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Melatonin reduces the need for sedatives in high-risk critically ill patients

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the need for sedatives, commonly used to keep patients adapted to critical illnesses and invasive procedures. Melatonin may also be beneficial due to its antioxidant and immune-modulating properties.

Methods: 82 high-risk critically ill patients treated with conscious enteral sedation were enrolled in a single-center, double blind RCT. At 8 p.m. and midnight, they received 3mg melatonin or placebo, from the 3rd ICU day until ICU discharge. The main outcome was the total amount of sedatives administered.

Results: Melatonin caused a reduction in the total amount of administered sedatives, analgesics, and antipsychotics ($p<0.01$). Other neurological indicators (pain, agitation, anxiety, delirium, sleep, need for restraints, need for extra sedation, nurse evaluation of sedation adequacy) also improved ($p<0.01$). An earlier weaning from neuroactive drugs ($p<0.01$) also led to an earlier weaning from mechanical ventilation ($p=0.04$), and reduced drug cost ($p<0.01$). Sepsis prevalence decreased during the ICU stay in patients treated with melatonin ($p<0.01$). Post-traumatic stress disorder prevalence did not differ between groups ($p=0.50$), nor did ICU ($p=0.48$) or hospital ($p=0.82$) mortality.

Conclusions: Enteral melatonin is safe and inexpensive; its use resulted in a decreased need for sedatives, with improved neurological indicators and potential advantages for other clinical outcomes. Further multicenter evaluations are now required to confirm these results. (Clinicaltrial.gov number: NCT00470821)

Melatonin reduces the need for sedatives in high-risk critically ill patients

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Abstract

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Background

The severity of illnesses, invasive procedures and the harsh Intensive Care Unit (ICU) environment make the use of sedatives necessary in high-risk patients[1]. Intravenous drugs are widely used because of their effectiveness and pharmacokinetic manageability; however, they have significant side effects[2], particularly evident in patients who need prolonged mechanical ventilation.

Recent literature[3-5] suggests a target of conscious sedation[6,7] and underlines the need to use the lowest drug amount, protocols, patient mobilization[8], daily awakening trial[5], and drugs with short half-lives. Despite guidelines[9], physicians and nurses typically keep levels of sedation deeper than desired[10-12]; this practice is widespread and probably causes avoidable side effects[13]. Conversely, daily interruption[5] of ultra-short half-life drugs could be deliriogenic[14], forcing the brain to endure fast and repeated fluctuations.

Enteral sedation is feasible early in the ICU stay, since the gut functions even in the most critical phases of diseases[15,16]. This policy has been adopted in our hospital guidelines since 2001[17]. Pharmacological coma is difficult to achieve with enteral sedatives; moreover, they do not allow hyperacute neurological fluctuations: their prolonged onset and offset[7] are useful in long-term patients who need a superficial and stable sedative treatment[1].

Almost all critically ill patients present a loss of circadian rhythms[18], and they report sleep deprivation as a major cause of discomfort in their ICU stay[19]. Both patients' perceptions and instrumental measurements demonstrate the inadequacy of sleep quality and quantity. The "sleeping phenotype" induced by sedatives is not restorative and presents differences from physiological sleep[20]; moreover, sedatives may even worsen sleep quality[21]. Low endogen melatonin levels may play an important role[22,23] in this context.

Melatonin is a hormone with hypnotic, antioxidant and immune-modulating properties[24]. Critically ill patients present dramatically reduced blood melatonin levels[22,23], both in terms of the nighttime peak[25] and basal daytime levels[18,22]. Whether such reduced values are determined by a reduced endogenous production or an increased consumption[26] is currently unknown. Whatever the reason, decreased blood melatonin levels are associated with sepsis severity, delirium, Post Traumatic Stress Disorder (PTSD), and the severity of sleep alteration during the critical stay[21,27].

Exogenous melatonin administration is a safe intervention[27]. This molecule has been shown to have effective hypnotic properties[28] when the endogenous levels are reduced. Prolonged administration of melatonin, has not been yet tested in critically ill patients for more than 4 continuous days[29]. It is a simple and inexpensive procedure, and it adequately restores endogenous levels[16]. Moreover, melatonin's anti-oxidant and immune-modulating[24] properties have proven clinically meaningful in septic shock rodent models[30] and in neonatal sepsis[31].

Outcomes

The main goal of the present study was to describe the effect of oral melatonin supplementation in decreasing the overall amount of sedatives administered[5], as prescribed by staff physicians blinded to the group assignment. Secondary outcomes were the overall amount of analgesics and antipsychotics administered, and the neurological parameters assessed by nurses blinded to the group assignment: Richmond Agitation-Sedation Scale (RASS)[32], sleep hours, duration of agitation, anxiety, pain, use of restraints, adequacy of sedative therapy. Other secondary outcomes were the prevalence of PTSD, the time to wean from neuroactive drugs and from mechanical ventilation, the costs of sedatives, ICU length of stay and mortality, and hospital mortality.

