Studies on circadian rhythm disturbances and melatonin in delirium

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Citation for published version (APA):
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Impact of melatonin on the incidence of delirium in hip fracture patients: A multi-center double-blind randomized controlled trial

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Submitted for publication
Abstract

Importance: Delirium is associated with a high risk of dementia, institutionalization and high mortality. Prevention of delirium might result in better outcomes. Sleep-wake rhythm disturbance is a key characteristic of delirium. Melatonin, which influences circadian rhythm could be effective in the prevention of post operative delirium in high risk groups.

Objectives: To investigate the effectiveness of melatonin vs placebo on the incidence and duration of delirium.

Design: Multi-center double-blind randomized controlled trial, performed between November 2008 and May 2012. A randomisation schedule, only known by the trial pharmacist, was made by computer, so patients and investigators were blinded.

Setting: This trial is conducted in an academic hospital and two non-academic teaching hospitals.

Participants: Patients aged 65 years or above who were scheduled for acute hip surgery.

Interventions: Patients received melatonin 3 mg or placebo in the evening for 5 consecutive days, starting within 24-hours after admission.

Main outcomes: The primary outcome was the incidence of post operative delirium. The duration of delirium was also monitored.

Results: 452 Patients were enrolled and randomized. Data were analyzed of 378 patients, based on the intention-to-treat principle. The mean age was 84 years, 63% of the patients lived at home prior to admission, and 56% had cognitive impairment. No effect of melatonin on the incidence of delirium was demonstrated: treatment group 55/186=29.6% versus 49/192=25.5% in the placebo group; difference = 4.1; 95% confidence interval for the difference = -0.05% to 13.1%; p=0.38. In the melatonin group, fewer patients experienced a delirium episode of longer than 2 days compared with the placebo group (25.5% vs. 53.5%) (p=0.02). There were no between-group differences in mortality or in cognitive or functional outcomes at a 3-month follow-up.

Conclusions and relevance: In this older hip fracture population, treatment with melatonin did not decrease the incidence of delirium. However, the findings suggest that melatonin may reduce the number of patients who experience a long lasting episode of delirium. Any reduction in the time suffering from delirium is important as delirium is frequently experienced as very unpleasant.

Trial registration: Dutch Clinical Trial Registry: NTR1576, MAPLE study. http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1576
Introduction
Delirium in older inpatients is associated with a high risk of dementia and other complications that translate into increased mortality and healthcare costs.(1, 2) The antipsychotic haloperidol has historically been the agent of choice for the treatment of delirium, and it has increasingly been administered as a prophylactic pharmaceutical treatment for delirium or to reduce symptoms including hallucinations or aggressive behavior.(3, 4) However, all antipsychotic treatments may induce serious cerebrovascular side effects and greater mortality, particularly in patients with dementia(5, 6), which has led to a serious warning against their use by the U.S. Food and Drug Administration (FDA).(7) Disturbances in the circadian sleep-wake rhythm are one of the core features of delirium. This characteristic has raised the hypothesis that the neurotransmitter melatonin and changes in its metabolism may be involved in the pathogenesis of delirium.(8, 9) Objective measurements show that melatonin metabolism is disturbed after abdominal and other surgeries, insomnia, sleep deprivation and stays in intensive care units (ICUs), which are all contributing factors for the occurrence of delirium.(10-13) Consequently, inpatients may benefit from melatonin supplementation therapy by maintaining or restoring their (post-operative) sleep-wake cycle.(14, 15) Although melatonin depletion is thought to be one of the mechanisms of delirium, there have been few studies investigating the impact of alteration of perioperative plasma melatonin concentration and possible effects on postoperative delirium.

Therefore, the primary objective of this study was to assess the effects of melatonin on the incidence of delirium in elderly patients admitted acutely due to hip fracture. Secondary outcomes were duration of delirium, severity of delirium, length of hospital stay and total dose of haloperidol and/or benzodiazepines used in patients with delirium, mortality during hospital stay and functional status, cognitive function and mortality at three months follow-up.

