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Mini Review

Current Research in Neonatal Hypoxic-Ischemic Anti-Inflammatory Therapeutics

del Arco L[1] and Alonso-Alconada D[2,3]*

[1]*Cruces University Hospital, Barakaldo, Bizkaia, Spain*

[2]*Department of Cell Biology and Histology, Faculty of Medicine and Nursing, University of the Basque Country, Leioa, Bizkaia, Spain*

[3]*Institute for Women's Health, University College London, London, United Kingdom*

***Corresponding Author**: Daniel Alonso Alconada, Department of Cell Biology and Histology, Faculty of Medicine and Nursing, University of the Basque Country, Leioa, Bizkaia, Spain.

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Abstract

A number of studies have reported that inflammation is critical in the evolution of neonatal encephalopathy, evidencing that there is a strong association between perinatal hypoxia-ischemia, the secondary inflammatory response to the insult and persisting neurodisability in survivors. Despite this process can be necessary to remove cell debris and to start regenerative processes, it can become in one of the leading pathogenic factors of neonatal brain damage. In the present review we focus on the current ongoing clinical trials on neonatal hypoxic-ischemic encephalopathy that are using anti-inflammatory compounds.

Keywords: *Neonatal Encephalopathy; Perinatal Hypoxia-Ischemia; Brain Injury; Inflammation; Therapeutics; Clinical Trials*

Introduction

Following perinatal hypoxia-ischemia, a bidirectional communication exists between the injured brain and peripheral innate and adaptive immune system, which can in turn modulate the progression of ischemic pathology. After the onset of the injury, brain cells release pro-inflammatory cytokines and chemokines that induce the recruitment of white blood cells [1]. The infiltration of macrophages can be both protective against hemorrhage and necessary to remove cell debris but can also be detrimental in ischemic injury, impairing tissue repair. Together with an increase in the concentration of reactive oxygen species [2] leading to oxidative stress by lipid peroxidation, both infiltrating cells from blood capillaries and microglia can continue secreting a number of inflammatory mediators that can exacerbate the damage [1]. These factors can include a wide range of molecules, being the most recognized the inflammatory cytokines tumor necrosis alpha, interleukins-1-beta, -9 and -18, chemokines like macrophage inflammatory protein-1 and macrophage chemoattractant protein-1, nitric oxide and matrix metalloproteinases [1], which have shown to be related with delayed cell death and brain injury [2].

This inflammatory response normally starts a few minutes/hours after the onset of the injury and can extend even for months to years, in a late phase of damage known as tertiary brain injury. This process can block neuroreparatory processes and affect brain development, leading to long-term neurological sequelae such as cerebral palsy and epilepsy and also to attention deficits and hyperactivity in children and adolescents [1]. Together, these data emphasize the significant contribution of infection/inflammation in the developing brain contributing to neonatal encephalopathy.

To date, therapeutic hypothermia is the only current standard clinical care for neonatal encephalopathy in high income settings. There is clear evidence that in intensive care settings therapeutic hypothermia reduces adverse outcome (mortality and neurodevelopmental disability) at 18 months of age (typical relative risk 0.75%, 95% CI 0.68 - 0.83) [3]. However, it offers a discrete reduction of 11% in risk of death or disability [4] and approximately 40% of infants have an adverse neurodevelopmental outcome despite hypothermic treatment [5].

Indeed, recent data suggest that cooling may be less effective in the presence of infection/inflammation [6-8]. In a clinical study evaluating how induced hypothermia could improve outcome in patients with severe bacterial meningitis, the trial was stopped early at the request of the data and safety monitoring board because of concerns over excess mortality in the hypothermia group [6]. In experimental models of neonatal brain injury, hypothermia was not neuroprotective in inflammation-sensitized hypoxia-ischemia induced by lipopolysaccharide administration, an effect particularly seen in the hippocampus and in the unligated hemisphere [7]. Further, therapeutic hypothermia was less protective in babies whose placenta showed chorioamnionitis [8], as described in a small prospective study of placental histology relative to magnetic resonance imaging in babies.

In order to reduce the undesirable consequences triggered by neonatal brain injury-induced inflammation, the use of anti-inflammatory medicines has been extensively studied and can be considered as another meaningful tool against hypoxic-ischemic brain injury. These pre-clinical studies have evaluated the therapeutic capacity of antioxidant molecules such as N-acetylcysteine or allopurinol, anti-inflammatory chemical compounds including the second generation of tetracycline and statins, or endogenous compounds like erythropoietin, endo-cannabinoids or melatonin [9-12].

