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REVIEW

Pharmacological and Non-Pharmacological Brain-Focused Clinical Practices for Premature Neonates at High Risk of Neuronal Injury

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ABSTRACT

Objectives: *Disruption of smooth intrauterine brain development is a significant consequence of premature birth that may lead to adverse neurological outcomes. Although noteworthy progress has been made in the management of prematurity, the rates of neonatal morbidity and neurodevelopmental disorders remain high, underlining the need to find clinical practices that particularly protect the central nervous system.*

Aim: *To identify recent articles regarding pharmacological and non-pharmacological brain-focused clinical practices (BFCP) for premature neonates at high risk of neuronal injury.*

Materials and methods: *We did an extensive search of PubMed and Google Scholar for relevant research published between 2000 and 2020.*

Results: *Nineteen full-length original research papers fulfilled the inclusion criteria and were selected for the purpose of the present review. Non-pharmacological BFCP intend to improve the neonate's experience in the NICU environment and can be applied by a multidisciplinary team, while pharmacological ones are related to novel molecules that aim to quell apoptosis and inflammation or promote neurogenesis.*

Conclusions: *In the future, a combination of pharmacological and non-pharmacological BFCP might be considered as the most promising protection and/or treatment provided in clinical practice to premature neonates at high risk of neuronal injury.*

Keywords: pharmacological, non-pharmacological, clinical practices, premature neonate, neuronal injury, molecules.

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INTRODUCTION

The third trimester of pregnancy is a period when the fetal central nervous system (CNS) grows intensively. A premature birth interrupts this sensitive process and compels brain development to resume in the potentially harmful environment of a Neonatal Intensive Care Unit (NICU). From numerous researches it is well known that brain is characterised by neuroplasticity, especially during early development, where generation of new synapses is excessive (1-5). Thus, brain-focused clinical practices (BFCP) for premature neonates (PNs) at high risk of neuronal injury (NI) are of great value.

Although significant progress has been made in the management of PNs, the rates of neonatal morbidity and neurodevelopmental disorders remain high, highlighting the need to find practices that particularly protect the CNS. The BFCP, also known as "Neurocritical", "Neuroprotective" or "Brain Sensitive" clinical practices, aim to support the developing brain, prevent or reduce neuronal cell death and minimise the adverse neurodevelopmental outcomes of the neonate at risk (6).

The aim of this narrative review of the literature is to present specific pharmacological and non-pharmacological BFCP for PNs at high risk of NI as well as to summarize how parental participation and interaction contributes to brain development. ❑

MATERIALS AND METHODS

An extensive search was conducted in PubMed and Google Scholar databases for relevant articles published between 2000 and 2020. Studies in languages other than English and those that either did not focus on the topic of our interest or had no clear results were excluded. The following Medical Subject Headings (MeSH) terms were used: "brain focused", "brain sensitive'', "brain oriented" "neurocritical", "neuroprotective", "premature", "preterm", "neonate", "newborn", "infant", "pharmacological", "clinical practices", "strategies" and "molecules". Nineteen full-length research papers fulfilled the inclusion criteria and included data to human neonates, being thus selected for the purpose of the present review.

Multidisciplinary team

The basic multidisciplinary team able to provide daily BFCP usually consists of a neonatologist, a paediatric/neonatal neurologist and midwifery or nursing staff who is specialised in neurological and intensive neonatal care. Neurosurgeons, neuroradiologists, developmental specialists, pharmacists, dietitians and occupational/physical therapists also participate when necessary. The multidisciplinary team should have a deep knowledge of usual neonatal neurologic disorders and their diagnosis, therapeutic hypothermia in case of hypoxic ischemic encephalopathy, neonatal reflexes, neuromonitoring and neuroimaging technologies, neuroprotective and antispasmodic medicine, palliative care and finally, follow up planning (7-9). Essential cooperation of the team can significantly increase early identification of PNs at high risk for NI.

Situations applicable to brain-focused clinical practices

Situations applicable to BFCP include neonatal brain injury (periventricular leukomalacia, intra/extracerebral haemorrhage, hypoxic ischemic encephalopathy, stroke), seizures, anatomical brain anomalies, kernicterus, CNS infections, genetic/metabolic/neurological disorders, congenital heart diseases, very low birth weight (<1500 grams) and extremely PN (gestational age <28 weeks) (10-12).