Methods

Study design

This randomized and controlled, double-blind study began for each patient during the evening of the 3rd ICU day. All ICU patients were treated according to local guidelines for sedation (Fig.1 and 1S). During the first 48 hours, only if necessary, a continuous propofol or midazolam infusion was allowed for invasive procedures and clinical stabilization. Enteral hydroxyzine and possibly lorazepam were immediately prescribed to reduce and rapidly discontinue intravenous drugs. In this phase, the sedation target varied from RASS -4 to 0.

From the third ICU day, RASS=0 was always indicated as the desired level, unless clinical needs dictated otherwise. Analgesics were administered before scheduled painful procedures and in case of noticed pain (Verbal Numeric Rating, VNR>3 or Behavioral Pain Scale, BPS>6). Once pain was adequately treated, if patients were not adapted (RASS>0) to mechanical ventilation or to the ICU environment, they received sedatives until the target RASS was reached. If patients manifested delirium a non-pharmacological protocol was used first, considering antipsychotics only after the resolution of organic-metabolic imbalances and withdrawal of deliriogenic drugs. Validated scales for neurological monitoring were used at least four times a day. Each morning, physicians blinded to melatonin treatment prescribed the therapy including analgesics, sedatives and antipsychotics, taking special care to prescribe the lowest effective dose. In presence of deeper-than-desired sedation levels, nurses decreased/withdrew the prescribed drugs. Conversely, according to clinical needs, an extra amount of sedatives was always allowed and registered. Sedative treatment was planned by physicians and judged by nurses, both blinded to the group assignment.

During the morning of the 3rd ICU day, eligible patients were randomly assigned to the melatonin or placebo group; each patient received a tablet containing 3mg melatonin at 8 p.m. and midnight (total 6mg melatonin per day) or two identical tablets without the active principle. This enteral supplementation continued until ICU discharge, unless the physicians in charge decided to suspend the treatment for clinical reasons. Two physicians (GM and GI), aware of treatment allocations, monitored for possible side effects, without participating in clinical decisions about sedative administration.

Eligibility and randomization

All patients admitted in the general ICU of a University Hospital (A.O. San Paolo – Polo Universitario) between July 1st, 2007 and December 31th, 2009 were screened for enrollment. The inclusion criterion was high-risk patients[33]. Exclusion criteria included age<18 years, absolute impracticability of gastrointestinal tract, status asthmaticus or intoxication as the reason for admission, chronic renal failure under renal replacement therapy, severe chronic liver failure (Child-Pugh class = C), HIV infection, home mechanical ventilation, estimated GCS at discharge < 12, previous diagnosis of any neuro-psychiatric disease, pregnancy or breast feeding and DNR orders during the first two ICU days. (Fig.2S)

Intervention

The first 2 ICU days represented the run-in study period, devoted to diagnosis, clinical stabilization, invasive procedures, adaptation to mechanical ventilation and weaning from intravenous sedatives because to the enteral ones, which began immediately after ICU admission (Fig.1). Informed consent was collected from able patients (2 of 96); for the others, a written declaration of received information was collected from relatives, according to our local Ethics Committee indications. As soon as their neurological conditions improved, patients were duly informed of the study and their written consent was obtained. The description of data collected and the definitions used are available in the Electronic Supplementary Material (ESM).

Treatment allocation was obtained through a computer-generated 8-patient block randomization procedure. After informed consent, a sealed brown envelope, progressively assigned to each patient at the end of the run-in period, was opened.

125 mg tablets containing 3 mg of pure melatonin (Helsinn, Biasca, Switzerland), and microcrystalline cellulose (70 mg), calcium phosphate (47 mg), magnesium stearate (2.5 mg) and sodium carboxymethyl cellulose (2.5 mg) were produced (Procemsa, Torino, Italy). Similar tablets without melatonin, for the patients assigned to the placebo group, were also prepared. All tablets were administered by nasogastric/naso-jejunal tube or by ileostomy, after crushing the tablet and mixing it with 20 ml of water, followed by another 20 ml to flush out the residue.

Statistical analysis

Sample size calculation for Wilcoxon rank-sum test was performed[34]. In the statistical software StudySize 2.0 (CreoStat HB, Frolunda, Sweden), the following parameters were entered: α=0.05, power=80%, hypothetical reduction of 30% in the overall hydroxyzine dose during the ICU stay[17] with the use of melatonin, number of patients per group = 1:1. Calculation determined the need to enroll 40 patients per group.

