+++	+	+
Excitotoxicity	magnesium sulphate	+++	+	+

developed cerebral palsy (CP) and 25–50% had cognitive impairments and behavioural disorders. Neocortical white-matter damage (WMD) is strongly associated with these disabilities [1]. Over the last three decades, considerable progress has been made in the perinatal management of high-risk preterm neonates, changing the landscape of pathological conditions associated with neurological impairments. Major focal destructive lesions are now less common, and the most common neuropathological lesions are diffuse WMD [2]. Consistent with this evolution, subtle reductions in the incidence of neurological impairments have been reported in population-based studies: in the EPICure 2 study, a higher proportion of babies admitted for neonatal care survived without disability in 2006 compared to those born in 1995 [3]. In the EXPRESS study, a high proportion (73%) of extremely preterm infants had no or only mild disability at 2.5 years of age, but no comparisons were provided in this study [4]. Although CP and other neurobehavioural disabilities are considered multifactorial, we investigated whether recent improvements in perinatal care and changes in pharmacological strategies during the perinatal period could have an indirect beneficial impact on the occurrence and consequences of brain lesions. This review systematically examines the most common pharmacological treatments administered during the perinatal period to very preterm infants for such an effect. Five categories of treatment were considered according to the perinatal mechanism leading to brain damage and are summarized in table 1.

Antenatal Steroids

The benefits of antenatal steroids (AS) administered to fetuses at risk of preterm delivery greatly outweigh the potential risks. Therefore, a single course of AS is routinely considered for preterm deliveries with a few exceptions. In the most recent meta-analysis of 21 studies (3,885 women and 4,269 infants) [5], in addition to its effect on respiratory distress syndrome (RDS), treatment with AS was associated with an overall reduction in cerebroventricular or intraventricular haemorrhage (IVH) [relative risk (RR) 0.54; 95% confidence interval (CI) 0.43–0.69] and severe IVH (RR 0.28; 95% CI 0.16–0.50). Antenatal exposure to betamethasone but not dexamethasone was reported to be associated with a decreased risk of cystic periventricular leucomalacia among very premature infants in a retrospective study [6]. In addition, necrotizing enterocolitis (RR 0.46; 95% CI 0.29–0.74) and systemic infections in the first 48 h of life (RR 0.56; 95% CI 0.38–0.85), two identified risk factors for brain lesions in preterm infants, were less frequently found in neonates born to mothers treated with AS. However, there is no evidence from this overview of a difference in the later incidence of CP between infants exposed to either antenatal betamethasone or dexamethasone.

Treatment with AS was associated with fewer developmental delays in childhood (RR 0.49; 95% CI 0.24–1.00). However, in adulthood, statistically significant differences have been no longer noted in terms of educational level, visual, hearing or intellectual impairment [5].

The association between AS and potential neuroprotection appears to be primarily due to the well-known link between severe RDS and IVH, but it is also possible that AS could enhance the maturity of intracerebral vessels and thus provide protection against IVH.

Overall, these data support the view that AS, through indirect pathways, could be capable of exerting a positive effect on the developing brain in very preterm infants.

Magnesium Sulphate

Magnesium sulphate (MgSO_4) is used as a maternal neuroprotective agent to prevent eclampsia in women with pre-eclampsia and as an anticonvulsant for the treatment of eclampsia. Several observational studies reported a variable reduction in the risk of CP, brain lesions or perinatal morbidity in preterm infants [7]. Four randomized controlled trials (RCTs) studying the use of antenatal MgSO_4 administration to mothers at risk of preterm delivery for fetal neuroprotection have been conducted [8–11]. While none of these 4 trials individually has reported any statistical differences in the rates of their primary composite outcome (death/CP), secondary analyses demonstrated a reduction in the rate of neonatal CP among infants exposed to MgSO_4 . The Doyle Cochrane meta-analysis included a fifth trial aimed at comparing MgSO_4 with placebo in women with pre-eclampsia [12] and demonstrated a significant reduction in CP in infants exposed to antenatal MgSO_4 (RR 0.68; 95% CI 0.54–0.87), confirmed within the neuroprotective-intent subgroup (RR 0.71; 95% CI 0.55–0.91). In addition, substantial gross motor dysfunction, measured in four trials, was lower (RR 0.61; 95% CI 0.44–0.85), and there was a significant reduction in the combined rate of death and CP in the neuroprotective-intent groups (RR 0.85; 95% CI 0.74–0.98). Two other meta-analyses have come to similar conclusions [13, 14]. However, a recent sequential trial analysis based on the Doyle Cochrane meta-analysis has revealed that the apparently conclusive positive effect may in fact be a false positive due to a random-risk error; thus, more data may be needed to confirm these associations [15].