Non-pharmacological brain-focused clinical practices

Non-pharmacological BFCP were firstly introduced by Altimier and Philips as seven distinct family-centered developmental core measures (13). They can be used by the whole multidisciplinary team but most often by nursing/midwifery staff, aiming to improve the neonate's experience in the NICU environment. The core measures include: (i) safeguarding sleep, (ii) position and handling, (iii) protecting skin, (iv) minimizing stress and pain, (v) optimizing nutrition, (vi) healing environment and (vii) partnering with families.

i. Safeguarding sleep

Providing sufficient rest and sleep to PNs critically contributes to neurosensory and memory

development, protection of brain plasticity and decrease of adverse consequences for learning, behaviour and function (13). Within a NICU, the quality and quantity of sleep is affected and in-

TABLE 1. Non-pharmacological brain-focused clinical practices for premature neonates

Safeguarding sleep
• Ensure protection of sleep cycles, especially active sleep • Promote rest periods of at least 60 minutes to complete a normal sleep cycle • Professional routine caregiving (diaper change, repositioning, oximeter site change, [a]CPAP break, laboratory tests) should be applied, as much as possible, in spontaneous awake periods of the [b]PN • Vital signs should be checked according to caregiver's professional judgment, ideally when the PN is awake • Hourly visual assessment of [c]IV sites, position and condition of the PN, without awakening it • Sedative drugs should be used cautiously, since they interfere with quiet and active sleep • Daily exposure to light, preferably natural, in order to establish a healthy circadian rhythm • Protect eyes when bright lighting is in need and avoid overhead spot lights • Promote prolonged periods of skin-to-skin contact with parents to ensure optimal sleep
Positioning and handling
• Maintain neutral head position with the head of the bed tilted upward to the highest position • Shoulders softly rounded forward, hands towards midline able to reach mouth for self-soothing, hips aligned and pelvis tucked, knees/ankles/ feet aligned and softly flexed • Avoidance of weighing and kangaroo care until day 4 for prevention of intraventricular hemorrhage. • Reposition if PN appears fidgety and uneasy - Teach also parents to reposition • Counteract the forces of gravity • Use positioning aids to mimic boundaries of the uterus and support the PN • Avoid raising feet above head during daily care so as to prevent increase of intracranial pressure • Prefer swaddle bathing • Suctions only when there is a clinical indication • Minimal handling
Protecting skin
• Humidify incubators for the first two weeks of life to reduce transepidermal water loss for [d]ELBW neonates • Change diapers every 2-4 hours during spontaneous awake periods to avoid diaper rash • Minimize adhesive use - Apply and remove adhesives cautiously • Apply transparent sticker tape on body areas which are exposed in continuing rubbing (knees, elbows) • Avoid skin breakdown from common sources such as thermal injury, CPAP devices, pressure ulcers • Use probes to relieve of hard surfaces • Teach parents to offer safe and nurturing touch through skin-to-skin care • Train parents on neonatal skin care practices such as massage

