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REVIEW

Potential benefits of melatonin to control pain in ventilated preterm newborns: An updated review

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Abstract

Infants admitted to neonatal intensive care units are repeatedly stimulated by painful events, especially if intubated. Preterm infants are known to have greater pain perception than full term infants due to immaturity of descending inhibitory circuits and poor noxious inhibitory modulation. Newborns exposed to repetitive painful stimuli are at high risk of impairments in brain development and cognition. Chronic pain is induced and supported by proinflammatory cytokines, free radicals, and reactive oxygen species creating a self- sustaining vicious circle. Melatonin is a neurohormone secreted by the pineal gland with antioxidant and anti-inflammatory functions. This review describes the in-depth beneficial effects of melatonin for pain control in ventilated preterm newborns. As yet, a minimal amount of literature has been undertaken to consider all its promising bioactivities. The rationale behind the use of melatonin for pain control has also been taken into account in this review. Besides, this review addresses safety concerns and dosages. The potential benefits of melatonin have been assessed against neurological disorders, respiratory distress, microbial infections, and as analgesic adjuvant during ventilation. Additionally, a possible approach for the use of melatonin in ventilated newborns will be discussed.

KEYWORDS
mechanical ventilation, melatonin, newborn, pain

INTRODUCTION

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." Because subjective reporting of pain is a fundamental prerequisite of this definition, infants would be excluded, but it is now recognized that the inability to communicate verbally does not negate the possibility that an individual is experiencing pain and needs appropriate pain-relieving treatment.[1] Pain perception and stress response may be greater in premature than in full term infants. Indeed, nociceptive pathways are fully functional by the 24th week of gestation, whereas dorsal horn synaptic connectivity and descending inhibitory circuits are still immature, causing poor input sensory localization and discrimination and poor noxious inhibitory modulation.[2–5]

Preterm infants are also likely to experience more pain because their stays in the neonatal intensive care unit (NICU) are longer than those of less premature or full-term infants. Invasive mechanical ventilation is a

main painful stress that exposes patients to other complications, such as ventilator-induced lung injury, pneumonia, and chronic lung disease. Moreover, research proved that pain experienced by preterm infants may alter brain development with long-term effects on the infant's behavior and neurological outcome.[6]

Repeated painful stimuli during early brain development can alter the brain microstructure and topographical organization of afferent thalamo-cortical projections, resulting in the development of the atypical somatosensory cortex.[7]

Despite that, a large prospective study conducted by France in 2008 found that specific pharmacological or non-pharmacological analgesia was administered in only about 50% of infants undergoing painful procedures.[8]

Melatonin is a neurohormone secreted by the pineal gland with antioxidant and anti-inflammatory functions.[9,10] Moreover, melatonin shows analgesic properties, with a promising role to control pain during mechanical ventilation in infants admitted to the NICU.[11]

The purpose of this article is to highlight the potential role of melatonin as an analgesic adjuvant drug to control pain in ventilated preterm infants, illustrating the most relevant evidences in this field.

PAIN, OXIDATIVE STRESS, AND BRAIN DEVELOPMENT IN PRETERM NEWBORNS

Painful stimuli activate both ascending signaling pathways and descending inhibitory feedback mechanism.

Hyperalgesia is the result of continuous peripheral afferent stimulation, which leads to the production of free radicals, the release of glutamate, and subsequent spinal sensitization.[12] Generally, a dynamic balance between reactive oxygen species (ROS) generation and elimination is maintained by antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase. However, painful stimuli cause an increase in free radicals that cannot be properly neutralized by the antioxidant system in preterm newborns.[13]

Preterm infants have a poor antioxidant system. Indeed, fetal levels of antioxidant enzymes increase progressively, with an exponential increase during the last 4–6 weeks of gestation.[13]

The increased energy requirement, following pain, causes a greater breakdown of adenosine triphosphate (ATP) into adenosine diphosphate and adenosine monophosphate (AMP), whereas adenosine is converted into hypoxanthine, xanthine, and acid uric, generating ROS. In turn, ROS promotes central sensitization of dorsal horn cells and activate spinal glial cells (SGCs) through several mechanisms involving the N-methyl-D-aspartate (NMDA) receptor, inhibition of gamma-aminobutyric acid transmission, and the activation of the transient potential of the receptor superfamily.[14–16] NMDA receptors involved in the pain stimuli transmission are more active during early life, inducing a great release of glutamate.[17] Glutamate, in turn, may trigger both oxidative stress and inflammatory reactions.[18,19] ROS induces also cyclooxygenase enzymes and prostaglandins production, amplifying the perception of pain.[20]

Finally, another mechanism that may increase ROS is inflammation and cytokine production. Cytokines are produced by peripheral nerve afferents, dorsal root ganglia, and SGCs, making a communication network between immune and neuronal cells.[21] A recent review analyzing the role of cytokines during pain states showed that initially circulating cytokines induce nociceptors to stimulate second order neurons in the spinal cord, and subsequently cytokines released by SGCs contribute to the cascade of inflammatory signals that lead to persistent pain.[22]

Increased oxidative stress biomarkers have been demonstrated in plasma of preterm and term infants undergoing painful procedures.[13,23,24]

A schematic diagram about cytokines and ROS involvement during pain transmission is shown in Figure 1.

