A double-blind placebo-controlled randomised pilot study of nocturnal melatonin in tracheostomised patients

Murad G Ibrahim, Rinaldo Bellomo, Graeme K Hart, Trevor R Norman, Donna Goldsmith, Samantha Bates and Moritoki Egi

ABSTRACT

Background and aim: Patients in the intensive care unit often suffer from lack of sleep at night. We hypothesised that nocturnal melatonin may increase observed nocturnal sleep in tracheostomised patients.

Design: Double-blind, randomised, placebo-controlled pilot study.

Setting: ICU of a tertiary hospital.

Participants: Thirty-two ICU patients with tracheostomy who were not receiving continuous sedation.

Methods: We administered either oral melatonin (3 mg) or placebo at 20:00. We collected pre- and post-dosage blood samples on Days 1 and 3 to confirm drug delivery. Primary outcome measure was number of hours of observed sleep at night, assessed by the bedside nurse. Secondary outcome measures included comparison of the incidence of agitation, assessed by score on the Riker Sedation–Agitation Scale, and requirement for sedatives or haloperidol to settle agitation.

Results: Pre-treatment melatonin levels in the two groups were similarly low: 4.8 pg/mL (95% CI, 2.4–7.5) for melatonin versus 2.4 (95% CI, 1.6–3.2) for placebo ($P = 0.13$). Post-treatment, melatonin levels increased significantly in the melatonin group compared with the placebo group (3543 pg/mL versus 3 pg/mL; $P < 0.0001$). However, subsequent observed nocturnal sleep was similar in the two groups: 240 minutes (range, 75–331.3) for melatonin v 243.4 minutes (range, 0–344.1) for placebo ($P = 0.98$). Observed diurnal sleep was also similar: 138.7 minutes (range, 50–230) with melatonin v 104 minutes (range, 0–485) for placebo ($P = 0.42$). The incidence of agitation was non-significantly higher in the melatonin group (31% v 7%; $P = 0.11$), while the requirement for extra sedation or use of haloperidol was slightly higher in the placebo group (57% versus 46%; $P = 0.56$).

Conclusion: Melatonin is well absorbed, and a standard dose increases blood levels approximately 1000-fold. However, in this pilot assessment, these high levels failed to increase observed nocturnal sleep or induce other observable benefits in tracheostomised ICU patients.

Crit Care Resusc 2006; 8: 187–191

Patients in the intensive care unit who are weaning from mechanical ventilation often have inadequate nocturnal sleep, with reversal of their sleep–wake cycle, arising from multiple factors.[1-7] Sleep deprivation can lead to patient agitation, particularly at night, and may require administration of either sedative or psychotropic drugs.[8,9] Sleep deprivation has also been associated with decreased respiratory responsiveness to hypercapnia, decreased respiratory muscle endurance and potential difficulty in weaning from mechanical ventilation.[5]

Melatonin (*N*-acetyl-methoxytryptamine) is a neurohormone secreted by the pineal gland, which controls the sleep–wake cycle in humans. Its secretion is suppressed by light and stimulated by darkness.[10] It has a circadian rhythm, which is disrupted in ICU patients, particularly in the presence of sepsis.[11] Melatonin has been given safely to humans in doses of 1–15 mg. Treatment results in 10 to 100 times the normal peak night concentration 1 hour after ingestion, followed by a decline to baseline values in 4–8 hours. Melatonin has been shown to be effective in treating jet lag,[12] and in helping restore normal sleep patterns in patients in psychiatric wards, with hastened sleep onset, improved quality and depth of sleep, and increased sleep duration.[13]

We hypothesised that there might be similar benefit in tracheostomised ICU patients weaning from mechanical ventilation and not receiving continuous sedation. We conducted a double-blind, placebo-controlled randomised pilot study comparing melatonin to placebo in such patients. The aim of the pilot study was to test whether nocturnal melatonin would help improve observed nightly sleep patterns in such patients.

Methods

The study was conducted between August 2003 and February 2005. It was approved by the Human Research Ethics Committee of the Austin Hospital, Melbourne, VIC. We obtained written informed consent from the patients or their next of kin. In the latter case, permission to proceed was further approved by the Victorian Civil and Administrative Tribunal of Victoria in Australia, as required by current legislation.

Table 1. Riker Sedation–Agitation Scale

Score	Category	Description
7	Dangerous agitation	Pulling at endotracheal tube, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side-to-side
6	Very agitated	Does not calm despite frequent verbal reminding of limits, requires physical restraints, biting endotracheal tube
5	Agitated	Anxious or mildly agitated, attempting to sit up, calms down on verbal instructions
4	Calm, cooperative	Calm, easily arousable, follows commands
3	Sedated	Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again, follows simple commands
2	Very sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands

Patients were eligible if they fulfilled the following criteria:

- tracheostomy in situ;
- weaning from mechanical ventilation;
- Glasgow Coma Score > 9; and
- sedative infusions or boluses stopped for > 12 hours.