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Minimizing pain and stress
• Cue-based caregiving to promote neurobehavioral organization • During stressful procedures take measures for comfort (swaddling, skin-to-skin care, breastfeeding, non nutritive sucking, oral sucrose, parental nurturing touch) • Use specific environmental / non-pharmacological / pharmacological interventions to prevent, reduce or eliminate the stress and pain • Allow PN to fully recover before continuing with routine caregiving so as to avoid programming abnormal stress responsiveness
Optimizing nutrition
• Lessen unpleasant perioral experiences, such as suctioning, and provide positive oral stimulation • Encourage non nutritive sucking at mother's expressed breast during gavage feeds • Choose a 1-piece, dipped pacifier made of a tasteless and odourless medical grade plastic to supply the PN with the taste and smell of breast milk during gavage feedings • Use colostrum for gentle oral care • Facilitate "early practice" breastfeeding sessions, long before discharge
Healing environment
Temperature • Support thermoregulation in order to minimize the consumption of oxygen and energy by the PN (stabilization in a preheated incubator, use of servo, avoidance of bathing in the first 24 hours of life, skin-to-skin contact) Touch • Facilitate early, frequent and prolonged skin-to-skin contact • Use gentle but firm touch cause PN cannot adjust to light touch – they become annoyed and feel insecure • Provide swaddle holding when parents are absent • Educate parents to cradle holding, positive/reassuring/still/therapeutic touch. The aim is to strengthen the early emotional bonding and communication between neonate and parents - The PN must realize that every contact does not cause pain or discomfort. Taste • Offer dipped pacifiers in breast/formula milk - Use breast milk for oral care Smell • Expose the PN to breast/formula milk smell • Familiarization of mother's scent with breast pad or soft cloth • Parents/Staff/NICU should avoid strong odours (alcohol, smoke, perfumes, deodorants, hand antiseptics, cleaners) Sound • Speak as quietly as possible within the NICU - Avoid loud laughters or conversations • Set mobiles, NICU phones, radio to the lowest level • Eliminate noise levels from incubators / ventilators / monitors according to NICU guidelines • Avoid moving / tapping / shutting the doors / placing things on top of the incubator • Remove water in tubing of ventilators / CPAP • Use ear muffs for neonates on [e]HFOV and in adjacent bed spaces Lighting • Use carefully procedural lighting which should be bedside • Protect eyes from direct ambient light during every examination and after post [f]ROP screening

[a]CPAP: continuous positive airway pressure; [b]PN: premature neonate; [c]IV: intravenous; [d]ELBW: extremely low birth weight; [e]HFOV: high frequency oscillatory ventilation; [f]ROP: retinopathy of prematurity

terference with active sleep can be frequent, therefore potentially leading to abnormal development of visual, auditory, somatesthetic, kinaesthetic, proprioception, chemosensory, olfactory and limbic system, as well as the hippocampus, pons, brainstem and midbrain (13, 14). Consequently, healthcare professionals and parents are encouraged to use practices that protect sleep in order to achieve neuronal and optimal neurosensory development. Specific practices that protect sleep cycles (11, 15, 16) are shown in Table 1.

ii. Positioning and handling

Due to weakness and gravity, a PN takes uncomfortable positions, which are characterized by rotation of the head and abduction of the upper and lower limbs (17). The head usually falls to the right side, gradually causing plagiocephaly and strengthening the nerve synapses in a direction different from that of the baseline, resulting in developmental delays and possibly significant neurological abnormalities to the neonate (18). Therapeutic positioning can promote rest, sense of security and optimal physiological/neurological/musculoskeletal development, improve lung and chest wall synchrony of respiratory improvements, reduce stress, stimulation and clinical imbalance (apneas, bradycardias, fall of oxygen saturation), decrease gastroesophageal reflux and finally normalize neurobehavioral organization (6, 17, 19, 20). Caregiving practices that eliminate positional deformities and maintain autonomic stability (21-25) are shown in Table 1.

iii. Protecting skin

Skin is the largest organ of a neonate's body and its integrity is necessary to survival, as every break can enable percutaneous entry of harmful pathogens into the body. Its sensory receptors detect and transmit messages relating to touch, pain, pressure and temperature (26, 27). The skin of a PN has unique features such as thinner epidermis layers, fewer fibrils and limited subcutaneous fat. Thus, they are more prone to epidermal stripping, insensible heat and transepidermal water loss, as well as more sensitive at hard surfaces. Proposed clinical practices for the protection of neonatal skin (25, 27, 28) are shown in Table 1.

iv. Minimizing pain and stress

A painful experience is prolonged and more intense in PNs as their mechanism of withdrawal is quite immature. Excessive neonatal stimulation resulting from perinatal trauma or other insults cause excitotoxicity in multiple areas of the developing brain (29). Repeated exposure to invasive procedures during a period of rapid neuronal proliferation and cell differentiation places very PNs at risk of permanent structural and functional changes in the brain (30). Long-term adverse effects in PNs are probably associated with continuous exposure to painful stimuli (31-33).