On the clinical side, early exposure of premature infants to painful stimuli may cause brain cells dysmaturation, impairing neurological and sensorimotor development.[25–27] Brain dysmaturation, expressed as white matter injuries and gray matter lesions, is the most important predictor of neurodevelopmental disorders. The exposure to procedural pain of prematurely born infants is associated with reduced width of the frontal and parietal loves of the brain, reduced functional connectivity in the temporal lobes, and smaller volumes of subcortical brain structures, including amygdala, thalamus, and basal ganglia.[28–30] Finally, Tortora et al. also demonstrated a relationship between alterations in thalamus and insular cortex connectivity and exposure to early postnatal painful events of premature infants.[7] Reduced brain volumes in very preterm infants have been associated with poor functional outcomes in childhood, such as impaired intelligence quotient, speech and attention, and poor behavioral outcomes.[31,32]

These results are supported by animal studies that have shown similar impairments in brain development and cognition in rat models with neonatal pain. Rats exposed to repetitive stimulation of the needle prick during the first weeks of life presented memory impairments, reduced locomotor activity, anxiety, depression, and reduced social behavior.[33,34] Likewise, preterm infants exposed to neonatal pain have a higher rate of internalizing behaviors, such as withdrawal, depression, and / or anxiety, than full-term infants later in life.[35,36] These negative behaviors can be evident as early as 18 months of age and persist throughout childhood and adulthood.[37,38]

ANALGESIC EFFECTS OF MELATONIN

Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone secreted by the pineal gland with several