Methods and design

Trial design
We conducted a multi-center double-blind randomized controlled trial in the Netherlands between November 2008 and May 2012. Full details of the study protocol are described elsewhere.(16) The study was conducted in compliance with the Helsinki Declaration and Good Clinical Practice guidelines. The study was approved by the Medical Ethics Committee of the Academic Medical Center with local approval of the other participating centers. Written informed consent was obtained from all patients or a legal representative in patients with cognitive impairment. No data safety or monitoring board was installed because melatonin was considered safe.(17, 18) This trial is registered with the Dutch Clinical Trial Registry (NTR1576).
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Participants and setting
The study population comprised patients of 65 years and above who were admitted acutely for surgical treatment of hip fracture. There was no restricture as to the type of treatment for the fracture (internal fixation, hemi-arthroplasty or total hip replacement). Further inclusion criteria were enrollment within 24 hours of admission and the willingness and capability to receive the study medication for the duration of the study based on the protocol. Patients on psychiatric medication apart from their delirium medication could continue their prescriptions throughout the study period. Exclusion criteria were present delirium at the time of inclusion, transfer from a ward of another hospital to the trial locations, anticipated postoperative intensive care unit (ICU) or coronary care unit (CCU) admission (logistic reasons), concomitant use of melatonin and the inability to speak or understand Dutch. The three trial locations were the surgical, orthopedic and trauma surgery wards of the Academic Medical Center in Amsterdam (a 1000-bed university teaching hospital), and the Tergooi Hospitals (a regional teaching hospital comprising 633 beds at two locations: Hilversum and Blaricum). Follow-up visits were performed by an experienced team of geriatric nurses at three months after enrolment.

Randomization and masking
After baseline assessments, patients were randomized to the intervention group (melatonin) or control group (placebo) in a 1:1 ratio. Randomization was stratified by study center with fixed blocks of ten patients within each stratum. Before the start of the study, a randomization schedule was generated by an independent statistician. The randomization list was maintained by the trial-pharmacist. Study medication tablets were manufactured and labeled according to Good Manufacturing Procedure guidelines.(19) Investigators, other staff personnel and participants and patients remained blinded until after the last patient had completed the study and follow-up at three months and data analyses had been completed.

Procedures
All patients of 65 years and older with an acute hip fracture were approached within 24 hours of admission by our research team, which comprised geriatricians and trained research nurses with experience in geriatrics. Patients were screened for eligibility and asked to participate. Included patients received study medication for five evenings, starting from the day of admission, at approximately 9 p.m. The medication comprised a tablet containing either 3 mg of melatonin (Tiofarma, Oud-Beijerland, The Netherlands) or a placebo. At baseline, demographic data, medical history, medication use and surgery-related characteristics were recorded. Functional status was assessed using the 15-item modified Katz Index of Activities of Daily Living (Katz-ADL) based on the two weeks prior to admission. The instrument was completed by the patient or by his/her closest relative in cases of cognitive impairment. Functional impairment was calculated using the added
number of impaired ADLs. (20) Cognitive functioning was assessed using the Mini-Mental State Examination (MMSE). (21) The MMSE is a validated 30-point questionnaire-based test that is used to screen for cognitive impairment. Primary caregivers were asked to complete the Informant Questionnaire on Cognitive Decline short form (IQQCODE-sf) by recalling the two weeks prior to the hip fracture and comparing this with ten years earlier. (22, 23) We defined ‘cognitive impairment’ as an IQCODE-sf score of ≥ 3.4 or dementia in the medical history. (24) The severity and number of comorbidities was scored using the Charlson comorbidity index. (25) Patients were asked whether they had ever experienced a delirium episode and if they had two falls within the last three months. The total amounts of haloperidol and other antipsychotics and benzodiazepines were recorded if applicable. Because different types of benzodiazepines were used, we present them in oxazepam equivalents. (26) In cases of delirium, patients received ‘perioperative care as usual’ based on the routine hospital delirium-protocol. At discharge, fracture characteristics, type of anesthesia, type of surgery, length of stay and mortality was registered for all patients and obtained from the medical notes. At three months follow-up, a MMSE was performed to assess global cognitive impairment and the patient or their closest relative was asked to complete a Katz-ADL index score. (21)

Outcomes
The primary endpoint was the incidence of delirium during the first eight days after the initiation of study medication. DSM-IV criteria were used for the diagnosis of delirium. (27) Subsequently, over eight days or until discharge, daily assessments for the presence of delirium were performed. For patients who were not delirious on day eight, daily assessments were terminated. For patients who were delirious at day eight, daily clinical assessments were continued to evaluate the duration of delirium until the symptoms of delirium resolved or until the patient was discharged. Secondary outcomes were duration of delirium (total number of days and percentage longer than two days), severity of delirium (percentage using ≥ 3 mg of total use of haloperidol), length of hospital stay and total dose of haloperidol and/or benzodiazepines in patients with delirium (in oxazepam equivalents), mortality during hospital stay and functional status, cognitive function, and mortality at three months follow-up.