Regarding stress, it is greatly aggravated during hospitalization in NICU because a PN experiences separation from the mother, frequent painful interventions but also multiple sensory stimuli. In the short term, stress can cause hypoglycaemia, cardiovascular instability, increased intracranial pressure and decreased arterial oxygen saturation. There is also evidence that repetitive stressful stimuli during this vulnerable period of brain development can negatively affect neuroplasticity (29, 34-36). Practices known to reduce infant pain and stress (25, 29, 37) are shown in Table 1.

v. Optimizing nutrition

Nutrition is a key determinant for the future health outcome of PNs. Early parental nutrition is essential to support the PN until full enteral feeding is established. Proteins are fundamental for promoting growth. Lipids are required for the physiological accretion of body fat and the lipid mass of neuron membranes, making them vital for brain development (38, 39). Glucose, the major source of energy for the brain, which is the most energy efficient organ, should be ideally infusing within 30-60 minutes when enteral feeding is not allowed (40). Breast milk is widely accepted as the optimal feeding form for PNs since it is the most well tolerated substrate for their immature gastrointestinal system. Higher IQ's, larger brain volumes and lasting effects on neurodevelopmental function have been reported in PNs fed exclusively with breast milk, specially for long duration (41, 42). Taking into account the clear benefits of breast milk, it is essential to educate and support mothers in establishing and maintaining an adequate milk supply for their PNs. Practices known to provide nutritional support and positive neonate-driven feeding experience (25, 37, 43) are shown in Table 1.

vi. Healing environment

Intrauterine environment protects the fetus from the intense external stimulation and consequently, it promotes normal sleep cycles and optimizes brain development. Due to the very nature of a NICU, PNs are inevitably subjected to constant sensory overload, including bright lights, loud and unpredictable noises, harmful odors, temperature fluctuations, discomfort manipulations and multiple painful procedures which can result in lifelong alterations in brain development (44). Practices known to provide an environment that promotes healing by reducing the impact of NICU environment on the neonate's developing CNS (11, 25, 37, 45) are shown in Table 1.

vii. Partnering with families

Parenthood of a PN is considered to be a quite critical and sensitive period as parents often experience a grief-like reaction because of the loss of a normal pregnancy, a pleasant birth experience and a healthy full term neonate. A premature birth and the physically unattractive appearance of a PN can create parental feelings of failure, anxiety, fear, uncertainty, frustration, depression and vulnerability (46, 47). Parents of a PN tend to focus on conditions and parameters essential for survival such as body weight, nutrition and vital signs, and they hesitate to bond and communicate with their child. Emotional detachment or delayed bonding can subsequently lead to parental distancing, non-optimal parenting and/or withdrawal of investment (48). Early and effective integration of the neonate's family in daily care can enhance brain development and connectivity by reducing stress levels on the PN (49, 50). Practices known to support parenthood and promote secure attachment are shown in Table 1.

Pharmacological brain-focused clinical practices

i. Neuronal injury mechanisms in premature neonates and therapies

Preterm brain is vulnerable to hypoxia-ischemia, excitotoxicity, inflammation, oxidative stress and poor nutrition. Exposure to such conditions can result in structural, biochemical and cell-specific injury.

Subplate neurons and oligodendrocyte precursors are more vulnerable in the preterm brain and, along with dysmaturational events in both white matter and neuro-axonal structures, they constitute a significant substrate for deep cerebral white matter injury (WMI) in PNs (51). The immature cerebral vasculature and cerebrovascular autoregulation system of PNs can difficult adapt to insults such as hypoxic, ischemic, inflammatory and infectious that set off a cascade of events leading to WMI (52). Intraventricular haemorrhage in PNs is mainly due to fragility of germinal matrix vasculature, platelet and coagulation disorders and finally, constant disturbances in the cerebral blood flow such as suctioning and fluctuations of the blood pressure (53). Furthermore, hypoxic ischemic encephalopathy occurs when fetal cerebral blood flow is interrupted by maternal, placental or fetal causes. Primary cell death results from hypoxia and rapid depletion of adenosine triphosphate ensued by reoxygenation and reperfusion that increase free radical formation, excitotoxicity and nitric oxide production, with the secondary energy failure contributing to late cell death. Ongoing injury and inflammation becomes chronic at the final tertiary phase. Other causes of perinatal brain injury include perinatal stroke, kernicterus, physical trauma during labour and birth, gene mutations, congenital infections, chorioamnionitis and certain maternal health conditions (54, 55).