In the present review, we focus on the current ongoing clinical trials on neonatal hypoxic-ischemic encephalopathy that are using anti-inflammatory compounds, described in table 1. All the data reported in the table were obtained from the ClinicalTrials.gov database on November 2017. These compounds include melatonin (an endogenously produced indoleamine primarily formed in the pineal gland; NCT02621944), chemical compounds like sildenafil (NCT02812433) and allopurinol (NCT03162653) and endogenous molecules like hydrocortisone (NCT02700828), erythropoietin (alone: NCT02811263, NCT03079167 or in combination with therapeutic hypothermia: NCT03163589, NCT01913340) and its re-engineered form darbepoetin alpha (NCT03071861).

Table 1: *Current ongoing clinical trials on neonatal encephalopathy using anti-inflammatory related compounds as treatment.*

Sildenafil Administration to Treat Neonatal Encephalopathy (SANE)					
Treatment	Allocation	Masking	Study arms	Recruitment Status/ Enrolment	NCT Number
Sildenafil	Randomized	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	• Active Comparator: Sildenafil Sildenafil 2 mg/kg/dose per os twice a day for seven consecutive days (from day 2 of life to day 9 of life) if brain injury on day 2 of life Intervention: Drug: Sildenafil • Placebo Comparator: Ora-Blend Ora-Blend 2 mg/kg/dose per os twice a day for seven consecutive days (from day 2 of life to day 9 of life) if brain injury on day 2 of life Intervention: Drug: Ora-Blend	Recruiting 80	NCT02812433
Mild Encephalopathy in the Newborn Treated With Darbepoetin (MEND)					
Treatment	Allocation	Masking	Study arms	Recruitment Status/ Enrolment	NCT Number
Darbepoetin Alfa	Randomized	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	• Experimental: Darbepoetin Alpha IV,10 mcg/kg/dose, Darbepoetin Alpha, one dose at <24 hours of age Intervention: Drug: Darbepoetin Alfa • Placebo Comparator: Placebo IV, Normal saline (placebo dose), one dose at <24 hours of age Intervention: Drug: Normal Saline	Not yet recruiting 40	NCT03071861
High-dose Erythropoietin for Asphyxia and Encephalopathy (HEAL)					
Treatment	Allocation	Masking	Study arms	Recruitment Status/ Enrolment	NCT Number
Erythropoietin	Randomized	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	• Active Comparator: Erythropoietin Erythropoietin 1000 U/kg IV, at about 1, 2, 3, 4 and 7 days of age (i.e., 5 doses)Intervention: Drug: Erythropoietin • Placebo Comparator: Placebo Normal saline IV (equal volume), at about 1, 2, 3, 4 and 7 days of age Intervention: Drug: Normal saline placebo	Recruiting 500	NCT02811263
Erythropoietin in Management of Neonatal Hypoxic Ischemic Encephalopathy					
Treatment	Allocation	Masking	Study arms	Recruitment Status/ Enrolment	NCT Number
Erythropoietin	Randomized	None (Open Label)	• Experimental: study group Within 4 to 6 hours after birth all cases with moderate to severe hypoxic ischemic encephalopathy will be enrolled in therapeutic hypothermia using total body cooling and temperature and Receive erythropoietin (1000 U/kg intravenously) on days 1, 2, 3, 5, 7 and 9 (six doses,first two doses will be daily from the first day and last 4 doses will be every 2 days) Intervention: Drug: Erythropoietin • Placebo Comparator: control group Within 4 to 6 hours after birth cases with moderate to severe hypoxic ischemic encephalopathy enrolled in therapeutic hypothermia using total body cooling and temperature and Receive normal saline on days 1, 2, 3, 5, 7 and 9 (six doses,first two doses will be daily from the first day and last 4 doses will be every 2 days) Intervention: Drug: normal saline	Not yet recruiting 40	NCT03163589
Erythropoietin for Hypoxic Ischaemic Encephalopathy in Newborns (PAEAN)					
Treatment	Allocation	Masking	Study arms	Recruitment Status/ Enrolment	NCT Number
Epoetin Alfa	Randomized	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	• Experimental: Erythropoietin Erythropoietin (epoetin alfa) 1000 IU/kg birth weight (capped at 4000IU daily) IV infusion, on Days 1, 2, 3, 5 and 7 of age Intervention: Drug: Epoetin Alfa • Placebo Comparator: Placebo IV normal saline (equiv. volume), on Days 1, 2, 3, 5 and 7 of age Intervention: Drug: Normal saline	Recruiting 300	NCT03079167
Effect of Allopurinol for Hypoxic-ischemic Brain Injury on Neurocognitive Outcome (ALBINO)					
Treatment	Allocation	Masking	Study arms	Recruitment Status/ Enrolment	NCT Number
Allopurinol	Randomized	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	• Active Comparator: Allopurinol Allopurinol, powder for injection (PFI), administered in two doses. First dose (20 mg/kg in 2ml/kg sterile water for injection) given as soon as intravenous access is established and no later than 30min postnatally and second dose (10mg/kg in 1ml/kg sterile water for injection) 12 hours thereafter. The second dose will only be administered to in infants on therapeutic hypothermia. Infants who recover quickly and do not qualify for and hence do not undergo hypothermia will not receive a second dose. Administration will be by continuous infusion using a syringe pump over 10min through secure venous access. Intervention: Drug: Allopurinol • Placebo Comparator: Placebo mannitol, powder for injection (PFI), administered in two doses. First dose (20 mg/kg in 2ml/kg sterile water for injection) given as soon as intravenous access is established and no later than 30min postnatally and second dose (10mg/kg in 1ml/kg sterile water for injection) 12 hours thereafter. The second dose will only be administered to in infants on therapeutic hypothermia. Infants who recover quickly and do not qualify for and hence do not undergo hypothermia will not receive a second dose. Administration will be by continuous infusion using a syringe pump over 10min through secure venous access. Intervention: Drug: Mannitol	Not yet recruiting 846	NCT03162653
Hydrocortisone Treatment In Systemic Low Blood Pressure During Hypothermia in Asphyxiated Newborns (CORTISoL)					
Treatment	Allocation	Masking	Study arms	Recruitment Status/ Enrolment	NCT Number
Hydrocortisone	Randomized	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	• Active Comparator: Hydrocortisone Hydrocortisone is the pharmaceutical term for cortisol, the principal glucocorticoid secreted by the adrenal gland Intervention: Drug: Hydrocortisone • Placebo Comparator: Placebo Isotonic sodium chloride is an aqueous solution of 0.9 percent sodium chloride which is isotonic with the blood and tissue fluid Intervention: Drug: Placebo	Recruiting 32	NCT02700828
Neonatal Erythropoietin And Therapeutic Hypothermia Outcomes in Newborn Brain Injury (NEATO)					
Treatment	Allocation	Masking	Study arms	Recruitment Status/ Enrolment	NCT Number
Erythropoietin	Randomized	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	• Active Comparator: Erythropoietin 1000 U/kg/dose x 5 doses Intervention: Drug: Erythropoietin • Placebo Comparator: Normal saline Intervention: Drug: Normal saline	Active, not recruiting 50	NCT01913340
Melatonin as a Neuroprotective Therapy in Neonates With HIE Undergoing Hypothermia					
Treatment	Allocation	Masking	Study arms	Recruitment Status/ Enrolment	NCT Number