Sample size
The sample size was calculated based on the incidence of delirium during the first eight days after the start of study medication. In the Academic Medical Center (AMC), the incidence of delirium in patients after surgical repair of hip fracture is approximately 50%. (28) Literature on medical intervention for the reduction of the incidence of delirium is rare but one study showed an absolute reduction of 13%. (29) A two group χ² test with a 0.05 two-sided level of significance will have 80% power to detect the difference between the control group proportion of 0.50 and a treatment group proportion of 0.37 (odds ratio of 0.587) when the sample size in each group is 226 (452 patients in total).
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Statistics
Data were analyzed based on the intention-to-treat principle, and secondarily by per protocol analysis. Baseline characteristics and outcome parameters were summarized with descriptive statistics. The between-group difference in the primary outcome (the incidence of delirium during the first eight days after the initiation of study medication) was analyzed using a $\chi^2$ test. The primary outcome was also analyzed using multivariable logistic regression including the stratification variable (treatment center) and imbalanced baseline variables into the model. Effect size was expressed in an adjusted odds ratio (OR). Continuous secondary outcome measures were analyzed using two-group t-tests or Mann-Whitney tests where appropriate. A predefined additional analysis was performed using data from patients with cognitive impairment at baseline because these patients may react differently to medication due to existing cerebral neurodegeneration dependent on the occurrence and duration of delirium. No interim analyses were performed. P-values < 0.05 were considered statistically significant.

Role of the funding source
This study is funded by an unrestricted grant from the Dutch National Program of Innovative Care for vulnerable older persons (grant number: 311020301). This is a program from ZonMw, a Dutch institute that funds health research and stimulates the use of knowledge to help improve health and healthcare in the Netherlands. Apart from the funding, there was no further involvement e.g. in the actual data collection, analysis, or preparation for publication. This investigator-initiated study is not sponsored by the manufacturer of Circadin®.

Results

Patients, recruitment and baseline data
Between November 2008 and May 2012, a total of 850 patients were assessed for eligibility within 24 hours of admission. Consent was obtained from 452 of the 748 eligible patients (60%) and was provided by substitute decision makers in 37% of these cases. After randomization, eight patients were excluded due to logistics failure. Thus, 444 patients were allocated to the trial treatment: 219 patients to melatonin and 225 patients to placebo. A number of patients were additionally excluded (n=33 in melatonin group, n=33 in placebo group) because the primary endpoint could not be measured. This concerned, for example, 18 patients who withdrew their consent. Four of these patients were cognitively impaired. The primary reasons for this withdrawal of consent were: second thoughts (n=8); withdrawal by the substitute decision maker (n=8); miscellaneous (n=2). An additional 31 patients with delirium were excluded. They should not have been included in the first place; however, due to the nature of the syndrome and the required observation time of 24 hours, the delirious state became more apparent at one day after inclusion. Of the 378 patients in the intention to treat analysis (114 in the AMC, 264 in the
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Tergooi Hospitals), 186 patients were randomly assigned to melatonin, and 192 patients to placebo (Figure 1). Baseline characteristics were well matched between the two study groups although the percentage of patients who used benzodiazepines at home was higher in the placebo group whereas more patients in the melatonin group had experienced a prior delirium (Table 1). The mean age was 84 years, 63% lived at home prior to admission and 56% showed cognitive impairment.