The fetal neuroprotective mechanisms of MgSO_4 have been partially elucidated through animal models, summarized in a review by Marret et al. [7]. Biological plausibility for the neuroprotective role of MgSO_4 comes from its reduction of inflammation and free radicals accumulation, its prevention of excitotoxic injury and its stabilization of blood pressure (BP).

The Cochrane review has concluded on the proven cost-effectiveness and feasibility of MgSO_4 therapy in preterm babies <32 weeks' gestational age (GA) [16, 17]. However, the adoption of this strategy has been slow because the clinical evidence is still very controversial; in particular, unresolved issues concerning the optimal regimen of MgSO_4 and the optimal GA at which the therapy is beneficial [18]. Nevertheless, the American College of Obstetricians and Gynecologists (March 2010), the Australian Research Centre for the Health of Women and Babies (March 2010) and the Society of Obstetricians and Gynaecologists of Canada (May 2011) have already published guidelines recommending that antenatal MgSO_4 administration should be considered for fetal neuroprotection.

Modulators of Inflammation/Infection

Many experimental and epidemiological studies support the view that inflammatory/infectious processes such as chorioamnionitis and postnatal sepsis are associated with WMD and poorer neurological outcome [19]. In preterm infants, drugs with anti-inflammatory or anti-infectious effects are commonly used. It is therefore a valid question to ask whether these drugs could interact with brain development.

Non-Steroidal Anti-Inflammatory Drugs

The current recommended indication for non-steroidal anti-inflammatory drugs (NSAIDs) in the preterm neonatal period is the curative medical treatment of persistent ductus arteriosus [20]. Experimental data indicate that NSAIDs could be neuroprotective in the developing brain in the context of systemic inflammation, through a reduction in brain prostaglandin E_2 synthesis by cyclooxygenase-2 inhibition at the blood-brain barrier [21].

Several years ago, early indomethacin was thought to be neuroprotective against the risk of IVH in preterm infants with a significant decrease in severe IVH [22–24]. However, the long-term effects on neurodevelopmental outcome were less convincing, with a lack of improved neurological outcome [25–28]. Currently, the use of indomethacin as a preventive strategy for IVH is not clearly recommended, although a prospective analysis of factors influencing white-matter abnormalities on MRI scans in extremely low GA infants has revealed a significant beneficial effect of indomethacin [29]. Unlike indomethacin, however, ibuprofen did not show any effect on the occurrence of IVH [30, 31].

Antibiotics

During pregnancy, antibiotics and AS are currently considered the standard of care in preterm prelabour rupture of membranes (pPROM) occurring before 32 weeks' GA even without proven infection. However, no consensus exists regarding the antibiotic to be used, apart from the avoidance of the amoxicillin-clavulanic acid combination due to the increased risk of necrotizing enterocolitis associated with it [32]. In case of pPROM, antibiotics reduce neonatal infections, surfactant use and oxygen requirement [33]. In contrast, no positive effect of antibiotics has been observed on neonatal death or morbidity in preterm labour with intact membranes [34].

Some antibiotics have demonstrated neuroprotective actions in animal models not through their bactericidal effects but through their anti-inflammatory properties (minocycline and fluoroquinolone) or anti-excitotoxic properties (ceftriaxone) [35–37]. While these findings are very encouraging, the potential of these antibiotics remains fairly limited due to their possible adverse effects in neonates.