Exclusion criteria included age under 16 years, pregnancy or breastfeeding, known allergy to melatonin, intestinal obstruction, ileus, gastroparesis or other conditions likely to affect enteral absorption of melatonin, or a likelihood that the patient would die within 24 hours.

Patients were randomly assigned through a computer-generated program to receive either melatonin or placebo. Patient allocation was known only to the hospital research pharmacist who dispensed the treatment. Patients, ICU staff and investigators were blinded to treatment allocation. The hospital pharmacy prepared the drugs in identical capsule form and dispensed them in identical containers labelled according to study number. Melatonin was given in the form of high performance liquid chromatography-purified melatonin at a dose of 3 mg (Melatonin, Natrol Inc, Cal, USA). All patients had a nasogastric tube in situ, through which the treatment drug was administered at 22:00. Treatment was continued for a minimum of 48 hours or until discharge from the ICU.

For each patient, we recorded age, sex, admission diagnosis, sedation-free period before melatonin administration, and APACHE II score on admission. We also recorded the total number of hours of observed sleep during the night (defined as between 22:00 and 06:00), and hours of observed sleep during the day (defined as between 06:00 and 22:00), as assessed by the bedside nurse. Observational criteria for the patient to be considered asleep included eyes closed, decreased motor activity, lack of interaction with the environment, and lack of purposeful activity.

The number of nocturnal procedures was recorded for each patient to assess sleep interruption. Routine procedures included suctioning of the tracheostomy tube, an early-morning wash and a morning chest x-ray. All medications used to sedate or settle the patient if agitated were also recorded.

The incidence of agitation was assessed using the score on the Riker Sedation–Agitation Scale,[14] recorded 8-hourly at 22:00, 06:00 and 14:00. A score of 5 or above was considered to indicate agitation (Table 1).

Melatonin levels were measured in blood samples taken on Days 1 and 3 at 21:30 (pre-dose), and 23:30 (post-dose) to ensure adequate melatonin absorption.

Finally, we recorded patients' vital status on discharge from hospital, as well as time to discharge from the ICU and from hospital.

Statistical analysis

The primary outcome measure for this pilot study was the duration of observed nocturnal sleep compared with diurnal sleep. Secondary outcome measures were the degree of agitation and the need for extra sedation or haloperidol treatment. Primary analysis was done on an intention-to-treat basis using the Mann–Whitney test.

As the length of ICU stay differed between patients, the average number of hours of sleep per patient was calculated by adding the total number of sleep hours during the night divided by the number of days in the ICU. The same approach was followed to calculate diurnal sleep.

Secondary analysis was done on a per-protocol basis as set before the trial. After data for the secondary outcome were collected, they were entered as nominal data (ie, patients with a Riker score $\geqslant 5$ were considered agitated, while those with a score $\leqslant 4$ were not; and patients were classified as either having received treatment to settle

Table 2. Patient demographic characteristics

Variable	Melatonin ($n = 14$)	Placebo ($n = 18$)
Mean age (years) (95% CI)	63 (54–72)	57 (46–68)
Male sex	8 (57%)	11 (61%)
Mean APACHE II score (95% CI)	19 (15–23)	18 (14–23)
Mean sedation-free time before therapy (hours) (95% CI)	33 (17–49)	38 (17–59)
Presence of agitation before therapy	5 (36%)	3 (17%)

Table 3. Melatonin concentration before and after drug administration (pg/mL) (median and interquartile range)

Time*	*P* value	Melatonin group	Placebo group
21:30	0.13	4.8 (2.4–7.5)	2.4 (1.6–3.18)
23:30	< 0.0001	3543 (1533–8100)	3.0 (1.6–9.3)

* Study drug was administered at 22:00.

agitation or not). The groups were compared using the χ^2 test. Correlation between the duration of night sleep and the number of procedures was assessed using the Spearman rank test.

Results

Thirty-two patients were enrolled in the study: 14 were randomly assigned to melatonin, and 18 to placebo. Patient characteristics are shown in Table 2.

Measured melatonin levels confirmed treatment allocation and adequate drug absorption (Table 3).

Analysis for the primary outcome on an intention-to-treat basis revealed that patients in the melatonin group had a similar median observed nocturnal sleep to those in the placebo group: 240 minutes (range, 75–331.3) versus 243.4 minutes (range, 0–344.1) ($P = 0.98$) (Figure 1A).

Median duration of observed diurnal sleep was also similar: 138.7 minutes for melatonin (range, 50–230) versus 104 minutes for placebo (range, 0–485) ($P = 0.42$) (Figure 1B).

