RESEARCH ARTICLE

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Melatonin decreases delirium in elderly patients: A randomized, placebo-controlled trial†

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Background: Disturbance in the metabolism of tryptophan and tryptophan-derived compounds (e.g., melatonin) may have a role in the pathogenesis of delirium.

Objective: To evaluate the efficacy of low dose exogenous melatonin in decreasing delirium.

Design: A randomized, double-blinded, placebo-controlled study.

Setting: An Internal Medicine service in a tertiary care centre in London, Ontario, Canada.

Participants: 145 individuals aged 65 years or over admitted through the emergency department to a medical unit in a tertiary care hospital.

Intervention: Patients were randomized to receive either 0.5 mg of melatonin or placebo every night for 14 days or until discharge.

Measurements: The primary outcome was the occurrence of delirium as determined by Confusion Assessment Method (CAM) criteria.

Results: Of a total of 145 individuals (mean age (standard deviation): 84.5 (6.1) years) 72 were randomly assigned to the melatonin group and 73 to the placebo group. Melatonin was associated with a lower risk of delirium (12.0% *vs.* 31.0%, $p = 0.014$), with an odds ratio (OR), adjusted for dementia and co-morbidities of 0.19 (95% confidence intervals (CI): 0.06–0.62). Results were not different when patients with prevalent delirium were excluded.

Limitation: An intention to treat analysis was not possible due to loss to follow-up.

Conclusion: Exogenous low dose melatonin administered nightly to elderly patients admitted to acute care may represent a potential protective agent against delirium. Copyright © 2010 John Wiley & Sons, Ltd.

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Introduction

Delirium is a common, life-threatening, and potentially preventable clinical syndrome that complicates hospital stays in at least 20% of patients 65 years of age or older. Delirium is associated with loss of independence, morbidity, mortality, and increased health care costs (Rudolph and Marcantonio, 2003; Inouye, 2006). The mortality rates among hospitalized patients with delirium range from 22 to 76% (Inouye, 2006). Moreover, delirium persists beyond 6 months in nearly one-third of patients. Subjects with persistent delirium are 2.9 times more likely to die (Kiely *et al*., 2009). Patients admitted to postacute skilled nursing facilities with delirium are

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more likely to experience complications, rehospitalization, and death (Marcantonio *et al*., 2005).

There has been little research into the basic mechanisms of delirium. Current understanding is that it is likely multi-factorial. Although delirium may result from a neuroanatomic abnormality (e.g., stroke), the majority of cases are associated with an imbalance of central neurotransmitters (Marcantonio *et al*., 2006). Melatonin, a pineal gland hormone felt to be important in sleep/wake regulation, could provide the link between delirium and disruption of the sleep/wake cycle in delirium (Figueroa-Ramos *et al*., 2009). In one study, urinary levels of melatonin metabolites were normal in patients without delirium, high in those with hypoactive delirium, and low in those with hyperactive delirium (Balan *et al*., 2003). This has lead researchers to postulate that delirium may be related to abnormal tryptophan metabolism (Lewis and Barnett, 2004). Lewis and Barnett suggested that melatonin supplementation might reduce delirium by decreasing the breakdown of both tryptophan and serotonin through negative feedback (Lewis and Barnett, 2004). It may be that melatonin simply resets the sleep/wake cycle, or may play a direct role in the prevention of delirium (Lewis and Barnett, 2004). Recent studies have shown that patients who develop postoperative delirium have lower serum levels of tryptophan (Robinson *et al*., 2008), and that high or very low tryptophan ratios are associated with an increased risk of delirium in critically ill patients (Pandharipande *et al*., 2009).

Melatonin supplementation has been suggested as a treatment option for sleep disturbance, delirium, or sepsis in postoperative or critically ill patients (Bourne and Mills, 2006). Hanania and Kitain reported the successful use of melatonin in treating severe postoperative delirium unresponsive to antipsychotics or benzodiazipines in a 53 year old patient, and to prevent another episode of postoperative delirium in a 78 year old patient with a history of postoperative delirium (Hanania and Kitain, 2002).

This study was undertaken to evaluate the efficacy of exogenous melatonin, given in physiologic doses, in reducing the occurrence of delirium in elderly patients admitted to acute medical care.