Focusing on neurological outcome, clinical data are only available for antibiotics used in the antenatal period. Antibiotic use in the context of pPROM was associated with a significant reduction in IVH (RR 0.67; 95% CI 0.49–0.91) and in abnormal cerebral ultrasound results prior to discharge (RR 0.81; 95% CI 0.68–0.98) [32]. The ORACLE I study was designed as a long-term follow-up of infants receiving prenatal antibiotics for pPROM and reported no demonstrable effect on neurological outcome compared to the absence of treatment [38]. In parallel, the same study design (ORACLE II) was adopted for a follow-up of prenatal antibiotics for preterm labour with intact membranes [39]. Surprisingly, prenatal exposure to antibiotics in this case was associated with an increased occurrence of CP at 7 years [odds ratio (OR) 1.93; 95% CI 1.21–3.09 for erythromycin]. The most recent review assessing the effects of prophylactic antibiotics administered to women in preterm labour with intact membranes reported that a marginally non-statistically significant (but of concern) increase was shown in any functional impairment and CP in any antibiotics groups versus placebo [40]. Thus, antenatal antibiotics only show short-term beneficial effects limited to the context of pPROM. In contrast, the evidence supports not giving antibiotics routinely to women in preterm labour with intact membranes in the absence of overt signs of infection.

Exogenous Surfactant

Surfactant therapy is one of the few treatments that decreases overall mortality in preterm newborns with RDS and has significantly changed clinical practice in neonatology that could strongly influence their neurodevelopmental prognosis [41].

Exogenous Surfactant and Changes in Cerebral Blood Flow Velocity

Early physiological studies indicated that surfactant administration produced a rapid improvement in ventilation associated with a transient and rapid change in cerebral blood flow velocity (CBFV), strongly correlated with an increase in carbon dioxide tension [42–44]. However, later clinical data have not revealed any change in CBFV following natural surfactant instillation [45]. From these results, a close monitoring of blood gases and a frequent adjustment of ventilation have been proposed to prevent potential neurological side effects caused by CBFV changes related to surfactant administration.

Exogenous Surfactant and IVH

In the early 1990s, a multicentre controlled study using beractant was stopped before enrolment was completed when an increased incidence of periventricular haemorrhage/IVH was reported in treated infants [46]. However, a review of a database including 17 studies and almost 1,700 infants did not confirm these results [47]. A recent Cochrane database analysis comparing the prophylactic and selective use of surfactant in newborns with RDS has revealed a borderline benefit of the prophylactic use in preventing IVH (RR 0.91; 95% CI 0.82–1.00) [48]. No difference in the risk of periventricular leucomalacia was observed between the two groups (RR 1.23; 95% CI 0.75–2.01).

Exogenous Surfactant and Neurological Outcome

A meta-analysis including 13 RCTs comparing surfactant treatment (prophylactic or rescue treatment: 2,218 infants) versus controls (2,090 infants) revealed that surfactant therapy was associated with a lower rate of mild disability at 1 year of age (OR 0.79; 95% CI 0.66–0.95) [49]. As previously reported, many factors interfere with long-term follow-up, and the effect was no longer observed in studies evaluating the infants at 2 years of age and at schoolgoing age, either in terms of neurological disabilities, IQ tests, learning problems, behavioural problems, or hyperactivity [50].

In summary, surfactant therapy has changed clinical practice in neonatology over the last decades, resulting

in an overall reduction in infant mortality of about 6% in the United States [51]. Long-term follow-up studies have not identified any increase or decrease in neurodevelopmental sequelae in surviving infants above 2 years of age.

Caffeine

Caffeine is a methylxanthine and a non-selective adenosine antagonist widely used in preterm infants to prevent apnoea of prematurity. The nucleoside adenosine may play an important role as a mediator of hypoxic injury in preclinical models of developing brain injury. When rodents are treated with adenosine receptor agonists, there is a marked reduction in white- and grey-matter volumes along with secondary ventriculomegaly and reduced myelination, similar to that seen in rodents exposed to hypoxia [52] or with diffuse periventricular leucomalacia [53]. Compounds that block the activation of adenosine receptors include caffeine, of which the potential role in the prevention of developmental brain injury has been poorly explored.