Figure 1: Flow Diagram; enrollment, randomization and follow-up

No effect of melatonin on the incidence of delirium was demonstrated; the incidence in the melatonin group was 55/186=29.6% versus 49/192=25.5% in the placebo group 95% confidence interval for the difference = -0.05% to 13.1%; p=0.38; (Table 2). Multivariate logistic regression, adjusted for the stratification variable (treatment center) and baseline imbalance (benzodiazepines use at home and prior delirium) also did not show a treatment effect (OR 1.14, 95% CI 0.71-1.83; p=0.58).
Fewer patients on melatonin experienced a long lasting episode of delirium (> two days) compared with patients receiving placebo (p=0.02) although the median duration of delirium days (2 days) was equal (Figure 2). The severity of delirium, expressed as the number of patients receiving 3 mg or more of haloperidol, was 45.5% in the melatonin group and 53.1% in the placebo group (p=0.44). In both treatment groups, the median length of hospital stay was 11 days (p=0.40). The median use of antipsychotics was 4.0 mg
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in the melatonin group and 5.0 mg in the placebo group (p=0.18). The median use of benzodiazepines, in oxazepam equivalents, was 63.4 mg (median) in patients assigned to receive melatonin and 75.0 mg in patients assigned to receive placebo (p=0.60). Mortality during hospital stay was 2.2% in the melatonin group and 2.1% in the placebo group (p=0.96). At three months, no between-group differences were demonstrated with regard to cognitive or functional outcomes. The median Katz-ADL index score in both groups was 9.0 (p=0.75). Cognitive impairment was present in 65% of the patients in the melatonin group versus 69.5% in the placebo group (p=0.41). We did not demonstrate a difference in the 3-month mortality rate, which was 10.3% and 10.8% in the melatonin and placebo group, respectively (p=0.90).

An additional analysis was performed in patients with cognitive impairment at baseline. No effect of melatonin on the incidence of delirium was demonstrated (treatment group 43/104 = 41.3% versus 37/106 = 34.9% in the placebo group (p=0.36)). In the melatonin group, fewer patients experienced a delirium episode of longer than two days (p=0.01).

Table 2: Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>Melatonin (n= 186)</th>
<th>Placebo (n= 192)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of delirium — no. (%)</td>
<td>55 (29.6)</td>
<td>49 (25.5)</td>
<td>0.38</td>
</tr>
<tr>
<td>Secondary outcomes (delirious patients)</td>
<td>(n=55)</td>
<td>(n=59)</td>
<td></td>
</tr>
<tr>
<td>Duration of delirium — days (IQR)</td>
<td>2 (1.0-3.0)</td>
<td>2 (1.0-3.0)</td>
<td>0.53</td>
</tr>
<tr>
<td>Delirium duration &gt; 2 days — no. (%)</td>
<td>14 (25.5)</td>
<td>23 (53.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Severity of delirium — no. (%) ( ≥ 3 mg haloperidol during delirium)</td>
<td>25 (45.5)</td>
<td>26 (53.1)</td>
<td>0.44</td>
</tr>
<tr>
<td>Length of hospital stay — days (IQR)</td>
<td>11 (6.0-14.5)</td>
<td>11 (8.0-17.0)</td>
<td>0.40</td>
</tr>
<tr>
<td>Use of antipsychotics — mg (IQR)</td>
<td>4.0 (1.5-7.5)</td>
<td>5.0 (3.8-8.3)</td>
<td>0.18</td>
</tr>
<tr>
<td>Use of benzodiazepines — mg (IQR) (in oxazepam equivalents)</td>
<td>63.4 (33.4-104.3)</td>
<td>75.0 (33.3-131.3)</td>
<td>0.60</td>
</tr>
<tr>
<td>Secondary outcomes (all patients)</td>
<td>(n= 186)</td>
<td>(n= 192)</td>
<td></td>
</tr>
<tr>
<td>Mortality during admission — no. (%)</td>
<td>4 (2.2)</td>
<td>4 (2.1)</td>
<td>0.96</td>
</tr>
<tr>
<td>Secondary outcomes at three months (all patients)</td>
<td>(n=147)</td>
<td>(n=159)</td>
<td></td>
</tr>
<tr>
<td>Katz-ADL —score (IQR)</td>
<td>9.0 (5-13)</td>
<td>9.0 (5-13)</td>
<td>0.75</td>
</tr>
<tr>
<td>Missing — no. (%)</td>
<td>3 (2.1)</td>
<td>6 (3.5)</td>
<td></td>
</tr>
<tr>
<td>Cognitive impaired — no. (%)</td>
<td>87 (65.0)</td>
<td>105 (69.5)</td>
<td>0.41</td>
</tr>
<tr>
<td>Mortality — no. (%)</td>
<td>39 (10.3)</td>
<td>41 (10.8)</td>
<td>0.90</td>
</tr>
</tbody>
</table>