Methods

Settings and participants

Eligible patients were at least 65 years of age and admitted through the emergency department to Internal Medicine in-patient services. Patients were approached directly in the emergency room or in their rooms by one of the three study clinicians (TA, CB, or MD), within 24 h of admission (up to 48 h was allowed on weekends). Patients were excluded from the study if they had an expected stay or life expectancy of less than 48 h, were unable to communicate in English or to take oral medications, had an intracranial bleed or seizures, had a markedly non-therapeutic international normalized ratio (INR) less than one or more than four while on warfarin, or had a known allergy to the study compounds.

All participants or their substitute decision makers provided informed consent. The study was approved by the Health Sciences Research Ethics Board (HSREB) at The University of Western Ontario and complied with the HSREB guidelines.

Randomization and intervention

Patients were assigned to one of the two arms of the study using computer generated blocked-randomization (block size: 4). Block randomization was selected to achieve balance in the number of subjects given our small sample size (Beller *et al*., 2002). As soon as they were enrolled, orders were written for study participants to receive the study drug (0.5 mg of oral melatonin or placebo) prior to sleep. The study medication was administered daily between 1800 and 2400 h depending upon patient availability and medication administration schedules. We felt compliance would be improved by flexible administration time, but also that evening administration would be most effective; the choice of administration time (between 1800 and 2400 h) was hence a compromise. The medication was provided in a double-blinded fashion. This regimen was continued until discharge, death or up to 14 days. Pharmacy kept the randomization code and undertook the randomization. The investigators did not become aware of treatment allocation until several months after study completion. In case of emergency, an independent physician could request unmasking of the treatment allocation.

The melatonin preparation used was one half of a 1 mg tablet of rapid dissolving melatonin, manufactured by General Nutrition Canada with the natural product number 80001380. Placebo tablets were lactose 100 mg tablets split in half, and were similar in appearance to the melatonin tablets. In Canada, melatonin undergoes extensive testing prior to being included in the Natural Health Products Directorate of Health Canada, and is available for sale, having met the licensing, manufacturing, labeling, and safety

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standards (Jansen *et al*., 2006). The physiological dose of melatonin is believed to be 0.3 mg (Dollins *et al*., 1994; Zhdanova *et al*., 1997; Olde Rikkert and Rigaud, 2001). However, a dose of 0.5 was selected for this study based on the closest dose that was readily available and approved in Canada at the time.

Outcomes and measurements

Baseline characteristics (age, sex, co-morbidities, and documented history of cognitive impairment or depression) were collected by the investigators from the medical chart. Participants were tested every 24–48 h using the Confusion Assessment Method (CAM) (Rudolph and Marcantonio, 2003; Inouye, 2003; Inouye *et al*., 1990) and the Memorial Delirium Assessment Scale (MDAS) (Rudolph and Marcantonio, 2003; Breitbart *et al*., 1997) for the presence and severity of delirium. The primary study outcome was delirium, defined according to the CAM criteria (Inouye, 2003; Inouye *et al*., 1990). The CAM criteria provide a standardized rating of delirium, which has been validated, and has a high sensitivity, specificity, and inter-observer reliability (Inouye *et al*., 1990).

Secondary outcomes included delirium severity as measured with the MDAS (Breitbart *et al*., 1997), a well known, validated delirium severity scale (Rudolph and Marcantonio, 2003), the use of as needed (PRN) sedatives and psychotropics, the use of restraints, as well as mortality, and length of stay. Sleep/wake cycle disturbance was also recorded based on item number 10 on the MDAS (Breitbart *et al*., 1997).

The CAM and MDAS were scored based upon observations on how study participants responded to a standardized interview, and on information from medical charts, nurses and caregivers. The interview included two general questions, 10-item orientation, immediate and delayed recall, and digit span (forward and backward). Additional questions to address perceptual and sleep disturbances were derived directly from the MDAS (Breitbart *et al*., 1997). Nurse interviews, chart documentation of sleep disturbances or of perceptual disorders, medication administration, physical restraint use, and the use of paid patient attendant services were also recorded. Specifically, the assessment of sleep disturbance was based on item 10 on the first completed MDAS rating of the patient's ability to sleep or stay awake during appropriate times. Direct observation during interview as well as reports from nurses or family was utilized. This item was scored as: 0 or none if "at night, patient sleeps well, during the day, has no trouble staying awake;"1 or mild if "at night, difficulty falling asleep or transient awakenings, needs medication to sleep well; and/or during the day reports periods of drowsiness or during interview is drowsy but can easily fully awaken;" 2 or moderate if "at night, repeated and prolonged night awakenings; and/or during the day, frequent and prolonged napping, or during the interview, can only be roused to complete wakefulness with strong stimuli; 3 or severe if "at night, total sleeplessness; and/or during the day, patient spends most of the time sleeping, or during the interview, cannot be roused to full wakefulness by stimuli" (Breitbart *et al*., 1997).