The patients' baseline characteristics and single-observation outcomes were analyzed by Student's t-test, by Wilcoxon rank-sum test, by Poisson regression and by the Fisher exact test, when appropriate. Weaning time was described with Kaplan-Meier curves and analyzed with unadjusted Cox proportional hazard models.

Analyses for repeated measures were performed for outcomes recorded during the entire ICU stay. 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. This statistical approach was planned to allow for simultaneous analysis of the net effect of group assignment (P_{Group}), the effect of time spent in the ICU (P_{Day}), and the cumulative melatonin effect, as calculated by multiplying the group (melatonin=1, placebo=0) and the ICU day from group assignment ($P_{Group*Day}$), in order to highlight the adjunctive effects of daily repeated melatonin administration. Sepsis prevalence during the ICU stay was analyzed by conditional fixed effects logistic regression.

Statistical analyses were independently performed with the statistical package Stata 12 (Stata Corporation, College Station TX, USA), by two groups of biostatisticians of the University of Milan.

Results

Case-mix

During the 30 months of the study, 1158 patients were admitted to the ICU (Fig. 2S). 1062 could not be enrolled because of inclusion and exclusion criteria; the most frequent reason for exclusion was short ICU stay. 96 patients were observed during the first 2 ICU days; 14 of them were not randomized because of discharge, death, or withholding consent. 41 patients were finally allocated to each of the two treatment groups.

Enrolled patients had high severity of illness at ICU admission and showed high intensity of treatment during their ICU stay. Baseline characteristics were not statistically different (Tab.1). Enteral administration of nutrition and drugs, including sedatives, was carried out through nasogastric tube (82%), nasojejunal tube (10%) or jejunostomy (8%), without differences between groups (Tab.1S). During the "run-in" period, the clinical characteristics of patients, administration of sedative drugs, invasive procedures and severity indicators did not differ between groups (Tab.1S, 2S, and 3S).

Outcomes

Melatonin administration caused a highly significant reduction in the need for all neuroactive drugs considered by local guidelines ($p<0.01$). (Tab.1 and 4S). Regarding secondary outcomes, weaning from

neuroactive drugs (HR 3.04, 95%CI 1.53 – 6.03) and from mechanical ventilation (HR 2.32, 95%CI 1.02 – 5.25) was achieved earlier in the melatonin treated patients (Fig.2) and the cost of drugs was significantly decreased (Tab.1 and 5S). No statistical differences were found in length of ICU stay, ICU and hospital mortality, or post-traumatic stress disorder (Tab.1).

Neurological observations

The sedative treatment was similar in adequacy and depth of desired sedation level (Tab.2). The RASS target was reached in about half of the observations, without differences between groups (p=0.12). Melatonin administration led to a significant reduction of deep sedation states (actual RASS from -3 to -5, p<0.01) in favor of conscious sedation states (actual RASS from -1 to 0, p<0.01). Moreover, melatonin determined a significant reduction of RASS-over-the-target observations (p=0.05), without increasing the RASS-under-the-target scores (p=0.50) (Fig.3 and Tab.6S).

A clinically relevant effect of melatonin administration was noted for all the observed neurological indicators (Fig.3 and Tab.6S): pain, anxiety, agitation, need for physical restraints and need for extra drugs were decreased (p<0.01). Sleep, as reported by nurses, decreased during the daytime and increased at night (p=0.03). Melatonin allowed for a reduction in administered drugs, both as to their daily amount (Tab.2) and for the number of unscheduled administrations (Tab.6S). Moreover, melatonin use led to a decreased need for intravenous drugs in favor of the enteral route (Tab.2).

Other clinical observations and side effects

Melatonin significantly improved septic state (Tab.2, Fig.3S and 4S), decreased the median daily SOFA score, white blood cell count, total blood bilirubin, and reduced the need for vasoactives (Tab.2 and 7S).

Melatonin decreased the prevalence of high-treatment days (Tab.2). The indole also allowed a progressive weaning from mechanical ventilation, by increasing the number of days on spontaneous breathing or with Continuous Positive Airways Pressure assistance, and decreasing the days with Pressure Support Ventilation or Pressure Control Ventilation (Tab2, Fig.2, and 8S).

No clinically relevant side effects attributable to the melatonin treatment were observed. Particularly, melatonin did not increase the need for inhaled bronchodilators (Tab.2) as reported elsewhere[35]. No clinically meaningful differences were noted in the other observed parameters, like body temperature, cardio-respiratory indicators, gastric residual volume or blood gases (Tab.9S). In this cohort of patients, no self-removal of endotracheal tubes was reported. Physicians in charge, blinded on the group assignment, decided to discontinue the treatment in 3 cases because of side effects: excessive sleepiness (1 patient for each group) and cutaneous rash after the first administration (1 patient in the placebo group). These three patients were considered in the intention-to-treat statistical analysis (Fig.2S).