Back et al. [54] have reported that caffeine enhances oligodendroglial maturation in a neonatal model of diffuse white-matter injury and reduces ventriculomegaly. Caffeine could potentiate neural plasticity, modulate synaptic activity and modify neural networks.

Recently, clinical studies have supported the view that caffeine has beneficial effects in preterm babies, and not only to treat apnoea of prematurity. In the Caffeine for Apnea of Prematurity (CAP) trial, exposure to caffeine was associated with reduced rates of bronchopulmonary dysplasia and patent ductus arteriosus [55]. The frequency and types of brain injury determined by cranial ultrasound were similar between patient groups. Brain ultrastructure demonstrated that caffeine treatment was associated with a decreased apparent diffusion coefficient and a more mature cerebral white-matter organization at term-equivalent age [56]. At 18–21 months of age, caffeine-treated infants had significantly lower rates of CP (4.4 vs. 7.3%) and cognitive delays (33.8 vs. 38.3%) than the control group [57]. However, at 5 years of age, the observed rates of the combined main outcome of death/disability revealed no effect of caffeine compared to placebo treatment [58]. Secondary analysis suggested that the improved motor function observed at 18–21 months of age in the caffeine group was sustained at 5 years, together with better scores in the coordination and visual perception fields. A dose-response trial revealed a significant

statistical improvement of general quotient development as assessed by the Griffiths Mental Development Scales in the high-dose group (GQ 98.0 vs. 93.6) [59].

Inhaled Nitric Oxide

Nitric oxide (NO) is a powerful vasodilator that plays a crucial role in vasodilating pulmonary arterioles. NO is also involved in the pathogenesis of several conditions, including brain ischaemia and neurodegenerative diseases [60]. Importantly, NO appears to be a key regulator of cerebral blood flow and inflammation, two major factors modulating brain injury. Surprisingly, despite its potential impact, neurological surveys of preterm infants exposed to inhaled NO (iNO) are rare and poorly reported. In a recent meta-analysis, Donohue et al. [61] reviewed 14 RCTs of preterm infants exposed to iNO for severe persistent pulmonary hypertension, including 7 follow-up studies and 1 observational study. Mortality rates in the NICU did not differ for infants treated with iNO compared with controls, and there was no evidence to suggest a difference in the incidence of CP (RR 1.36; 95% CI 0.88–2.10), neurodevelopmental impairment (RR 0.91; 95% CI 0.77–1.12) or cognitive impairment (RR 0.72; 95% CI 0.35–1.45).

Nevertheless, the neurodevelopmental effects of iNO continue to be investigated. Indeed, exogenous iNO under experimental conditions is capable of exerting both beneficial and detrimental effects in the developing brain, depending on its concentration and the time period of exposure [62]. Consistent with this, preclinical data in animal models of the brain damage observed in preterm and term neonates and adults suggest that at low doses, iNO could decrease the oxidative burst frequently observed in the perinatal period by scavenging oxygen-derived free radicals [63].

In the past, it was feared that iNO would increase the incidence of intracranial haemorrhage in critically ill preterm neonates, because NO is known to increase bleeding time and inhibit platelet aggregation [64]. However, later clinical studies have shown that there is no significant increase in intracranial bleeding in preterm neonates. Moreover, both Schreiber et al. [65] and Kinsella et al. [66] have noted a lower incidence of severe IVH and periventricular leucomalacia in iNO-treated preterm infants, and another recent report reveals beneficial effects of iNO on long-term neurological outcomes in premature infants [67]. However, this has not been confirmed in 3 large multicentre RCTs.