All the assessments were carried out by research assistants and experienced clinicians blinded to group assignment. All underwent intensive training on the use of the instruments, through didactic sessions followed by testing several delirious and control patients previously diagnosed by an independent geriatrician. Inter-rater reliability was tested (on several control and delirious patients) and assured on all outcome measures prior to study commencement.

For the primary analysis of the efficacy of the intervention, delirium was considered a binary outcome (present or absent) according to its earliest occurrence, and only one episode of delirium per patient was counted.

Statistical analysis

Data were collected on standardized forms and entered into SPSS, v. 16 (SPSS Inc., Chicago, Illinois) by one research assistant.

Baseline characteristics including age, sex, medical co-morbidity (the mean number of chronic medical conditions), number of routine medications, and history of dementia, mild cognitive impairment or depression were compared in the two groups. Fisher's exact tests were used to compare categorical variables and independent *t*-tests (unequal variances) were used for continuous variables.

A Fisher's exact test was used to assess the effect of the intervention on the dependent outcome, delirium. Results were also calculated excluding individuals delirious at the time of enrollment (prevalent delirium). Multiple logistic regression was used to adjust for statistically significant ($p < 0.01$) group differences in baseline characteristics.

To identify possible covariates to include in the multiple regression used to estimate the relationship between melatonin use and delirium, bivariate analyses examining associations between mean age, sex, dementia, number of co-morbidities and the number of

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regular medications and the presence of delirium were done.

For the secondary outcomes, bivariate relationship between treatment group and delirium severity, use of as needed psychotropic medications, use of restraints, death and length of stay, variables shown in the literature to affect delirium severity or that are routinely collected as part of patient care, were determined (Fisher's exact test for categorical variables or independent *t*-tests for continuous variables).

Results

Sample description

From 29 October, 2007 to 29 February, 2008, a total of 293 patients were screened. Ninety four were excluded. Thirty (10%) had a projected hospital stay and/or life expectancy of 48 h or less, 24 (8.2%) were unable to take oral medications, 17 (5.8%) had an INR out of range on warfarin, 16 (5.5%) were unable to communicate in English, and seven (2.4%) had known seizures or an intracranial hemorrhage. Fifty patients (17.2%) declined to participate.

One hundred and forty nine people were enrolled, with follow-up ending on February 29th, 2008 (see Figure 1). Of these, four were not randomized, leaving 145 that were randomized to either placebo ($n = 73$) or melatonin ($n = 72$). CAM data could not be collected on nine participants assigned to the melatonin group and 10 assigned to the placebo group due to several reasons, including early discharge or patients' death, patients being away for procedures or tests at the time of assessment, or change in patients' initial conditions resulting in significant aggressiveness, or inability to