Discussion

This study was designed to evaluate the effect of oral melatonin on ICU sedative administration. On the whole, the conscious sedation state was desired and reached in almost 80% of the observations in this population of high-risk critically ill patients. Moreover, an exclusively enteral approach was feasible in 82% of ICU days. In this context, melatonin proved effective in permitting a marked decrease in the use of neuroactive drugs. At the same time, melatonin induced an improvement in several neurological targets, including pain, agitation, anxiety, need for restraints and hours of sleep. Similar results have been noted in other studies.[36,37]

These results were probably due to several reasons. First, the selection criteria used. In this population of high-risk critically ill patients, both severe (SAPS II > 32) and complex (mechanical ventilation > 2 days), each therapeutic decision could have had a significant impact on the outcome[33]. Second, the patients were kept consciously sedated as soon as possible; this target was met in about two-thirds of their ICU stay. Third, the use of the enteral route allowed for the maintenance of a stable and "conscious" level of sedation thanks to favorable pharmacokinetics of the enteral sedatives used. The staff continuously tried to solve issues related to the alteration of the gastro-intestinal tract, as prescribed by hospital guidelines for nutrition of critically ill patients, including frequent placing of post-pyloric tubes.

Costs for neuroactive drugs were more than halved, despite melatonin costs, thanks to the marked reduction in the amount administered. These costs, even in the control group, were much lower than those reported in the literature[38]: hydroxyzine and lorazepam are less expensive than propofol and midazolam. New drugs and approaches (dexmedetomidine, sevoflurane) are even more expensive[39]. Remifentanil was not used as it is not included in the local guidelines: its very short offset makes it unsuitable for patients requiring long-term ventilation[40].

The observations related to respiratory weaning and sepsis progression are too weak to be considered authoritative. Nevertheless, they deserve to be considered as hypotheses-generating observations. The difference between groups in mechanical ventilation weaning became evident after a week of melatonin administration, suggesting that the clinical role of melatonin is mediated by a cumulative effect in the reduction of sedatives[2] and by its immune-modulating effect, both requiring some time to become clinically relevant.

The effects of melatonin on signs of sepsis are not exclusively explained by the reduction in analgesics and sedatives. Although the literature shows that infections are higher in the deeply sedated critically ill patients[2], the pharmacological effects of melatonin on the immune system, suggested by both animal models and preliminary observations on humans, convincingly document the antiseptic action of melatonin[30,31]. These effects may have clinical relevance in the "late sepsis" of ICU long-stayers. When the stay is longer than a month, the outcome is highly influenced by infection (ventilation-acquired pneumonia, infections related to invasive procedures and tubes, opportunistic infections) and by procedures supporting immune defenses (nutrition, glycemic control, tracer elements, etc). The present study did not highlight differences in secondary outcomes such as mortality, length of stay, or psychiatric disorders, but the power was not adequate.

Study limitations

The present report is from a single center study. Enteral sedation is a locally consolidated clinical procedure, but it requires particular attention and problem solving skills; physicians and nurses need to be trained and strongly motivated to successfully perform this procedure.

Conclusions

To the best of our knowledge, this is the first trial to describe the effects of prolonged, oral melatonin supplementation in ICU patients treated with conscious sedation. Melatonin was shown to be safe, simple and cost-effective; it resulted in a decreased need for sedatives, analgesics and antipsychotics, with improved neurological indicators and potential advantages on other clinical outcomes. The use of melatonin in these situations should be explored in more extensive, multicenter trials. In the meantime, considering the absence of observed side effects, melatonin administration can be considered a useful intervention to wean high-risk critically ill patients from sedatives.

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Table 1. **Baseline characteristics of the patients and outcomes.***