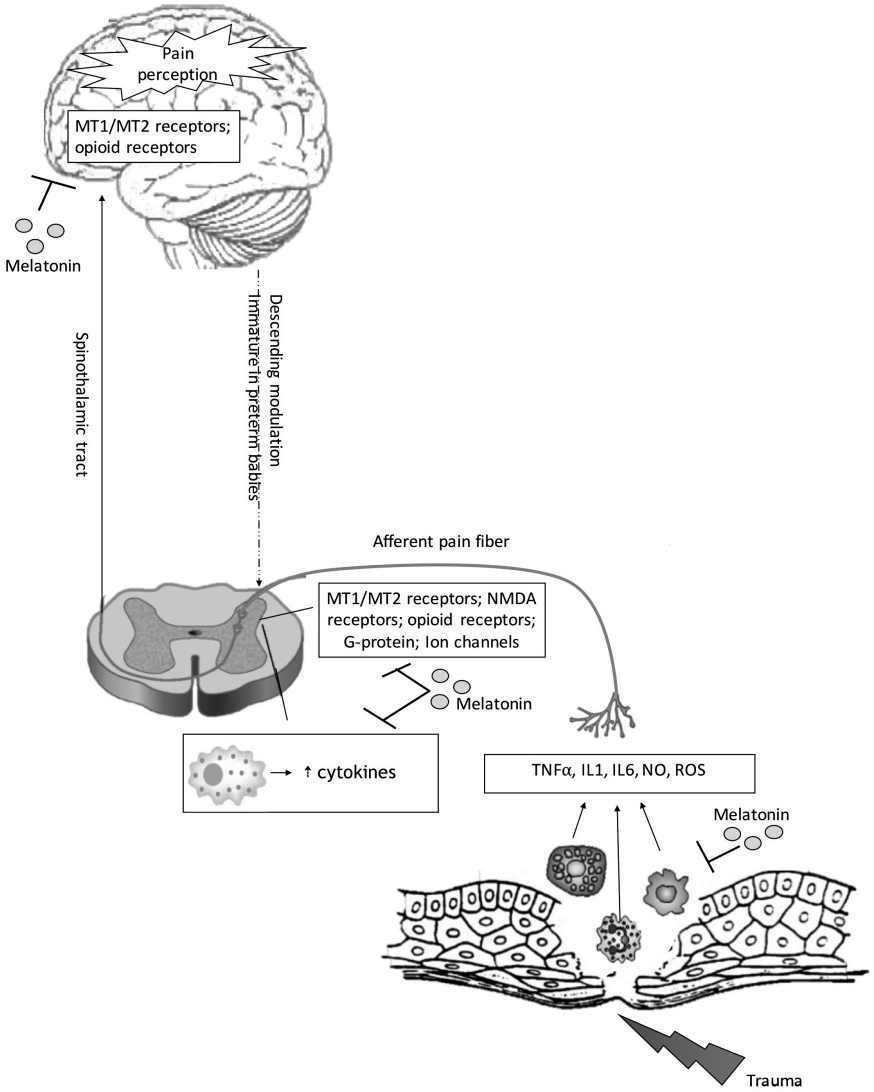

FIGURE 1 Schematic diagram of the role of cytokines and ROS during pain states. Melatonin acts via its MT1/MT2 receptors in the spinal cord and in brain and by its interaction with other receptors such as opioid and NMDA. Abbreviations NO, nitric oxide; ROS, reactive oxygen species, IL, interleukin); TNF, tumor necrosis factor; MT1/MT2, melatonin receptors; NMDA, N-methyl-D-aspartate

important functions, including regulation of the circadian rhythms, modulation of season changes, and antioxidant and anti-inflammatory effects.[39–42] Released melatonin has a half-life of 20–30 min and is metabolized primarily in the liver. The endogenous indoleamine melatonin in the fetus has a maternal origin, and, after birth, the full-term newborns have an irregular melatonin secretion for 3–5 months, leading to a transient melatonin deficiency in neonatal period and in the first months of life. Prematurity delays the maturation of the neurological network that controls melatonin secretion, leading to poor secretion for an even longer period.[43] Therefore, exogenous melatonin administration appears to be a promising strategy in the treatment of neonatal morbidities in which free radicals or inflammatory mediators have a leading role.[44] Several studies on the effect of melatonin in nociceptive modulation have reported its analgesic capacity for various types of pain.[45–47] The physiological mechanism of the analgesic effect of melatonin is not yet clear, however, it seems to act on two levels: both directly on the Gi-coupled melatonin receptors, MT1 and MT2, distributed in the pain control regions of the central nervous system such as lamina I-V and X of the spinal cord, thalamus, hypothalamus, spinal trigeminal tract, and trigeminal nucleus leads, and indirectly through its inflammatory and antioxidants effects.[48,49] Activation of melatonin receptors leads to reduction of cyclic AMP levels, activation of K+ channels and inhibition of $Ca2^{+}$ channels, resulting in inhibition of the membrane potential of neurons.[50] Furthermore, melatonin interacts with other receptors, including opioidergic, benzodiazepinergic, muscarinic, nicotinic, serotonergic, and adrenergic receptors, and also promotes the release of β-endorphin from the pituitary gland.[49,51] As for the anti-inflammatory and antioxidant effects, melatonin appears to decrease hyperalgesia by reducing

inflammation and tissue damage. In fact, it inhibits the production of nitric oxide (NO), proinflammatory cytokines by lymphocytes, and macrophages, on the other hand it neutralizes ROS by acting directly as a free radical scavenger and stimulating antioxidant enzymes, such as glutathione peroxidase, glutathione reductase, and superoxide dismutase [10,52,53]

The analgesic activity of melatonin during endotracheal intubation and mechanical ventilation was evaluated in 60 premature infants of 32 weeks of gestation or less. Two groups, each of 30 newborns, treated with 10 mg/kg of intravenous melatonin + fentanyl or fentanyl alone were compared.[54] Neonatal Infant Pain Scale (NIPS) score resulted similar in the two groups before, during, and after 5 min from intubation procedure. After intubation, pain response was assessed at 12, 24, 48, and 72 h of invasive ventilation using the Premature Infant Pain Profile (PIPP) scale. The pain scale was significantly lower in the group of patients treated with intravenous melatonin 10 mg/kg and fentanyl compared to infants managed with standard medication. The use of melatonin as an adjunct analgesic therapy during procedural pain was suggested. There might be a role for melatonin in premedication for nonemergency intubation in the neonate, especially if preterm.

Melatonin can be administered intravenously and orally. The most frequent method of administration is oral. The pharmacokinetic profile of oral pharmacological doses of melatonin in preterm neonates was recently reported by Carloni et al.[55] using three different doses of melatonin: 0.1, 0.5, and 5 mg. The results showed that a single intragastric administration of these drug doses to preterm infants resulted in high peak plasma concentrations, higher time of maximum plasma concentration (T_{max}) values than in adults, and a plasma half-life of melatonin ranging from 7.98 to 10.94 h.[55] The high peak plasma concentrations and the long half-life indicate that, in the neonatal clinical setting, it is possible to obtain and maintain high serum concentrations using a single administration of 0.5 mg melatonin repeated every 12/24 h. Long-term studies have never shown major side effects after oral administration of melatonin in children.[52]

