High Endogenous Melatonin Levels in Critically Ill Children: A Pilot Study

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Objective To evaluate the serum melatonin levels in critically ill pediatric patients and to test the effect of light on the melatonin's circadian rhythm. Data on melatonin secretion in critically ill pediatric subjects are lacking.

Study design We investigated the serum melatonin levels of 16 sedated and mechanically ventilated patients in a pediatric intensive care unit. Children (mean age, 5.1 ± 3.1 years) were randomly assigned to a dark-exposed or to a light-exposed group to evaluate the effects of light on serum melatonin concentrations. Blood samples for serum melatonin analysis were collected at 10 p.m., 1 a.m., 3 a.m., 5 a.m., 8 a.m., and 12 p.m.

Results The melatonin circadian rhythm was severely disrupted in critically ill children; light exposure lowered serum melatonin even in a context of highly altered circadian cycle; melatonin peaks were greater for healthy age-matched children.

Conclusion The high melatonin levels in the critically ill children may be a response to counteract the elevated oxidative stress associated with serious diseases. Whether these elevated melatonin levels confer any beneficial effects in pediatric critically ill patients remains unknown. *(J Pediatr 2013;162:357-60)*.

Melatonin is an endogenously produced indolamine principally synthesized in the pineal gland from the neurotransmitter serotonin.[1] In mammals, the melatonin rhythm is generated by an endogenous circadian master clock in the suprachiasmatic nucleus of the hypothalamus, which is entrained by the light/dark cycle during a 24-hour period. Hence, melatonin secretion normally is low during the daytime, increases soon after onset of darkness, and peaks in the middle of the night to gradually decrease during the second half of the night. In addition to its timekeeping functions, melatonin is involved in reproductive physiology and in the regulation of body temperature.[2]

Furthermore, melatonin has important antioxidant properties as the result of direct and indirect effects. Melatonin directly scavenges reactive oxygen species (ROS), prevents lipid peroxidation, reduces mitochondrial hydroperoxide levels, and restores glutathione homeostasis. Moreover, melatonin has indirect antioxidant effects because it stimulates the activities of the enzymes involved in the glutathione cycling.[3] Melatonin reduces nuclear factor kappa-light-chain-enhancer of activated B lymphocytes binding to DNA, probably by preventing its translocation to the nucleus.[4] This in turn reduces the production of proinflammatory cytokines and chemokines. Finally, melatonin has been shown to reduce recruitment of polymorphonuclear leukocytes to inflammatory sites.[5]

In an intensive care unit (ICU), the rhythmic signals from the environment (eg, perturbation of the light/dark cycle) that are able to entrain endogenous rhythms to function as a Zeitgeber are abolished. Furthermore, ICU and the pediatric ICU (PICU)[6] are noisier than usual hospital settings and sleep–wake disturbances frequently are recognized as a problem for critically ill patients.[7] A reduction in plasma melatonin levels and disturbances of circadian rhythms have been shown in adult critical care patients undergoing mechanical ventilation.[8-11] Mundigler et al[12] found an impaired circadian rhythm of melatonin secretion in sedated critically ill patients with severe sepsis. Perras et al[13] detected no differences in plasma melatonin levels in critically ill patients during a regular light/dark cycle compared with healthy individuals.[14,15] Data on melatonin secretion in patients in the PICU are lacking. The purpose of this investigation was to study the circadian rhythm of serum melatonin levels and to test the effect of light on the rhythm in pediatric critically ill patients, during ventilator treatment and sedation.

Methods

This prospective study was conducted in the PICU at University Hospital of Messina between November 2010 and August 2011. Inclusion criteria were as follows: age >1 month, estimated need for invasive mechanical ventilation >2

ICU	Intensive care unit
PICU	Pediatric intensive care unit
PRISM	Pediatric Risk of Mortality
ROS	Reactive oxygen species

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The authors declare no conflicts of interest.

0022-3476/$ - see front matter. Copyright © 2013 Mosby Inc. All rights reserved. http://dx.doi.org/10.1016/j.jpeds.2012.07.019

