

Optimizing Neonatal Outcomes with Melatonin - Huge Promise but Slow Progress

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In this elegant review by D'Angelo and co-authors, *Neuroprotective role of Melatonin in neonatal brain Injury: 20 years after the first administration in Newborn⁽¹⁾*, the progress since 2000 with melatonin as a potential therapy in neonatal brain injury is described. The authors are a stellar group who have pioneered our understanding of melatonin for several decades and performed the “first in baby” melatonin studies.

After birth, newborns are melatonin deficient until 3-5 months old, when rhythmicity is attained; this deficiency is exacerbated and extended with brain injury. Given melatonin's diverse beneficial effects and its reassuring safety profile, it is remarkable how slow progress has been in introducing melatonin to optimize outcomes in high-risk pregnancies and sick babies. The developing brain is highly vulnerable to oxidative stress; melatonin achieves its powerful neuroprotective effects through potent antioxidative mechanisms, immunomodulation, preserving mitochondrial integrity and promoting brain repair (**Figure 1**).

Several factors contribute to the slow progress in translating melatonin into clinical use. One factor is the lipophilic nature of melatonin; although this allows access into every organ and cell with ease (including the placenta and blood brain barrier), solubility enhancers such as ethanol are required to obtain a desired, high concentration solution. The use of ethanol as an excipient has been a confounding factor in several pre-clinical and clinical studies, making these studies difficult to translate. A safe GMP grade intravenous formulation is urgently needed.

A second factor relates to the paucity of adequately powered clinical trials. Recently, the five trials in neonatal encephalopathy (NE), involving 215 infants were systematically reviewed⁽²⁾. Limitations of these trials include their small size, inconsistent melatonin dosing regimens, lack of pharmacokinetic data, and a paucity of neurodevelopmental follow up.

A third related factor is the complete absence of any clinical studies achieving “therapeutic” melatonin levels. Both *in vitro*⁽³⁾ and pre-clinical piglet studies⁽⁴⁾ suggest the neuroprotective efficacy of melatonin is *concentration dependent*, with serum levels of 15-30mg/L required within 1-3h after hypoxia-ischemia to achieve optimal effects. This level is 10,000 times higher than the physiological surge at 4am we experience as part of the circadian rhythm (typically 60pg/mL). Intravenous doses of 20-30 mg/kg every 24h are typically needed, although this requires further assessment in human newborns. Harnessing the full potential of melatonin's efficacy requires attention to achieving optimal

levels and timing; in NE ensuring therapeutic levels are reached within the first 1-3h after birth and maintained during the secondary phase of injury is vital. Future studies must incorporate therapeutic drug level monitoring.

Whilst there is compelling pre-clinical data of melatonin's neuroprotective efficacy, clinical studies significantly lag behind. Other promising neuroprotective therapies for NE, such as erythropoietin⁽⁴⁾ and mesenchymal stem cells⁽⁵⁾ are moving along the translational pipeline; new concepts which may optimise protection include staggering therapy according to phase of injury and pre-treatment with melatonin⁽⁶⁾. Researchers, pharmaceutical companies, funding bodies, and clinicians need to combine efforts so that high risk babies can benefit from melatonin's healing powers.

Figure 1: Melatonin for Neonatal Encephalopathy – Mechanism of Action. Created with BioRender.com

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