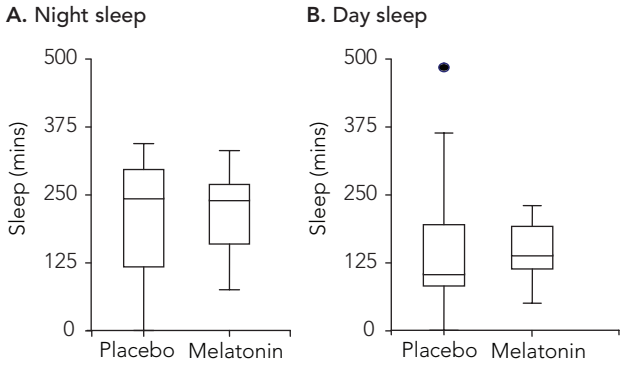
Five patients were excluded from further per-treatment analysis, two because they did not receive the medication (protocol violation), one because his condition deteriorated before treatment and he died within 24 hours, another because he developed a bowel leak with inability to receive enteral preparations and required continuous propofol. A final patient received the medication only for one night. On this per-treatment analysis, patients in the melatonin group had a similar median observed nocturnal sleep to placebo: 237.8 minutes (range, 75–331.3) versus 252.5 minutes (range, 98.3–344) ($P = 0.55$). Median observed diurnal sleep was also quite similar: 133.2 minutes for melatonin (range, 50–230) versus 122.7 minutes for placebo (range, 82.8–264.4) ($P = 0.88$).

We also compared the number of procedures done at night between the two groups. The median number of procedures during the night was similar: 3.7 procedures for melatonin compared with 4.6 for placebo ($P = 0.16$). There was no direct correlation between the number of nighttime procedures and the total hours of observed sleep ($r = 0.06$; $P = 0.76$) (Figure 2).

The incidence of agitation post-therapy was non-significantly higher in the melatonin group at 31% (4 of 13 patients) compared with 7% (1 of 14) in the placebo group ($P = 0.11$).

The requirement for extra sedation or haloperidol treatment was non-significantly higher in the placebo group at 57% (8 of 14 patients) compared with 46% (6 of 13) in the melatonin group ($P = 0.56$), with two patients receiving haloperidol in each group.

Figure 1. Box plot of observed sleep



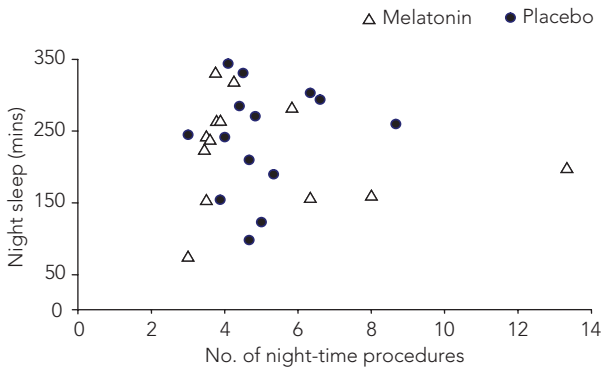
Key: *Box = interquartile range (25th to 75th percentiles). Line across box = median. Vertical lines = range (up to 1.5 interquartile values). Dot = outlier.*

Discussion

Sleep deprivation is a common problem in ICUs.[1-7] There is often reversal of the night-to-day sleep cycle, because of impaired circadian rhythm.[15-17] This can lead to difficulty in weaning from mechanical ventilation,[5] and increased patient agitation.[8,9] Multiple factors contribute to this common problem, including invasive procedures and routine nursing care, turning on of lights to facilitate these procedures, increased levels of noise because of high activity, and lack of patient isolation.[1,2,18,19] Other causes include prior sedation for days, waking up in a new environment, the presence of sepsis,[11] the effect of certain drugs (eg, β-blockers and corticosteroids), and the use of sedative and analgesic drugs to facilitate procedures or transport. Drugs such as morphine are known to interfere with rapid eye movement sleep, and benzodiazepines can reduce slow wave sleep.[5]

Melatonin, or *N*-acetyl-methoxytryptamine, is a neurohormone secreted by the pineal gland in response to absence of light. The pineal gland receives photic stimulation from the retina via the suprachiasmatic nucleus of the hypothalamus and the sympathetic nervous system. Light results in hyperpolarisation of the retinal photoreceptors, resulting in

Figure 2. Correlation between number of night-time procedures and duration of sleep



suppression of the retino–hypothalamic–pineal axis, and thus inhibition of melatonin release. On the other hand, darkness causes increased release of the neurotransmitter norepinephrine, leading to activation of the system and secretion of melatonin. Thus, melatonin secretion is suppressed by light and stimulated by darkness.