MELATONIN ADMINISTRATION DURING MECHANICAL VENTILATION

Tracheal intubation is a stressful, painful, and dangerous procedure both for changes in vital parameters and for possible trauma to the airways.[56] In addition to the intubation procedure, mechanical ventilation is also a stressful and painful event that promotes the production of proinflammatory cytokines with long-term effects on the newborn's brain and behavioral development.[57]

The premedication with sedatives, analgesics, and muscle relaxants has long been a consolidated practice in adults and children, but the role of continuous analgesia or sedation in preterm infants is controversial. However, to date, premedication prior to endotracheal intubation is recommended in neonates, because studies on both premature and full-term infants showed that it makes it easier for the intubation procedure and limits pain, stress, and worsening of vital signs.[58]

Latest guidelines of the Italian Society of Neonatology on the management of pain control in the newborn suggested premedication of intubation with fast-acting opioids (fentanil or remifentanil) associated or not with benzodiazepines (commonly midazolam), in order to facilitate the procedure and reduce pain and stress.[59] When rapid recovery of spontaneous respiratory activity is required, it is preferable to use drugs with a short half-life (remifentanil among opioids) or with a low degree of respiratory depression (propofol).[60,61]

Although several studies in children and adolescents have shown that melatonin may have benefits as an analgesic therapy for procedural pain, data on its efficacy in premature infants are still lacking.[43,61]

Over the last year, the role of melatonin in intubated and mechanically ventilated patients has also been investigated in adults with coronavirus disease 2019 (COVID-19). Ramlall et al.[62] demonstrated that melatonin exposure is associated with a positive outcome both in terms of duration of mechanical ventilation and attenuation of lung inflammation.

The reduction in mechanical ventilation time could be explained by the fact that melatonin not only has analgesic and sedative power without any respiratory depressant effect, but its antioxidant effect also protects against ventilator-associated lung damage.[63] The treatment of melatonin for ventilated preterm infants might reduce pain-related stress and it may protect the lungs from oxidative stress and inflammation.

The protective role of melatonin in ventilated infants has been demonstrated.[11,54] In 2005, the proinflammatory cytokines were measured before and after treatment with melatonin in 110 preterm newborns with respiratory distress syndrome of III or IV degrees that needed invasive mechanical ventilation.[11] In this randomized study, the authors divided the patients into two groups (melatonin and placebo) and demonstrated that if infants received melatonin they had lower proinflammatory cytokines in the tracheobronchial aspirate and better clinical outcomes in terms of chronic lung disease development.[11] In 2012, Gitto et al.[54] evaluated also plasma concentration of IL-6, IL-8, IL-10, and IL-12 before and after 24, 72 h, and 7 days of mechanical ventilation. Comparing preterm newborns treated with and without melatonin, serum levels of pro-inflammatory cytokines were similar before endotracheal intubation, whereas it was significantly lower at subsequent times in patients treated with melatonin.

Although available data on the use of melatonin in infants support safe and effective use, further well-designed studies are needed before clear consensus and guidelines can be developed.

CONCLUSIONS

Preterm infants requiring intensive care are exposed to painful stimuli during hospitalization, such as invasive mechanical ventilation. Because pain can be harmful because it causes hemodynamic instability, low oxygenation, and impaired brain development, neonatal pain prevention and management is imperative. To date it is well known that pro-inflammatory cytokines play a key role in the induction and maintenance of pain.

The analgesic power of melatonin seems to be linked both to its direct action on melatonergic, opioidergic, benzodiazepinergic, muscarinic, nicotinic, serotonergic, and adrenergic receptors, and indirectly to its inflammatory and antioxidant effects. Furthermore, the antioxidant effect of melatonin appears to decrease lung inflammation, shortening the duration of ventilation, and improving the outcome of lung disease.

In summary, given the various positive effects in controlling chronic pain and reducing oxidative stress, melatonin may be a neuroprotective agent with analgesic properties and without any respiratory depressants or other significant side effects. These characteristics make melatonin a safe and promising analgesic substance suitable for the treatment of preterm newborns with lung diseases undergoing mechanical ventilation. Further studies are warranted to investigate the analgesic and sedative effects of melatonin in preterm infants with lung disease undergoing invasive mechanical ventilation.

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CONFLICTS OF INTEREST

No conflicts of interest exist for this article.

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APPENDIX
LIST OF ABBREVIATIONS

NICU	neonatal intensive care unit
ATP	adenosine triphosphate
AMP	adenosine monophosphate
ROS	reactive oxygen species
SGCs	spinal glial cells
NMDA	N-methyl-D-aspartate
NO	nitric oxide