Characteristic	Placebo (N = 41)	Melatonin (N = 41)	*P Value*
Age — yr	65±15	68±15	*0.28*
Male sex — no. (%)	28 (68.3)	21 (51.1)	*0.18*
Weight — kg	79.7±19.0	74.5±13.4	*0.21*
SAPS II score at admission	44.1±15.3	45.7±18.2	*0.68*
Admission type — no. (%)			
Medical	25 (61.0)	27 (69.5)	
Surgical scheduled	4 (9.7)	5 (12.2)	*0.80*
Surgical unscheduled	12 (29.3)	9 (21.9)	
Admission from — no. (%)			
Ward	18 (43.9)	16 (39.0)	
Emergency room	12 (29.3)	12 (29.3)	*0.96*
Operating theatre	11 (26.8)	13 (31.7)	
Diagnosis — no. (%)			
Pneumonia - Lung diseases	15 (36.6)	18 (43.9)	
Pancreatic diseases	8 (19.5)	7 (17.1)	
Cardiocirculatory arrest - Severe arrhythmia	2 (4.9)	4 (9.8)	
Acute myocardial infarction	4 (9.8)	3 (7.3)	*0.92*
Gastrointestinal diseases	6 (14.6)	5 (12.2)	
Trauma	3 (7.3)	1 (2.4)	
Others	3 (7.3)	3 (7.3)	
Cause of admission — no. (%)			
Acute respiratory failure	41 (100)	41 (100)	*>0.99*
Heart failure	13 (31.7)	9 (22.0)	*0.46*
Septic shock	9 (22.0)	5 (12.2)	*0.38*
Acid-base or metabolic diseases	9 (22.0)	9 (22.0)	*>0.99*
Comorbidities — no. (%)			
Severe chronic liver diseases	3 (7.3)	6 (14.6)	*0.48*
Chronic Obstructive Pulmonary Disease	10 (24.4)	15 (36.6)	*0.34*
Neurological diseases	5 (12.2)	2 (4.9)	*0.43*
Asthma	1 (2.4)	0 (0)	*>0.99*
Main outcome			
Total administered enteral sedatives — mg			
Hydroxizine	2700 [100-8050]	300 [0-2100]	*<0.01*
Lorazepam	1 [0-84]	0 [0-8]	*<0.01*
Total administered intravenous sedatives — mg			
Propofol	20 [0-980]	0 [0-40]	*<0.01*
Midazolam	0 [0-63]	0 [0-0]	*<0.01*
Total administered analgesics — mg (Morphine equivalents)	2.5 [0-82.5]	0 [0-20]	*<0.01*
Total administered antipsychotics — mg (Haloperidol)	0 [0-15.9]	0 [0-3]	*<0.01*
Secondary outcomes			
Length of stay — days			
In ICU	12 [9-29]	15 [9-21]	*0.99*
High treatment	12 [6-29]	11 [7-18]	*0.67*
Low treatment	1 [0-3]	2 [0-5]	*0.21*
Mortality — no. (%)			
In ICU	14 (34.1)	10 (24.4)	*0.47*
In hospital	15 (36.6)	14 (34.1)	*0.82*
Diagnosis of Post Traumatic Stress Disorder	0/5 (0)	2/9 (22.2)	*0.50*
Costs for drugs — €			
Total per patient	21.27 [1.23-69.50]	5.64 [2.15-13.75]	*<0.01*
Per ventilation day	1.59 [0.25-3.12]	0.50 [0.23-1.24]	*<0.01*

*Table 1. Baseline patient characteristics and outcomes. Variables are presented as mean ± standard deviation, median [interquartile range] or absolute numbers (%). Comparisons were made by Student's T-test, by Poisson regressions, Wilcoxon rank-sum test or Fisher exact test, when appropriate. Main outcome is the sum of pharmacological therapy administered during the study period. N denotes number of patients, SAPS II denotes Simplified Acute Physiology Score, ICU denotes Intensive Care Unit; CAM-ICU denotes Confusion Assessment Method for the ICU.

Table 2. **Daily monitoring. ***

Neurological variables	**Placebo (N = 825)**	**Melatonin (N = 523)**	***P Value*** *Group*	*Day*	*Gr·Day*
Mean daily enteral sedatives — mg					
Hydroxizine †	300 [150-600]	100 [0-300]	*0.01*	*<0.01*	*<0.01*
Lorazepam †	0 [0-4.2]	0 [0-0]	*0.17*	*<0.01*	*0.21*
Mean daily intravenous sedatives — mg					
Propofol §	0 [0-4800]	0 [0-3600]	*0.04*	*<0.01*	*0.52*
Midazolam §	0 [0-720]	0 [0-480]	*0.37*	*0.24*	*0.35*
Mean daily analgesics — mg					
Morphine equivalents §	0 [0-250]	0 [0-120]	*<0.01*	*<0.01*	*<0.01*
Mean daily antipsychotics — mg					
Haloperidol †	0 [0-2]	0 [0-1]	*0.05*	*0.05*	*0.59*
Type of sedation — days (%)					
Enteral	599 (78.6)	435 (86.5)	*<0.01*	*<0.01*	*<0.01*
Intravenous or mixed	163 (21.4)	68 (13.5)			
Adequacy of sedative therapy — days (%)					
Insufficient	62 (14.6)	22 (6.8)			
Adequate	353 (83.1)	298 (91.4)	*0.33*	*0.42*	*0.84*
Excessive	10 (2.4)	6 (1.4)			
RASS target — days (%)					
0	457 (72.9)	396 (89.0)			
- 1	58 (9.2)	14 (3.2)			
- 2	75 (12.0)	22 (4.9)	*0.15*	*<0.01*	*0.27*
- 3	24 (3.8)	13 (2.9)			
- 4	13 (2.1)	0 (0.0)			
Clinical indicators					
High treatment – days (%)	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*
Septic state — days (%)					
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)			
Ventilation – days (%)					
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)			
Pressure Control Ventilation	22 (2.7)	1 (0.2)			
Drugs — days (%)					
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 2**. Drug doses are reported as the daily amount administered during the study period. The calculation of septic state for each ICU day was performed by blind observers after ICU discharge, according to ACCP/SCCM Consensus Conference (Crit Care Med 1992;20(6):864-74). Variables are presented as absolute number (%), median [interquartile range]†, or median [min/max]§. 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.
N denotes the total of daily observations during the study period, RASS denotes Richmond Agitation Sedation Scale; SIRS denotes Systemic Inflammatory Response Syndrome.