Melatonin secretion also has a circadian rhythm, with peak levels between 02:00 and 04:00, and trough levels during daytime. The average peak melatonin concentration at night is 60 pg/mL, which gradually declines to trough levels of 10 pg/mL during the daytime.[10]

The circadian rhythm of melatonin is disrupted in ICU patients, particularly in the presence of sepsis.[11] Previous studies have indicated that abnormal sleep patterns in ICU patients are associated with impaired melatonin secretion compared with general-ward patients.[15] Other studies have indicated that melatonin might be effective in inducing sleep in patients in psychiatric wards or as treatment for jet lag.[12,13,20,21]

We hypothesised that melatonin might help increase nocturnal sleep, and perhaps thereby reduce the incidence of agitation.

Our study revealed clinically relevant information. First, our patients showed profound suppression of nocturnal melatonin release, with blood levels close to 10% of normal. Second, enteral melatonin administration was successful in achieving good absorption and led to blood levels which were close to 1000 times higher than baseline levels and close to 50 times higher than normal levels. However, the dramatic changes in melatonin blood levels had no discernible effect on observed night-time sleep, and there was no reduction in the incidence of patient agitation or need for sedative or antipsychotic medications.

There are many potential causes for this failure of melatonin to induce adequate improvements in observed nocturnal sleep in these ICU patients. A likely important factor was the continued interruption of the sleep cycle by the high level of noise, turning on of lights, or routine care and procedures, which may have a more powerful effect on observed sleep than even the pharmacological levels of melatonin achieved. It is also possible that the imbalance in other hormone and neurotransmitter levels in critical illness may oppose the effect of melatonin. Hence, we were not able to replicate the findings of studies in non-ICU settings.

Furthermore, we were able to assess only observed sleep, not actual sleep. Observed sleep was chosen as is easy to assess and has practical relevance to nursing care and patient management. To reveal differences in the amount of slow wave or rapid eye movement sleep would have required more sophisticated equipment, which of itself would hinder sleep, requires further manipulation and is logistically difficult to use in the ICU. Finally, the clinical significance of any such differences would remain unclear. Our study, given the observed standard deviation, had a $>80\%$ power to detect a 30% difference at $P<0.05$. Thus, it is possible that smaller differences exist between the melatonin and placebo groups, which could not be detected by our pilot study. However, the slightly favourable trend for placebo does not support this notion.

Finally, it is theoretically possible that such high levels of melatonin were achieved with a 3 mg dose at 22:00 that, even during the daytime, melatonin blood levels were sufficiently high to promote diurnal sleep as well. Daytime sleep would have then occurred and made nocturnal sleep more difficult. However, with a median melatonin level of 3000 pg/mL at 23:30 and a half-life of 60 minutes,[22] the expected melatonin blood level at 08:00 would be back in the normal daytime range. This makes promotion of daytime sleep an unlikely explanation for our findings. Furthermore, diurnal sleep was similar in the two groups.

The study highlights important issues relating to the ICU environment and its interference with nocturnal sleep. In particular, we noted a similar but high number of procedures in the two groups (median of 3.7 for melatonin compared with 4.6 for placebo). These procedures included frequent suctioning, repeated arterial blood gas measurements, insertion of lines, blood sampling and chest x-rays at 05:00, and also, depending on the patient's condition, cardiac output measurements and haemofiltration care.

Some procedures are considered a high priority and need to be done promptly. However, one can argue that, for patients whose condition is stable, minimising the number of procedures at night might improve night-time sleep, which might then facilitate physical and mental recovery. In most Australian ICUs, routine blood sampling and chest x-rays are done quite early in the morning in preparation for the morning round. It may be more physiological to

perform these activities 2–3 hours later. We note that, in our patients, the overall amount of observed sleep was short, at about 6 hours per day.

Sleep homeostasis in the ICU is a complex issue with many interfering factors. Administration of a pharmacological dose of melatonin failed to induce greater observed night sleep in this environment when compared with placebo. Neither did it influence the incidence of agitation or the requirement for extra sedation or haloperidol treatment. The average number of procedures in the ICU at night is probably too high to allow good night-time sleep and restoration of a normal sleep–wake cycle or slow wave–rapid eye movement sleep with any agent currently available. Further studies and strategies are required to find better ways of improving the amount and quality of sleep in ICU patients.

Author details

Murad G Ibrahim, Advanced Trainee in ICU[1]
Rinaldo Bellomo, Intensivist, Director of ICU Research[1]
Graeme K Hart, Intensivist, Deputy Director of ICU[1]
Trevor R Norman, Psychologist[2]
Donna Goldsmith, Intensive Care Research Nurse[1]
Samantha Bates, Intensive Care Research Nurse[1]
Moritoki Egi, Intensive Care Research Fellow[1]

1 Department of Intensive Care and Department of Medicine, University of Melbourne, Austin Hospital, Melbourne, VIC.

2 Department of Psychiatry, University of Melbourne, Austin Hospital, Melbourne, VIC.

Correspondence: rinaldo.bellomo@austin.org.au

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