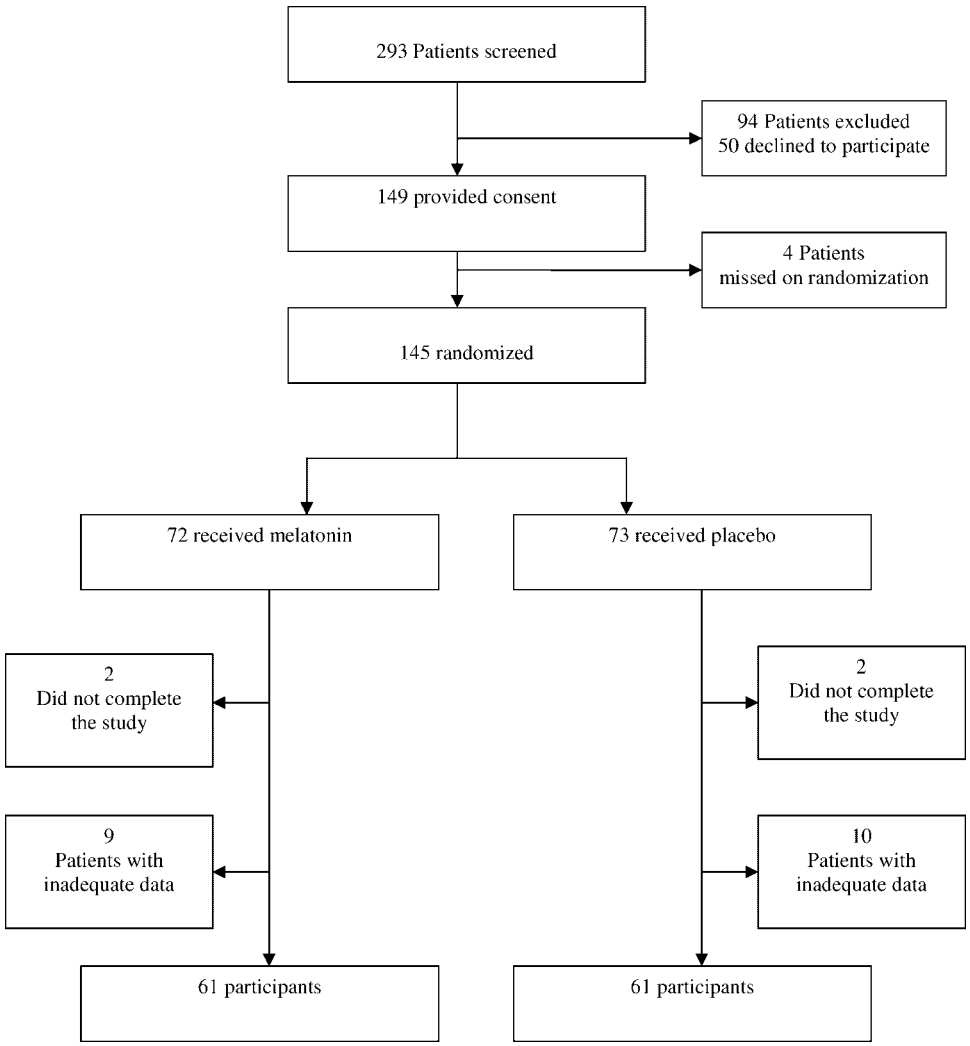

Figure 1 Study flow diagram.

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communicate due to a depressed level of consciousness, precluding an adequate assessment for delirium. Two patients from each group withdrew their consent (did not wish to participate in testing). The final population was therefore comprised of 61 participants in the melatonin arm and 61 in the placebo arm. There was no significant difference in the number of delirium assessments performed for patients in the placebo (4.2) and the melatonin arms of the study (4.4) ($p = 0.55$).

There were no statistically significant differences in baseline characteristics between the two groups (see Table 1).

Overall effectiveness

A significantly smaller proportion of participants experienced delirium on melatonin as compared to placebo (12.0% *vs.* 31.0%, $p = 0.014$) with an unadjusted OR of developing delirium on melatonin of 0.29 (95% confidence intervals (CI): 0.11–0.74). After excluding individuals with prevalent delirium, defined as being CAM positive on enrollment (9 in the placebo group and 5 in the melatonin group), melatonin was still associated with a lower risk of delirium (19.2% in the placebo group and 3.6% in the melatonin group, $p < 0.02$), or a relative risk reduction of 0.19 (absolute risk reduction of 15.6% or number needed to treat of 6.4).

To account for missing data, a conservative sensitivity analysis was done; assuming all individuals with missing data had delirium rates equal to the placebo rate. In this case, rates of delirium would be 22/71 (31.0%) and 10/70 (14.3%), respectively, in placebo and melatonin groups (Pearson Chi-Square = 5.60, $p = 0.02$). Alternatively, in the worse case scenario, assuming that only missing individuals on melatonin developed delirium whereas none on placebo did, the difference was no longer significant (Pearson Chi Square test: 0.29, $p = 0.5$).