Experimental animal studies demonstrate the neuroprotective role of neurotrophic factors such as the brain-derived neurotrophic factor (BDNF), glial-derived neurotrophic factor (GDNF), epidermal growth factor (EGF), nerve growth factor (NGF) as well as insulin-like growth factor-1 (IGF-1), sonic hedgehog (Shh) and erythropoietin (EPO). Moreover, the neurotrophin family is critical for the development, survival and differentiation of neurons of the peripheral nervous system and CNS, while it also plays a crucial role in neuroregeneration after pathologic conditions (54). It is tested and reported that intraventricular NGF administration might be an effective and safe supplement therapy in pediatric patients with severe hypoxic ischemic brain injury (56). However, it has not been evaluated in clinical trials yet.

Moreover, vascular endothelial growth factors (VEGFs) are cytokines that stimulate angiogenesis and vasculogenesis, an important fact for the elimination of the infarct volume and arterial blood supply with an alternative route to the

ischemic region (57). *In vivo*, exogenous administration has been demonstrated only in rat models (58). Heparin-binding EGF-like growth factor (HB-EGF), hepatocyte growth factor (HGF), granulocyte macrophage colony-stimulating factor (GM-CSF) and progranulin (PGRN) are less studied growth factors in mouse brain that increase neurogenesis and neuronal survival and also decrease infarct size and neuronal apoptosis (57).

Finally, another treatment that is currently in clinical use for PNs consists of antenatal administration of corticosteroids to women with threatened preterm labour, which is strongly associated with reducing neonatal mortality and morbidities, including IVH (59, 60).

ii. Molecules evaluated in clinical trials

Prematurity significantly increases the risk of NI and the combination with other perinatal phenomena, such as intrauterine hypoxia, infection and inflammation, makes the development of treatment strategies quite difficult.

Although major advances have been made in the prevention and management of neonatal brain injury, HIE is still an unresolved and significant condition of PNs. As brain cooling is the only known treatment for HIE and is allowed only in PNs with gestational age ≥35 weeks (61), pharmacological practices relating to novel molecules are of great importance for therapeutic potential after HIE. To date, therapies for PNs have been mostly ineffective in improving neurodevelopmental outcomes. However, few exciting therapies that aim to quell apoptosis and inflammation or promote neurogenesis have been evaluated in clinical trials (62).

Erythropoietin (EPO) is a 34-kDa glycoprotein with multiple neuroprotective effects. It has been studied in many clinical trials but results remain controversial. High-dose EPO treatment administered to extremely PNs from 24 hours after birth through 32 weeks of postmenstrual age has been reported not to reduce the risk of severe neurodevelopmental impairment or death at two years of age (NCT01378273), while in another trial, repeated low-dose EPO treatment did eliminate the risk of long-term neurological disability in very PNs with no obvious adverse effects (NCT02036073).

Topiramate (TPM) is a neuroprotective agent that has been found to reduce seizure activity and mortality in cooled neonates with HIE, although with not statistical significance (EudraCT: 2011-005696-17). Similarly, administration of TPM in neonates with HIE treated with hypothermia was safe but did not reduce the combined frequency of mortality and severe neurological disability (EudraCT: 2010-018627-25).

Allopurinol is a xanthine oxidase inhibitor that reduces the production of oxygen radicals as superoxide. A significant beneficial effect has been suggested in moderately asphyxiated neonates treated with allopurinol in a meta-analysis of two previous clinical trials (63). A European multicentre trial (Phase III) is still ongoing, with the aim to evaluate the effect of postnatal allopurinol administration in full term neonates with HIE in addition to standard care (NCT03162653).

Xenon is a monoatomic gas that crosses the blood–brain barrier within a short time and can provide potential neuroprotection after asphyxia by different mechanisms. However, administration of inhaled xenon in asphyxiated neonates between 36-43 weeks of gestation within six hours of birth assigned to moderate hypothermia was unlikely to improve the neuroprotective effect of cooling after birth asphyxia (NCT00934700).