Table 2. rhEpo for neuroprotection in preterm infants

Studies	Year	n	Inclusion criteria	rhEpo dose	Neurodevelopmental outcome			p
					criteria	rhEpo	placebo	
Newton	1999	40	≤1,250 g	500 or 1,000 U/kg/week	MDI at 17 months	95.4±9.9	94.6±18.7	NS
Ohls	2001	102	≤1,000 g	1,200 U/kg/week	% MDI <70 at 18–22 months	31%	36%	NS
					% PDI <70 at 18–22 months	31%	13%	<0.05
					% CP at 18–22 months	19%	18%	NS
Bierer	2006	12	≤1,000 g	1,200 U/kg/week	% MDI <70 at 18–22 months	96±11/78±7*		<0.05
Neubauer	2010	146	<1,000 g	750 or 1,500 U/kg/week	IQ score at 10–13 years	90.8±17.2	81.3±21.1	<0.005
					normal development	55%	39%	<0.05
McAdams	2013	35	<1,000 g	500, 1,000 or 2,500 U/kg (3 doses)	cognitive score from 4 to 36 months	Δ score = 5.3		0.044
					motor score from 4 to 36 months	Δ score = 7.5		0.026
Fauchère	ongoing	420	<32 weeks	3,000 U/kg (3 doses)	MDI at 24 months	results expected in 2014		
Juul	ongoing	940	<28 weeks	1,000 U/kg (6 doses) and then 400 IU/kg/week until 33 weeks	MDI and PDI at 24–26 months	results expected in 2018		

MDI = Mental development index; PDI = physical development index; IQ = intelligence quotient; NS = non-significant. * Epo concentrations: ≥500 <500 mU/ml.

Recombinant Human Erythropoietin

Apart from its well-known haematopoietic effects, erythropoietin (Epo) and its receptor (EpoR) are widely expressed in central nervous system cells and play a key role in brain development. Epo has been shown to have neurotrophic and neuroprotective effects in a wide variety of experimental paradigms [68]. Several mechanisms by which Epo results in neuroprotection have been recognized. Epo decreases glutamate toxicity, induces the generation of neuronal anti-apoptotic factors, reduces inflammation, decreases NO-mediated injury, and has direct antioxidant effects.

Little information is known about the neurological impact of Epo in preterm infants. Two studies reported no significant influence of a haematopoietic dose of recombinant human Epo (rhEpo) on the neurocognitive outcome of very preterm infants at 18–22 months of age [69, 70]. Bierer et al. [71] were the first to report that infants with elevated Epo concentrations had higher Mental Development Index scores at a corrected age of 18–22 months in a small cohort of extremely low birth weight (ELBW) infants. In a non-randomized study, Neubauer et al. [72] reported that rhEpo-treated infants had better developmental outcomes (55 vs. 39% with normal development, $p < 0.05$) and composite IQ scores (90.8 vs. 81.3, $p < 0.005$) between the ages of 10 and 13 years com-

pared to the placebo group. The neuroprotective effect of rhEpo treatment was more significant in preterm infants with IVH. Table 2 summarizes the results of studies using haematopoietic doses of Epo in preterm infants.

Conversely, a pilot study in 45 very preterm infants showed no difference in terms of either survival without brain injury or retinopathy (53 vs. 60%, OR 0.76; 95% CI 0.24–3.20) or of short-term outcome in rhEpo-treated infants compared to placebo-treated controls [73]. In ELBW infants, an early high dose of rhEpo was well tolerated with no increase in morbidity or mortality, and was correlated with a modest improvement in neurodevelopmental outcome up to 36 months' postmenstrual age [74, 75]. Multicentre trials enrolling ELBW infants are ongoing or being planned. The completion of recruitment and primary outcome measurements are expected for 2014 and 2018 (table 2). In addition to rhEpo treatment, iron supplementation and subsequent serum ferritin levels may have a positive impact on motor performances at 24 months of age [76].

In conclusion, only 1 study has demonstrated a neuroprotective effect of rhEpo treatment at haematopoietic doses, but these results should be interpreted with caution until the results of high-dose rhEpo trials are reported.

Treatment of Haemodynamic Failure

Systemic hypotension in preterm infants has been correlated with increased mortality, cerebrovascular lesions and neurodevelopmental morbidity. The 3 meta-analyses available in the Cochrane Library that compared the effectiveness of early volume expansion and inotropes in increasing BP in preterm infants drew conflicting conclusions [77–79]. None of them demonstrated any significant difference in neonatal mortality at discharge, the incidence of cerebrovascular lesions or CP. Nevertheless, in 1 randomized trial, surviving infants treated with dobutamine had a significantly higher general quotient when evaluated using the Griffiths Mental Development Scales at 3 years [80].