Melatonin	Non-randomized	None (Open Label)	• Experimental: Participants 1-10 This group will receive a 0.5 mg/kg enteral dose of Melatonin. The first dose will be administered via enteral route within 12 hours of life with a target of 6 hours of life. The melatonin will be administered as a single dose for the first 5 participants in allowing the investigators to determine if the dosing frequency has the potential to decrease in the elimination with hypothermia. The next 5 subjects who will receive multiple doses if there are not any safety concerns. • Experimental: Participants 11-20 This group will the Melatonin dose of 3 mg/kg enteral, only if the group Participants 1-10 has meet the safety goals. The first dose will be administered via enteral route within 12 hours of life with a target of 6 hours of life. The melatonin will be administered as a single dose for the first 5 participants in allowing the investigators to determine if the dosing frequency has the potential to decrease in the elimination with hypothermia. The next 5 subjects who will receive multiple doses if there are not any safety concerns. • Experimental: Participants 21-30 This group will receive Melatonin dose of 5 mg/kg enterally, only if the group Participants 11-20 has meet the safety goals. The first dose will be administered via enteral route within 12 hours of life with a target of 6 hours of life. The melatonin will be administered as a single dose for the first 5 participants in allowing the investigators to determine if the dosing frequency has the potential to decrease in the elimination with hypothermia. The next 5 subjects who will receive multiple doses if there are not any safety concerns. Additionally, the participants will have the following test performed: Magnetic Resonance Imaging (MRI), Neurological Outcome Assessment, Generalized Motor Assessment (GMA), Pharmacokinetics, and safety monitoring. Interventions: ○ Drug: Melatonin ○ Other: Magnetic Resonance Imaging ○ Other: Pharmacokinetics ○ Behavioral: Neurological Outcome Assessment ○ Behavioral: Generalized Motor Assessment	Recruiting 30	NCT02621944

Conclusion

In an effort to improve the clinical course of neonatal brain injury, a number of clinical studies are underway to determine optimal treatments using anti-inflammatory drugs. Further studies are needed to determine the optimal dose and interval of administration of every single compound tested. The use of synergic strategies, such as the association between hypothermia and some of these anti-inflammatory treatments, may lead to a larger neuroprotective effect on the brain thus improving the neonatal outcome.

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Conflict of Interest

The authors declare no conflict of interest.

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