Table 1 Baseline characteristics

Characteristic	Placebo ($n = 61$)	Melatonin ($n = 61$)	p-value
Age			
Mean (SD)[a]	84.6 (6.2)	84.3 (5.9)	0.80
Range	73–98	75–103	
Sex			
Male	24 (39%)	28 (46%)	0.58
Co-morbidities			
Mean (SD)[a]	5.2 (1.9)	5.3 (2.3)	0.48
Range	2–10	2–12	
4 or more	52 (85%)	48 (79%)	0.65
MCI[b]	7 (12%)	12 (20%)	0.82
Dementia	13 (23%)	11 (18%)	1.0
Depression	5 (8%)	6 (10%)	1.0
Medications			
Mean (SD)[a]	6.5 (3.1)	6.5 (3.0)	0.81
Range	1–20	2–16	
Median	6.0	6.0	
4 or more	50 (83%)	48 (81%)	0.81

[a]Standard deviation.
[b]Mild cognitive impairment.

Secondary outcomes

There were no statistically significant differences in delirium severity, average length of hospital stay, or need for sedation or restraint use. Further, melatonin did not have a statistically significant effect on sleep as recorded in the MDAS (see Table 2). The mortality in both groups was not significantly different.

Adverse events

Two patients on melatonin reported side effects that might have been secondary to the study medication or related to delirium directly. One reported nightmares and had to be taken off the medication. Another patient reported feeling like he was ''floating around and talking to his dead wife.'' However, this resolved by the next night.

Discussion

In this double-blinded placebo controlled trial, low-dose melatonin administered nightly was effective in decreasing the risk of delirium. Moreover, melatonin supplementation was well tolerated in this acutely ill patient population with multiple co-morbidities. This is in keeping with previous data that have shown melatonin to be a safe drug, particularly in the elderly and cognitively impaired (Baskett *et al.*, 2001; Zhdanova *et al.*, 2001; Singer *et al.*, 2003; Leger *et al.*, 2004; Karasek, 2007).

To our knowledge, this is the first clinical trial suggesting that a pharmacologic intervention may decrease delirium occurrence in medical in-patients (Siddiqi *et al.*, 2007; Bourne *et al.*, 2008). In the surgical setting, neuroleptics (Kalisvaar *et al.*, 2005) and cholinesterase inhibitors (Liptzin *et al.*, 2005) have been studied as potentially preventative agents. However, in these trials, pharmacologic interventions did not decrease delirium occurrence, although haloperidol did decrease delirium duration and severity (Kalisvaar *et al.*, 2005). Non-pharmacological

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Table 2 Primary and secondary outcomes and adverse outcomes by treatment group

Outcome	Placebo ($n=61$)	Melatonin ($n=61$)	p-value
Delirium (assessed with CAM[a])	19 (31%)	7 (12%)	0.01
Incident delirium (excluding prevalent delirium[b])	10/52 (19.2%)	2/56 (3.6%)	0.01
Initial MDAS[c]score[d] (SD)[e] (all participants)	4.4 (4.6)	5.2 (4.3)	0.31
Initial MDAS[cd]score (SD)[e] (if developed delirium)	11.4 (3.0)	10.5 (5.3)	0.77
Use of paid patient attendant services	3/60 (1 missing) (5.0%)	2/57 (4 missing) (3.5%)	0.52
Restraints	6 (10%)	4 (7%)	0.74
Use of PRN[f] sedatives	38 (62%)	33(54%)	0.46
Mean LOS[gh] (SD)[e]	14.5 (21.6)	18.5 (26.4)	0.36
Sleep disturbance[i]			
None	37 (60.7%)	39 (63.9%)	0.81
Mild	21 (34.4%)	18 (29.5%)	
Moderate/severe	3 (4.9%)	4 (6.6%)	
Deceased	8 (13%)	6 (10%)	0.78

[a]Confusion Assessment Method.
[b]Prevalent delirium was defined as those cases that were CAM positive at the first CAM assessment.
[c]Memorial Delirium Assessment Scale
[d]This is the mean of the first recorded MDAS score among those who were delirious.
[e]Standard deviation.
[f]As needed.
[g]Length of stay.
[h]When calculating mean LOS, a value of 17 (mean LOS) was imputed when missing in three cases: 2 placebo and 1 melatonin cases.
[i]Based on item 10 on the first completed MDAS rating patient's ability to sleep or stay awake during appropriate times.

interventions may prevent delirium as suggested by some studies in both the medical (Inouye *et al*., 1999) and surgical setting (Marcantonio *et al*., 2001). Some trials have also suggested that non-pharmacologic interventions may decrease delirium duration, length of hospital stay and mortality (Lundstrom *et al*., 2005).