A more recent random-effects meta-analysis compared various strategies to sustain BP in preterm infants, including inotropes, volume expansion and hydrocortisone [81]. Dopamine administration was significantly more effective at sustaining BP than dobutamine, colloid, or hydrocortisone. Despite increased cerebral blood flow in dopamine-treated neonates, there were no statistically significant differences in adverse neurological outcome between dopamine and dobutamine, epinephrine, colloid or hydrocortisone administration. A recent study has investigated the relationship between BP, inotrope therapy and in-hospital outcomes to identify a BP threshold below which antihypotensive therapies could be beneficial [82]. For the 15 definitions of low BP investigated, no therapy was prescribed to 3–49% of infants, but paradoxically, therapy was administered to 28–41% of infants without low BP, suggesting that factors other than low BP contribute to the decision to use antihypotensive therapies. Despite an increased incidence of severe IVH in treated infants (22 vs. 11%, $p < 0.01$), this difference did not persist after regression analysis.

In conclusion, there is no evidence that the treatment of systemic hypotension with a specific molecule could result in short- or long-term improvements of neurological outcome, and outcomes were not improved with antihypotensive therapy whatever the definition of low BP used [82, 83].

Pain, Analgesia and Sedation

A major issue of concern to neonatologists is the potential delayed toxicity of the perinatal environment, interventions and drugs. Except in preterm infants under-

going surgery [84], whether systematic analgesia or sedation in the NICU results in improved short-term outcome is a matter of debate [85, 86].

Animal experiments have revealed a variety of effects of most analgesics, sedatives and anaesthetics, depending on the species, exposure conditions and experimental design [87]. Pain itself can also cause long-term behavioural changes in animals [88]. Extrapolations of these results to humans should be carried out with caution, considering differences in pharmacokinetics, the equivalence of developmental stages, nutritional support, and nociceptive stimuli between most models [89].

To date, no prospective clinical trial has used long-term neurodevelopmental outcome as a primary outcome for the assessment of pain management. Even sucrose analgesia, which is extremely widespread and effective for minor procedures, has never been assessed for its long-term outcome [90], although one study reported no change in short-term outcomes [91]. On the other hand, despite the need for large trials of analgesics and/or sedatives designed to assess long-term neurodevelopment as the primary outcome, these would be considered ethically unacceptable in light of the short-term effectiveness in providing pain relief of most of these drugs.

Based on the existing evidence, 4 studies have analyzed the relationship between exposure to neonatal analgesic/sedative drugs and outcome at schoolgoing age [92–95]. None of these trials were designed to assess long-term outcomes. Surprisingly, the 2 largest trials of morphine versus placebo in ventilated neonates have yielded contradictory results concerning severe brain injury: Simons et al. [96] noted a protective effect of morphine on all grades of IVH, while Anand et al. [97] saw an increase in severe IVH in a subgroup of infants.

An observational study has reported an association between painful experience and poor neurodevelopmental outcome at 18 months [97]. Conversely, no difference was observed between the groups in a 5-year follow-up of Simons et al.'s [96] study. In the NEOPAIN study, impairment in neurodevelopmental subtests were reported for the morphine group compared to the placebo group in one centre, which, however, recruited less than 10% of the patients [98]. Finally, a retrospective analysis of infants recruited in the EPIPAGE cohort using a propensity score to compare infants who had received analgesia/sedation on at least 7 consecutive days with controls found no positive or negative effect of this treatment at 5 years [93].

Conclusion

Common practice in perinatal care has profoundly changed over the last three decades. Similarly, during the last few years, we have observed a significant decrease in the incidence of major brain lesions in preterm infants and a trend towards a decrease in neurological impairment. This review shows that, while specific neuroprotec-

tive drugs are still awaited, recent advances and changes in perinatal care have been associated with unexpected but significant decreases in the incidence of both severe brain lesions and neurological impairment. The greatest benefits on the developing brain could result from an indirect positive impact of AS, an exogenous surfactant and possibly MgSO_4 as well as caffeine.

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