Efficacy and safety of melatonin in newborn infants

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Abstract
Newborns are prone to oxidative stress. Melatonin is an endogenously produced antioxidant with a broad spectrum of antioxidative functions. Studies related to the toxicity of melatonin have not uncovered unexpected toxicity in humans even when given in high doses. Several clinical studies have been the first to demonstrate that the melatonin reduces oxidative stress in newborns with asphyxia, sepsis, distress or surgical stress. This paper reviews the use of melatonin in the newborns for the treatment of many conditions where there is excessive ROS production.

Keywords: melatonin, oxidative stress, newborn, preterm infant, safety

Introduction
Oxidant- and nitrogen-derived metabolites, collectively termed reactive oxygen (ROS) and reactive nitrogen species (RNS), respectively, are persistently produced in aerobic organisms. Women, infants, older persons, and those with tissue damage [1, 2] and tissue injury [3] and disease [4] are prone to oxidative stress. Newborns and especially infants born prematurely are especially prone to oxidative stress [3]. The reasons for this are several: Infants often are exposed to high oxygen concentrations, have infections or inflammation, have reduced antioxidant defense processes, and have high levels of free iron that are required for the Fenton reaction leading to the production of the highly toxic hydroxyl radical [4]. Oxidative stress likely contributes to the severity of several newborn conditions to the extent that Saugstad [5, 6] coined the phrase “oxygen radical diseases of newborns.” This idea implies that oxidative-inflammatory stress affects a variety of organs, often simultaneously, and gives rise to different signs according to the organ most damaged. Saugstad includes bronchopulmonary dysplasia/chronic lung disease (CLD), retinopathy of prematurity, and necrotizing enterocolitis in this category. Subsequently, it became clear that free radicals are involved in periventricular leukomalacia [7] as well as in the ductus arteriosus and pulmonary circulation [8-10]. Melatonin is an endogenously produced [11, 12] antioxidant which has a broad spectrum of antioxidative functions [13-14]. Studies related to the potential toxicity of melatonin have not uncovered unexpected toxicity [15-19] or severe adverse effects even when given in very high doses [17]. Melatonin was first recognized as having neuro-hormonal functions [16-20]. Subsequently, melatonin and its metabolites were found to have important antioxidant properties owing to their direct and indirect antioxidant actions [21-25]. It directly scavenges reactive oxygen/nitrogen species, reduces oxidative stress, improves the function of mitochondria, and restores glutathione homeostasis [26–30]. Melatonin also reduces NF-κB binding to DNA, probably by preventing its translocation to the nucleus [31–34]. This, in turn, reduces the production of pro-inflammatory cytokines and chemokines that also induce free radical damage. Melatonin inhibits neutrophil and polymorphonuclear leukocyte oxidative damage [35]. Several clinical studies provided the first evidence that the melatonin reduces oxidative stress in newborns with asphyxia, sepsis, distress or surgical stress. Melatonin has proven to be highly beneficial in these disorders [17, 37-40]. Aim of this study is the review of the use of melatonin in the newborns for the treatment of many conditions characterized by excessive ROS production.

Analysis of the studies
Data derive from six previous published studies [17, 37-41] on the use of melatonin in the neonatal period and through a review of medical records of the babies included in these studies. The studies were performed in the NICU of University of Messina and was approved by the Local Ethical Committee and performed only after parental consent. This review analyzes: the total number of neonates treated with melatonin, the doses typically used, the most common dose prescribed, the modality of administration, the efficacy of melatonin, the possible side effects, and long term effects after discontinuation.

Discussion
Melatonin is extensively used in newborns. A total of 85 newborns were included in the studies. The most common dose prescribed, the modality of administration, the efficacy of melatonin, the possible side effects, long term effects after discontinuation were assessed. The studies were performed in the NICU of University of Messina and was approved by the Local Ethical Committee and performed only after parental consent. This review analyzes: the total number of neonates treated with melatonin, the doses typically used, the most common dose prescribed, the modality of administration, the efficacy of melatonin, the possible side effects, and long term effects after discontinuation.

The second study concerned asphyxiated newborns. Ten asphyxiated infants received a total of 20 mg of melatonin (2 doses of 10 mg separated by a 1-h interval) dissolved in 5 mL of a 1:1 solution of saline and at 24 and 48 hours after birth. Ten other asphyxiated newborns were compared as control group. All 10 asphyxiated newborns were considered as normal control group [37].

The third study concerned surgically treated newborns. Infant with birth weight of 2000 g or less was given a total of 10 doses of melatonin (10 mg/kg) given over 4 hours, divided into four doses separated by 2-hour intervals. Ten other newborns with birth weight of 2000 g or less who received a placebo were compared as control group [38].

The fourth study concerned newborns with sepsis. Ten newborns received a total of 80 mg of melatonin (2 doses of 40 mg separated by 1-h interval) over a period of days or weeks. Melatonin also improved the clinical outcome of the septic newborns as detected by the culture score. Three of 10 non treated asphyxiated newborns died by 72 hr after birth; all the asphyxiated and control infants survived. In the first study on RDS syndrome [40], three of 10 non treated asphyxiated newborns died by 72 hr after birth; all the asphyxiated and control infants survived. In the first study on RDS syndrome [40], three of 10 non treated asphyxiated newborns died by 72 hr after birth; all the asphyxiated and control infants survived.
Data on elevated inflammatory cytokines in infants who develop BPD was previously documented [40, 56]. Melatonin therapy can selectively block some components of inflammation and likely reduce the severity of RDS in preterm newborns [38]. In the study on RDS [41], inflammatory mediators were measured and melatonin was used as a treatment in an attempt to modify the measured parameters.

The cytokine response to surgical stress in neonates has been studied reporting controversial results. IL-6 level seems to respond to surgery in a similar fashion as observed in adults. It rises in the postoperative period with a peak at 12 hours [61, 62] remaining elevated up to 24 to 48 hours postoperatively [63]. Similarly, IL-8 shows a rapid increase in the first hours, then returns to preoperative values after 24 hours [62]. Recently, the postoperative values of IL-6 in neonates undergoing major surgery have been studied showing no significant increase [44]. Compared to healthy neonates, NOX are end products of NO metabolism, and enhanced formation of NO has been described in different pathologic conditions such as asphyxia, sepsis, or inflammation [65]. NOX also have been studied as marker of oxidative stress [17]. In study about surgical newborns [39], has been shown significant increase in cytokines and NOX levels in both groups treated with melatonin compared with healthy neonates after operation. This condition represents an oxidative stress status with possible harmful effects for the patients. Also we tested for the first time whether melatonin would modify serum inflammation and oxidative stress parameters and improve the clinical course of surgical neonates operated on for major malformations. The comparison of serum parameters between melatonin-treated and untreated surgical newborns confirms the anti-inflammatory effect of melatonin. The data indicate that the 10 infants treated with melatonin improved already at 24 hours after treatment onset. No similar improvement was observed in the 10 surgical newborns who did not receive melatonin.

Several clinical and experimental studies have confirmed that melatonin has low toxicity [6-68]. There is general agreement that melatonin therapy has a remarkably safety profile, even when children are treated with higher doses. Also in our study we demonstrated that adverse advent correlated with melatonin-treatment are often self limiting and in any case serious. Moreover, several complications with long-term melatonin therapy in children have not been reported. It seems likely that melatonin treatment might result in a wide range of health benefits, improve quality of life and reduce healthcare costs, and may help to limit complications associated with prescription drug use in children as has been shown for adults [67, 68]. Overall, as a result of its wide spectrum of actions, melatonin would appear to be a highly beneficial molecule with unexploited clinical potential.

References


