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CLINICAL EFFECTS OF MELATONIN IN HIGH RISK CRITICALLY ILL

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INTRODUCTION

Endogenous blood melatonin in critical patients is often dramatically low, in both basal levels and night peaks. Exogenous supplementation could determine hypnogogue, immunomodulating and antioxidant effects. Prolonged administration (possible undesirable effects: sleepiness, bronchospasm, accumulation) has not previously been described in critically ill.

OBJECTIVES

Evaluating safety and clinical effects of oral melatonin in high-risk critically ill [1] treated with conscious sedation [2].

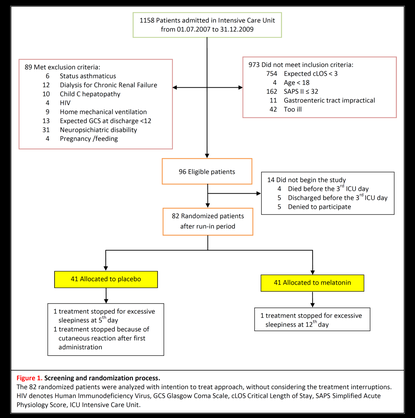

Figure 1. Screening and randomization process.
The 82 randomized patients were analyzed with intention to treat approach, without considering the treatment interruptions.
HIV denotes Human Immunodeficiency Virus, GCS Glasgow Coma Scale, cLOS Critical Length of Stay, SAPS Simplified Acute Physiology Score, ICU Intensive Care Unit.

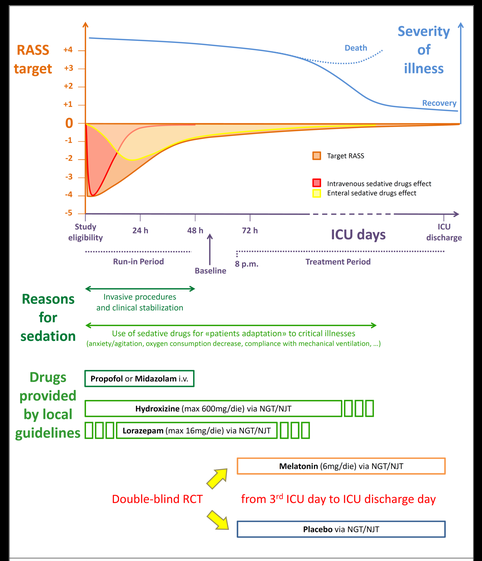

Figure 2. Study Design.
The possibility to randomize each high-risk critically ill patient was established during the first 2 days once got the inclusion criteria (run-in period), when the clinical conditions may require "deep sedation" (RASS target from 0 to -4) obtained by intravenous drugs. After that, according to local guidelines, begun the "conscious sedation" period (RASS target from 0 to -1) obtained by enteral sedatives. In this period, patients underwent a double-blind, randomized, placebo-controlled treatment (from 3rd ICU day to ICU discharge); clinical indicators were recorded four times a day during the whole ICU stay.
RASS denotes Richmond Agitation Sedation Scale; ICU denotes Intensive Care Unit; i.v. denotes intravenous; NGT denotes Naso-Gastric Tube; NJT denotes Naso-Jejunal Tube; RCT denotes Randomized Controlled Trial.

METHODS

Double-blind RCT between placebo and melatonin (3 mg x 2), administered daily at 8 and 12 pm from the third ICU day until discharge. Inclusion/exclusion criteria: Figure 1. Study design and sedation protocol: Figure 2.

RESULTS

82 patients enrolled: age 72 [60–77] years, SAPS II 41 [34–54], Mechanical Ventilation 11 [6–22] days.
Diagnosis: 18 pancreatitis, 37 pneumonia or ALI/ARDS, 23 acute heart diseases, 4 trauma.
Admission type: 55 medical, 19 unscheduled surgery, 8 scheduled surgery.
Melatonin fastened weaning from sedative and analgesic drugs and from mechanical ventilation (Figure 3). It decreases the prevalence of infection with a higher effect in long term patients (Figure 4). Melatonin also guaranteed better hemodynamic stability (Table 1).
Neurologic monitoring demonstrated a melatonin significant effect in ameliorating all the observed characteristics (Table 2); particularly, melatonin helped in restoring a quite normal circadian rhythm. Differences in length of stay and ICU/hospital mortality were not significantly different.
Undesirable effects were not reported.