Magnesium sulfate ($MgSO_4$) has anti-inflammatory properties and prevents excitotoxic damage through N-methyld-aspartic acid (NMDA) receptor blockade. A meta-analysis published in 2017, including several randomized controlled trials, demonstrated the neuroprotective effects of $MgSO_4$ given antepartum in women with imminent preterm birth (<33 weeks of gestation). Particularly, it reduced the combined risk of fetal/infant death or cerebral palsy (64). A multicenter randomized controlled trial of near term and term neonates with moderate or severe HIE evaluated the effect of $MgSO_4$ as an additional pharmacologic neuroprotective agent to supplement the neuroprotective role of therapeutic hypothermia in contrast to therapeutic hypothermia plus placebo, but it found no differences in short-term adverse outcomes (death, seizures and intracranial hemorrhage) between the two studied groups (NCT01646619).

Melatonin is an indoleamine that easily crosses the blood-brain barrier and has multiple protective roles such as antioxidant, anti-inflammatory, anti-apoptotic, trophic and mitochondria-protective functions. A quite recent trial in asphyctic neonates with gestational age greater than or

TABLE 2. Pharmacological brain-focused clinical practices evaluated in clinical trials involving HIE and their possible neuroprotective effects

Molecules Studied	Possible Neuroprotective Effects
Erythropoietin	Acutely, neurotrophic, anti-inflammatory, anti-excitotoxic, anti-oxidant, and anti-apoptotic effects. Long term, neurogenesis and oligodendrogenesis
Topiramate	Antiseizure effects
Allopurinol	Reduces free radical formation and in high dosages also acts as a free-radical scavenger and free iron chelator
Xenon	As an inhibitor of NMDA glutamate receptors might reduce neuronal injury caused by excessive glutamate concentrations; Lessen seizures; Reduces apoptosis by activation of anti-apoptotic factors
Magnesium Sulfate ($MgSO_4$)	Alleviates neuronal cell damage by binding to the magnesium site on [a]NMDA glutamate channel
Melatonin	Free radical scavenger activity and stimulation of anti-oxidant enzymes; immunomodulatory effects; anti-inflammatory and anti-apoptotic properties; triggers neuron generation; minimizes cell death and improves neurodevelopmental outcomes
Autologous Cord Blood Cells	Decrease neurological impairment; Potentially reduce brain injury due to anti-inflammatory and immunomodulatory mechanisms, release of neurotrophic or growth factors that stimulate endogenous neurogenesis

[a] NMDA: N-Methyl D-Aspartate

equal to 36 weeks investigated the effect of melatonin as adjuvant pharmacological therapy to hypothermia treatment on biochemical, neurophysiologic, radiological and long-term neurodevelopmental outcomes (EudraCT: 2012-000184-24). It concluded that melatonin administered intravenously in addition to cooling therapy in neonates with HIE improved cognitive development at the age of 18 months, but it should be considered a preliminary approach due to the low number of participants.

Autologous cord blood cell therapy has both neuroprotective and neuroregenerative properties and, because of its long therapeutic time window, low immunogenicity and certain availability, it has attracted much attention for neonates with HIE. Intravenous infusion of autologous umbilical cord blood cells has been studied in clinical trials including neonates with HIE (NCT00593242, NCT02256618), showing that the therapy is feasible and safe.

The above novel molecules that help PNs to reduce the burden of NI together with their possible neuroprotective effects (63, 65-72) are shown in Table 2. ❑

CONCLUSION

Brain focused clinical practices encompass all strategies and interventions that promote optimal development of the brain, support adaptive neuronal connectivity and prevent NI. They represent an advanced approach to the care of high risk PNs with focus on interactive experiences and neuroprotective molecules that bring hope to forthcoming treatments. In the future, a combination of pharmacological and non-pharmacological BFCP might be considered as the most promising protection and/or treatment provided in clinical practice to PNs at high risk for NI. However, future clinical trials will be needed to document their long-term benefits. ❑

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