In this study, we chose to use a melatonin dose that approximated the physiological dose, thereby possibly restoring melatonin levels to near-normal levels without undesirable side effects that may be seen at higher doses (Zhdanova *et al*., 1997; Olde Rikkert and Rigaud, 2001; Jansen *et al*., 2006). Melatonin's safety and low cost (9 cents per 1 mg tablet in Canada) make it an attractive agent that can be used in conjunction with non-pharmacological interventions, for decreasing delirium. Furthermore, it poses a potential advantage over multifaceted interventions when it comes to adherence and cost.

Results of our study also support a possible pathogenic role of melatonin or serotoninergic neurotransmission in delirium symptoms. We believe that the effect of melatonin was independent of its potential sleep effect. We did not detect any significant difference in subjective sleep quality. Furthermore, the effect of melatonin supplementation on sleep is still controversial (Buscemi *et al*., 2005; Van den Heuvel *et al*., 2005; Zhdanova, 2005; Ebert *et al*., 2006; Kamil and Gammak, 2006).

Melatonin administration did not decrease delirium severity, length of hospital stay, restraint or sedative use, or mortality. These results are similar to the landmark Yale delirium prevention trial (Inouye *et al*., 1999), in that once an initial episode of delirium had occurred the intervention had no significant effect on the severity of delirium, further supporting the role of delirium prevention.

Our study also highlights the vulnerability of patients with dementia to the development of delirium. In our study, patients with dementia were nearly 15 times as likely to develop delirium, which is higher than previously reported in the literature (Elie *et al*., 1998). This may be due to the fact that our sample was generally older and sicker, and deserves to be further confirmed in larger studies. More importantly, this should draw attention to the importance of targeting prevention efforts and policies toward this population.

This study has several strengths. It was randomized, double-blinded, and placebo-controlled. The two groups were well balanced in terms of known delirium risk factors, and the proportion of those with delirium in the placebo group was similar to what would be expected in this patient population. Another strength was the regular assessment of patients for delirium with standardized, validated instruments.

Limitations of our study include its small sample size, preventing an examination of the effects of specific medication classes on delirium. Complete data collection was not possible for some participants, who, as previously explained, may have been involved with

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other tests/procedures at that time of data collection. A sensitivity analysis intended to account for lost data was done. In the unlikely situation that all patients lost to follow-up in the Melatonin group developed delirium while none of the patients lost to follow-up in the placebo group did, there would have been no statistically significant difference in the proportion with delirium between the Melatonin and the placebo group. If however, we assumed that placebo rates of delirium occurred in all patients lost to follow-up, then the study findings were still significant and in favor of the Melatonin group. Although we measured some variables associated with delirium, other possible risk factors such as dehydration and visual impairment were not measured. Measurement of other variables (e.g., dementia and depression) used patient (or caregiver) report or chart documentation, rather than formal assessment for those conditions, which may have lead to biased prevalence estimates. However given the randomized allocation to treatment, there is no reason to suspect that these variables would be differentially distributed in the two groups and these limitations are unlikely to introduce systematic bias to results. Moreover, the prevalence of dementia in our sample is in keeping with the prevalence of dementia in this age group (The Canadian Study of Health and Aging, 1994; Cummings, 2004; Chertkow, 2008). Finally, in order to improve compliance and encourage participation, our study did not use objective sleep measures, such as actigraphy, which would have given us a better understanding of the effect of melatonin supplementation on sleep in this population, and the possible interaction between sleep quality and delirium.

Conclusions

Our study provides evidence that nightly melatonin supplementation may have a role in decreasing delirium in elderly patients admitted to acute care. Future research is required to confirm the potential protective role of melatonin in larger studies and in different populations, such as surgical, critically ill, or long term care patients.

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Conflict of interest

None of the authors or study team members has had any conflict of interest or any affiliation or relation with any melatonin producing organization.

KEY POINTS

- Delirium is a major cause of morbidity and mortality.
- Low dose melatonin was effective in decreasing delirium in elderly patients admitted to acute care.
- This is likely independent of the effects of melatonin on sleep, supporting a possible role of tryptophan metabolism in the pathogenesis of delirium.
- Low dose melatonin was well tolerated.

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