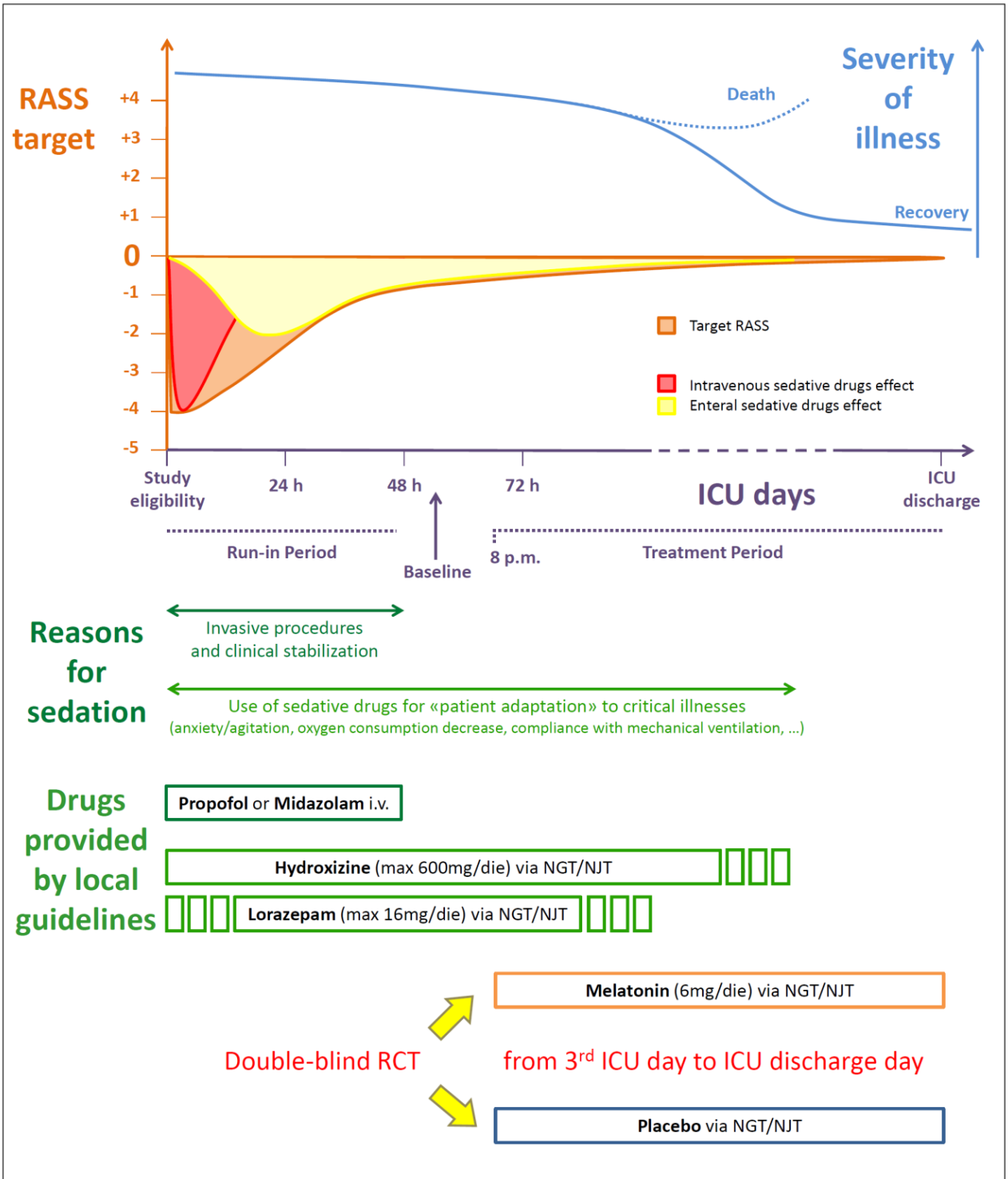

Figure 1. Study Design.
The possibility to randomize each high-risk critically ill patient was established during the first 2 days after the inclusion criteria were met (run-in period), when the clinical conditions required "deep sedation" (RASS target from 0 to -4) obtained by intravenous drugs. After that, according to local guidelines, the "conscious sedation" period (RASS target from 0 to -1) obtained by enteral sedatives was initiated. In this period, patients underwent a double-blind, randomized, placebo-controlled treatment (from 3rd ICU day to ICU discharge).
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.

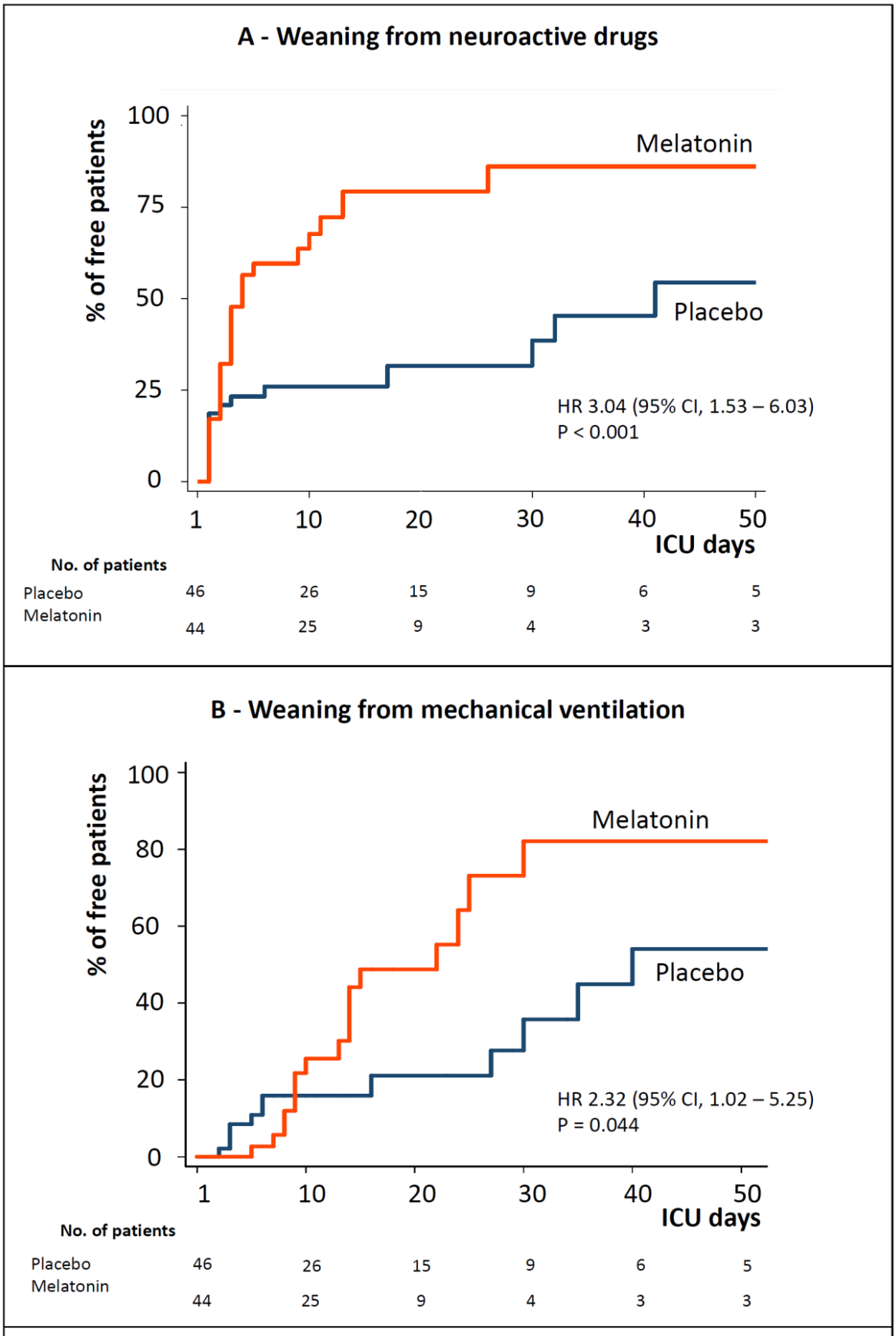

Figure 2. Kaplan Meier analysis of weaning from sedative and analgesic drugs (A) and from mechanical vetilation (B).

