

Plenty of Pain in Neonates: The Mission to Find a Treatment for the Complications of Premature Birth

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It is widely accepted that the neonatal brain is not merely a junior version of the adult central nervous system. The neonatal nervous system is unique in its immature features, vulnerability to chemical, physical and genetic damages, and high plasticity in response to environmental inputs [1]. The complications of premature birth, developmental disorders and consequent pathological and/or behavioral deficits, constitute major challenges for clinical pediatricians and for researchers as well. Studying brain disorders in neonates is complicated by the inability of pediatric researchers to communicate with the infants and the lack of appropriate animal models of prematurity. One major emerging field of study in neonatal research is pain. For a long time, researchers commonly believed that neonates do not feel pain as adults do; however, recent studies have shown that neonates may be more sensitive to pain because of their underdeveloped inhibitory tracts [2].

In the Neonatal Intensive Care Unit (NICU), premature babies undergo a number of potentially tissue-damaging, painful procedures such as heel sticks, intubations and catheter insertions that are believed to be a root cause of several long-term complications. Adolescents and adults who suffered excessive painful stimuli as neonates may develop altered pain sensitivity, learning deficits, and psychiatric and attention disorders [3]. Despite the significance of this problem, very little research has been invested in either understanding the mechanisms linking painful stimuli, prematurity, brain development and adulthood complications or in finding a remedy for this ailment. Still, several therapeutic approaches have been adopted with variable outcomes [4]. Most pharmacological agents (opioids and/or topical anesthetics) have failed to show efficacy in treating neonatal pain. Morphine, for example, is highly toxic for neonatal development. On the other hand, ketamine, an NMDA receptor antagonist, has neuroprotective effects against neonatal pain [5] although other reports have shown that it causes neuronal apoptosis in the immature brain [6]. Several other non-pharmacological therapeutic methods (music, oral sweet nutrition, maternal care and skin-to-skin holding and breastfeeding) are widely in use, but with different reported efficacies. While the mechanisms of these non-pharmacological methods are not confirmed, they may produce stimulatory ascending signals that inhibit painful stimuli using endogenous analgesic pathways [7]. In our article recently published in *Molecular Pain*, entitled "Erythropoietin reduces neuronal cell death and hyperalgesia induced by peripheral inflammatory pain in neonatal rats" [8], we have shown markedly enhanced neuronal survival and reduced long-term complications in a rat model of neonatal pain treated with human recombinant Erythropoietin (EPO).

In this investigation, the challenge to understanding the mechanisms of neonatal pain-related complications given the scarcity of animal models prompted us to adopt the formalin injection protocol in the paws of neonatal rats to mimic premature neonatal pain. Formalin was subcutaneously injected in the paws of neonatal rats at postnatal day three through five with or without concomitant injections of EPO. Formalin injection significantly increased neuronal cell death in the somatosensory cortex, hippocampus and hypothalamus, enhanced pain sensitivity and decreased exploratory behaviors. While EPO

treatment alone did not affect neuronal survival, inflammatory cytokine expression or behaviors, EPO significantly reduced brain cell death and restored normal pain sensitivity and normal exploratory behaviors after formalin injection. Interestingly, EPO treatment showed a noticeable effect in maintaining normal cerebral blood flow after the inflammatory insult indicating that EPO may have an analgesic central effect which maintains normal neuronal activity. Moreover, EPO increased brain and body weights which were significantly decreased after formalin injection. In summary, EPO produced several neuroprotective effects in our rat model of neonatal pain and reversed complications arising from formalin injection mediated neonatal pain.

EPO is an endogenous hormone primarily responsible for erythropoiesis. Moreover, EPO is naturally occurring in human neonate and adult tissues, in neonate and adult cerebrospinal fluid and in human breastfeeding milk. Endogenous EPO not only helps in erythropoiesis but also plays important roles in neuronal tissue development and in immunity [9]. Given its pleiomorphic effects, several trials of basic and clinical research have demonstrated noteworthy neuroprotective and neurotrophic effects of EPO in the treatment of different animal models of stroke. Despite its failure as a treatment for human stroke patients [10], EPO did not lose hype for being a valuable drug for a variety of diseases in adults and neonates as well especially because of its anti-apoptotic and anti-inflammatory functions. EPO has been a drug of choice with minimal side effects in the treatment of anemia of chronic diseases in adults and in extremely ill preterm babies.

Today, around 50,000 preterm babies are born every year. Given the tremendous clinical consequences of prematurity, further studies are definitely needed to understand the mechanisms of prematurity-induced complications and develop appropriate FDA approved medicines for treating this neglected disorder. We believe that a drug with pleiomorphic mechanisms of action like EPO would be most suitable for treating such a complicated disorder. This kind of scientific investment might alleviate the suffering of thousands. Ultimately, however, the understanding of how neonatal pain might cause these psychiatric disturbances will help to better identify therapeutic targets and thus agents for this debilitating disorder.

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Received January 05, 2012; Accepted January 06, 2012; Published January 15, 2012

Citation: Mohamad O, Yu SP (2012) Plenty of Pain in Neonates: The Mission to Find a Treatment for the Complications of Premature Birth. *J Pain Relief* 1:e103. doi:10.4172/2167-0846.1000e103

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