Table 1. **Clinical data.**

Variables	Placebo (N = 825)	Melatonin (N = 523)	Group	P Value Day	Gr-Day
High treatment — no. (%)	733 (88.9)	475 (80.1)	0.05	<0.01	0.03
Sequential Organ Failure Assessment — points	3 [2 -5]	2 [1-4]	0.39	<0.01	<0.01
Sepsis — no. (%)					
None	265 (32.9)	245 (46.8)			
SIRS	119 (14.8)	112 (21.4)			
Sepsis	263 (32.6)	114 (21.8)	0.16	0.46	<0.01
Severe Sepsis	84 (10.4)	33 (6.3)			
Septic shock	75 (9.3)	20 (3.8)			
Blood values					
White blood cells (·10³/mm³)	13.8±6.9	11.9±5.7	0.81	0.83	<0.01
Platelets (·10³/mm³)	275±192	250±139	0.28	0.06	0.01
Creatinin (mg/dl)	1.8±1.5	1.5±1.4	0.54	0.43	0.12
Blood urea nitrogen (mg/dl)	47±29	45±26	0.88	0.70	0.45
Aspartate transaminase (UI/l)	62±60	74±105	0.17	0.26	0.20
Alanine transaminase (UI/l)	72±128	67±84	0.89	0.80	0.43
Total bilirubin (mg/dl)	2.8±3.6	2.5±3.3	<0.01	<0.01	<0.01
Physical examination					
Body temperature (°C)	36.9 [36.5-37.4]	37.0 [36.5-37.5]	0.47	0.27	<0.01
Heart rate (bpm)	94.6±15.5	91.1±14.9	0.27	<0.01	0.5
Systolic blood pressure (mmHg)	129.01±18.4	129.21±21.5	0.9	<0.01	0.02
Diastolic blood pressure (mmHg)	57.35±12.90	60.77±15.09	0.85	0.10	<0.01
Gastric residual volume>250 ml (%)	26 (3.8)	17 (3.5)	0.91	0.03	0.54
Respiratory rate (bpm)	22.48±6.80	22.28±5.90	0.91	0.04	<0.01
Venous pH	7.40±0.17	7.42±0.04	0.42	0.38	0.62
Peripheral oxigen saturation	97.78±4.39	98.23±2.07	0.14	0.90	0.79
Carbon dioxide venous pressure	48.5±8.1	49.6±9.2	0.55	0.53	<0.01
Ventilation (%)					
Spontaneous Breathing	104 (12.7)	126 (21.4)			
Continuous Positive Airway Pressure	138 (16.9)	189 (32.1)	0.54	0.02	<0.01
Pressure Support Ventilation	554 (67.7)	272 (46.3)	0.91	0.04	<0.01
Pressure Control Ventilation	22 (2.7)	1 (0.2)			
Drugs — no. (%)					
Vasoactive catecholamines	93 (11.3)	32 (5.4)	0.29	0.01	<0.01
β blockers	39 (4.7)	18 (3.1)	0.56	<0.01	<0.01
Inhalational antiasthmatics	126 (15.3)	135 (23)	0.68	<0.01	0.23

Table 1. Measurements of clinical parameters during the study period. Observations were registered daily. Variables are presented as absolute number (%), median [interquartile range], or mean ± standard deviation. Comparisons were made by cross-sectional time-series regression models (random-effects, and population-averaged linear models) or by multilevel mixed-effects Poisson regressions, when appropriate.