Patients were considered weaned if not receiving any drug or any form of ventilation support for at least 48 consecutive hours. The observation of clinical course indicators began at ICU admission. Statistical analysis was performed with Cox proportional hazards model.

ICU denotes Intensive Care Unit, HR Hazard Ratio, CI Confidence Interval.

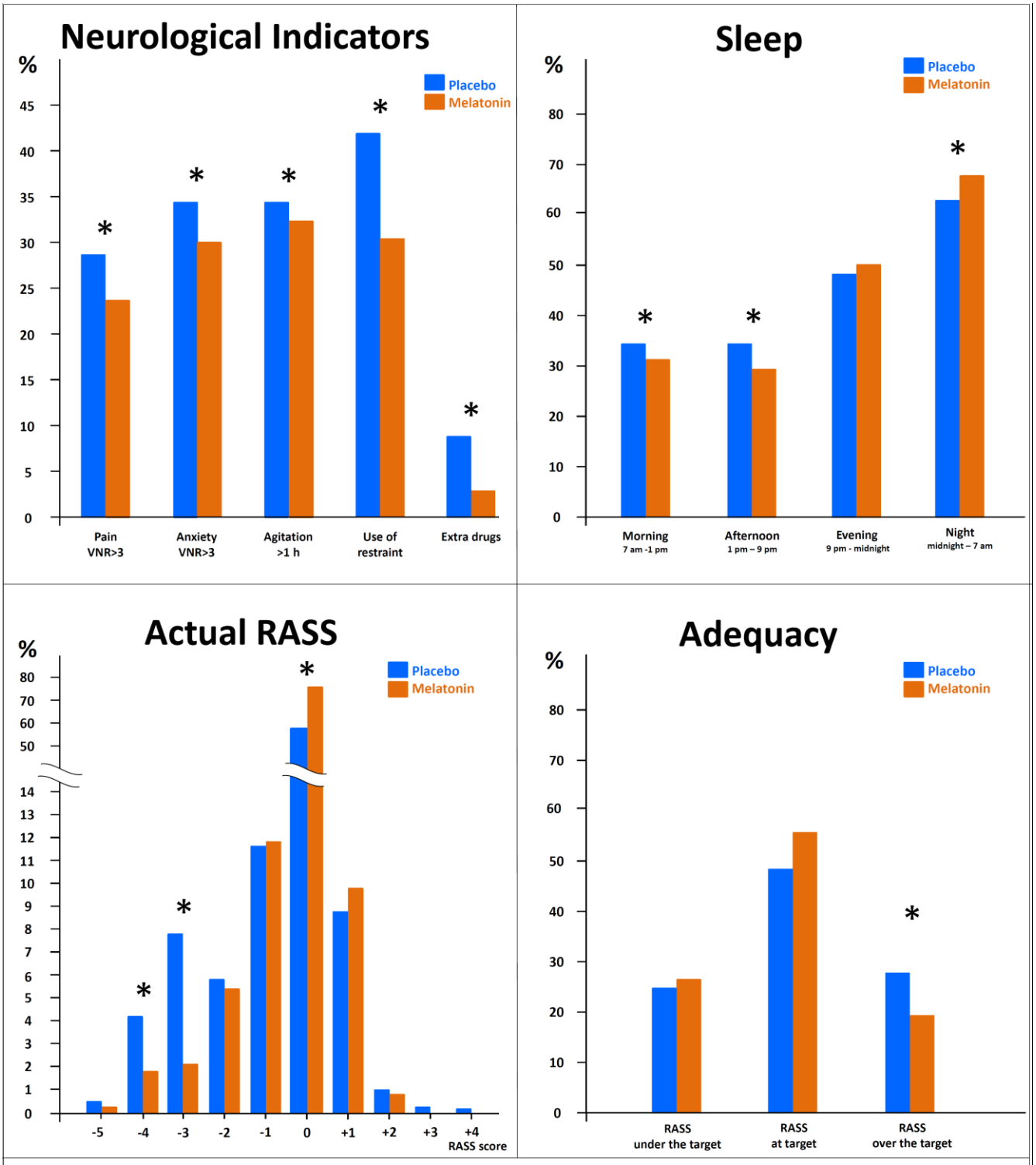

Figure 3. Neurological Monitoring.
Neurological characteristics recorded during the study period. Hours of sleep were reported as by clinical judgement. Each morning, the physician in charge established the RASS target for that day, while the nurses reported the actual RASS four times a day.
VNR denotes Verbal Numeric Range, RASS denotes Richmond Agitation Sedation Scale. CAM-ICU denotes Confusion Assessment Method for the Intensive Care Unit.