days. The risk of mortality was assessed by the Pediatric Risk of Mortality (PRISM) score[16] and was used to evaluate indirectly the severity of the illness and the need for mechanical ventilation. Children were excluded if their legal guardian refused to participate in the study. This study was approved by the local institutional ethics committee, and written informed consent was obtained from the patients' legal guardian. Patients underwent sedation and analgesia according to local guidelines; the attending intensivist was responsible for judging the adequacy of sedation level and the management of infusion rates, assessing the COMFORT (alertness, calmness, respiratory response, movement, mean arterial pressure, heart rate, muscle tone, facial expression) score.[17] At enrollment, patients randomly were assigned to a dark-exposed or to a light-exposed group to evaluate the effects of light on serum melatonin concentrations. In the former group, all lamps on the ward were turned off at 11 p.m. to obtain complete darkness (<1 lux) until 7:00 a.m. In the latter group, artificial white light (500-800 lux), typical of the illumination of hospital rooms and similar to domestic lighting in Italy, remained on during the night. The study began on PICU day 2 from intubation starting at 10 p.m. and lasting 14 hours. Blood samples for serum melatonin analysis were collected at 10 p.m., 1 a.m., 3 a.m., 5 a.m., 8 a.m., and 12 p.m. from central venous catheters placed in the femoral vein of patients before the beginning of the study. Extreme attention was paid to maintaining darkness at night when the blood samples were taken via central venous catheters in patients included in the dark-exposed group; a dim light was used for the collection of samples during the dark span. Samples were collected in plastic tubes without anticoagulant agents. Serum samples were immediately separated by centrifugation and stored at −20°C until assayed.

Melatonin in human serum was measured by an ELISA kit (DRG Melatonin ELISA - EIA-1431, DRG International Inc, Mountainside, New Jersey) according to the manufacturer's instructions. Optical density was measured with an iMark Microplate Absorbance Reader (Bio-Rad Laboratories, Inc, Hercules, California) at 405 nm. Each analysis was performed in triplicate; the calculated coefficients of variation for intra- and interassay were 7.4% to 9.7% and 8.5% to 9.8%, respectively.

Statistical Analyses

The results were analyzed to verify normality of distribution using the Kolmogorov–Smirnov test. For not normally distributed data, nonparametric statistical tests were used. Statistical analysis of serum melatonin levels between the dark- and light-exposed groups was performed with the Wilcoxon signed rank test and linear mixed effects models with random intercepts for a multivariate analysis between the two groups at all the times of the study. The Friedman test was used to compare values at different time points in all 2 groups. Spearman correlation coefficient was performed to analyze the relationship between serum melatonin levels and peaks, sedation, anthropological parameters, and patients' risk of mortality (measured by the PRISM). *P* values less than .05 were considered statistically significant.

Results

Sixteen critically ill patients were enrolled. All children were prepuberal. Patients' characteristics are presented in Table I. All patients were mechanically ventilated and sedated with midazolam (2.3 ± 1.7 μg/kg/min) and fentanyl (2.1 ± 1.7 μg/kg/h).

Melatonin serum peaks in 14 of the 16 patients studied were greater compared with the values reported in the literature for healthy age-matched children.[18] As expected, melatonin peaks were greater, although not significantly, in subjects 1-5 years of age (385 ± 205 pg/mL) compared with individuals 6-9 years of age (248 ± 196 pg/mL; *P* value .196). Waldhauser et al[18] observed nocturnal melatonin levels of 210 ± 35 pg/mL (mean ± SE) in children aged 1-5 years and 133 ± 17 pg/mL in children aged 5-11 years. Conversely, 2 patients had low melatonin levels without any peak in melatonin secretion.

The serum melatonin rhythm was found to be altered in all but one patient. Only 3 of 16 children had a melatonin peak at 1 or 3 a.m.; 1 was in the dark-exposed group and 2 were in the light-exposed group. The distribution of melatonin rhythms in dark- and light-exposed group subjects is shown in the Figure. Values of serum melatonin for each time point are shown in the Table II. Linear mixed models indicated that the exposure to the light significantly, and negatively, influenced the serum levels of melatonin in this population of critically ill children ($P < .001$).

No correlation between melatonin secretion and sedation drugs (fentanyl and midazolam) or inotropic therapy was observed. Ten patients required continuous intravenous inotropic support with dopamine (7.7 ± 2.2 μg/kg/min). None received other drugs known to interfere with melatonin metabolism, such as beta-blocking agents, norepinephrine, corticosteroids, or clonidine. None had liver or renal failure at the time of the study. The correlation between body weight and melatonin values resulted in no statistically significant differences. Finally, no correlation was found between PRISM score and serum melatonin levels or between PRISM score and melatonin peaks.

Table I. Characteristics of the 2 groups of patients

	Dark-exposed (n = 8)	Light-exposed (n = 8)	*P* value
Sex, male	3 (37.5%)	4 (50%)	.614
Age, months	61.8*	59.7*	.674
Weight, kg	17.5*	16.5*	.888
PRISM score	36*	38.5*	.401
Respiratory failure	4 (50%)	4 (50%)	
Pneumonia	1 (13%)	1 (13%)	
Hemolytic uremic syndrome	1 (13%)	0 (0%)	.736†
Traumatic brain injury	2 (13%)	2 (25%)	
Polytrauma	0 (0%)	1 (13%)	

*Median.
†χ^2 test.

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