Table 2. **Neurological indicators.**

Variables	Placebo (N = 3335)	Melatonin (N = 2414)	Group	P Value Period	Gr-Per
Pain (VNR ≥ 3) — no. (%)	955 (28.6)	571 (23.7)	0.33	0.14	<0.01
Anxiety (VNR ≥ 3) — no. (%)	1143 (34.3)	720 (29.8)	0.10	<0.01	<0.01
Agitation length > 1h — no. (%)	1136 (34.1)	777 (32.2)	0.12	<0.01	<0.01
Sleep — hours per nurse shift					
Morning (7am-1pm)	2.0±1.8	1.9±1.8	0.28	<0.01	<0.01
Afternoon (1pm-9pm)	2.7±2.2	2.3±2.3	0.81	<0.01	<0.01
Evening (9pm-midnight)	1.4±1.3	1.5±1.6	0.92	<0.01	0.22
Night (midnight-7am)	4.3±1.8	4.5±1.9	0.83	<0.01	0.03
Need for restraints — no. (%)	920 (41.8)	579 (31.1)	0.40	<0.01	<0.01
Delirium — no. (%)	71 (4.8)	65 (4.7)	0.77	0.44	<0.01
RASS (point)	0 [-1-0]	0 [0-0]	0.08	<0.01	<0.01
Nurse shifts with extra sedation — no. (%)	167 (5.0)	56 (2.3)	<0.01	0.04	0.71
Nurse shifts with extra neuroactive drugs — no. (%)	248 (7.4)	82 (3.4)	<0.01	0.06	0.48

Table 2. Neurological monitoring during the study period. Observations were registered four times a day. Variables are presented as absolute number (%), or mean ± standard deviation. Comparisons were made by cross-sectional time-series regression models (random-effects, and population-averaged linear models) or by multilevel mixed-effects Poisson regressions, when appropriate.
VNR denotes Verbal Numeric Range, RASS denotes Richmond Agitation Sedation Scale

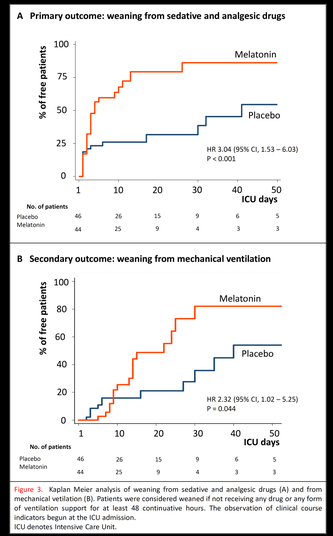

Figure 3. Kaplan Meier analysis of weaning from sedative and analgesic drugs (A) and from mechanical vetilation (B). Patients were considered weaned if not receiving any drug or any form of ventilation support for at least 48 continuative hours. The observation of clinical course indicators begun at the ICU admission.
ICU denotes Intensive Care Unit.

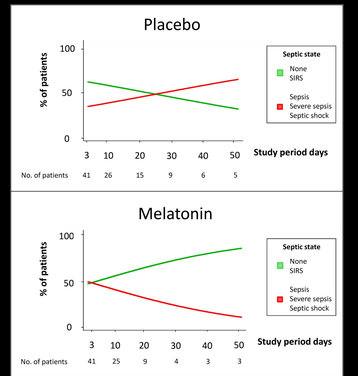

Figure 4. Septic state of enrolled patients.
The figures represent the percent of patients in that septic state considering the total number of patients still recovered in ICU in that day of their study period. The septic state was calculated according to the SCCM/ACCM criteria after the patients discharge, by patients charts revision operated by blind researchers. Comparisons were made with conditional fixed effects logistic regression, P<0.001.
SIRS denotes Systemic Inflammatory Reaction Syndrome, ICU denotes Intensive Care Unit

CONCLUSIONS

Melatonin administration was shown safe and useful regarding cardio-respiratory and neurological recovery. It determined fastened sepsis resolution in both lab measurements (WBC,PLT, bilirubin) and clinical observations (SOFA, septic state) probably due to its immunomodulating action and reactive oxygen species scavenging. The Melatonin group had faster ventilation weaning, probably due to lower sedation; nurse-observed decreased sleep hours in the morning/afternoon and increased in the night highlighted a quite restored circadian rhythm. Gastric residual volume was not different, as the need for bronchodilators; no excessive sleepiness was shown. No differences in ICU length of stay or ICU/hospital mortality were reported, being this study not powered for these outcomes. In two post-hoc analyses, Melatonin decreased MV days (p = 0.013 in patients treated > 7 days) and ICU mortality (p = 0.047 in patients treated > 40 days), suggesting the necessity of new and adequately powered studies for long-term ICU patients. (Clinicaltrial.gov n° NCT00470821)

REFERENCES

1. Iapichino G, et al. Crit Care Med. 2006;34:1039–1043.
2. Cigada M, et al. Journal of Critical Care. 2008;23:349–353.