Data denote medians (IQR) or numbers (%).
Discussion
In this multi-centre double-blind randomized controlled trial that involved elderly patients who underwent acute surgery for hip fracture, we observed that there was no effect of melatonin on the incidence of delirium. The per protocol analysis did not yield any other result. Also, there was no effect in the subgroup of patients who received the study medication before operation. However, we observed that fewer patients on melatonin experienced a delirium of longer than two days when compared with patients receiving placebo although the median duration of delirium days (2 days) was equal. There were no between-group differences in the other secondary outcome parameters during hospital admission and at the three-month follow-up.

The results of this study indicate that in vulnerable elderly patients with hip fracture, melatonin is not effective in preventing post-operative delirium. Recently, two randomized controlled trials showed a substantial decrease in the incidence of delirium in the melatonin group of 33% to 9% and 31% to 12%.(14, 15) The first study, conducted in elective surgery patients, had some methodological quality drawbacks due to a lack of clarity on the randomization procedure and blinding methods.(15) With regard to the
latter study, there are two important differences when compared with our study. (14) That study achieved a reduction in incidence of delirium of 31% to 12% in patients admitted to an internal ward and patients were treated prophylactically with 0.5 mg melatonin. To address the first point: previous measurements in the AMC showed an incidence of delirium of approximately 50% in hip fracture patients. (30) In this study, which was performed within the same wards at five years later, the incidence was revealed to be approximately 30%. Improvement in perioperative care by all involved specialties including supportive care by our geriatric consultation team likely underlies this remarkable decrease in incidence of delirium. (31, 32) In view of this relatively low incidence rate in this vulnerable patient group with major precipitating factors, e.g. hip fracture followed by acute surgery, it may be difficult to achieve any additional treatment effect. To address the second point: we used 3 mg of melatonin because this dose is the most frequently used dose in studies with melatonin including clinical trials. However, information on the effects of melatonin supplementation, on required doses and on supplementation durations is lacking. (33) This higher dose used in our study may have influenced the physiological concentrations during the day and therefore, the effect.

The median duration of delirium was similar between the groups. However, there is some indication that perioperative melatonin supplementation results in fewer patients with long durations ( > 2 days) of delirium. Any reduction in the time suffering from delirium is important as delirious experiences involve very unpleasant feelings, such as fear and anxiety or a feeling of being threatened. Many patients have unpleasant memories and flashbacks. (34)

Melatonin has chronobiotic and nonchronobiotic properties. It is possible that melatonin simply resets the sleep-wake cycle via its influence on the biological clock. (35) Melatonin may otherwise play a direct role in the pathophysiology of delirium. Delirium is thought to be primarily caused by central nervous system inflammation and dopaminergic dysfunction. Melatonin is one of the many anti-inflammatory molecules that are produced at the sites of lesions during the recovery phase of an inflammatory response, and it is involved in the modulation of central dopaminergic functions. (36-40) The fact that these actions require time to become effective after supplementation could underlie the finding that melatonin was not effective on the incidence but that it could affect duration after a critical period of two days. (41)

The strength of this study is our pragmatic trial approach with a minimal set of exclusion criteria. The inclusion percentage was 60% of eligible patients. This percentage is higher than in any of the comparable studies in vulnerable elderly populations. (42) Therefore, these results have good external validity and can be extrapolated to other hip fracture populations. (43) Furthermore, we applied a clear delirium definition using the gold standard for delirium. (27)

A limitation of this study is the loss of statistical power due to multiple reasons as explained in flow chart. This high rate of attrition is inherent to studies performed in vulnerable older patients, as the two main independent factors that are related to
increased attrition are increasing age and cognitive impairment.(44) We initially reached the predefined sample size of 452 patients but due to the exclusion of a number of patients after randomization (see Figure 1), we were only able to analyze data from 378 patients, which increases the probability of a type II error. However, given the absence of any treatment effect of melatonin on the incidence of delirium, a much larger sample size would have been necessary to reach statistical significance and we argue that this would not have resulted in any clinical relevant effect on incidence. Also, we had planned in advance to express the severity of delirium using the Delirium Rating Scale-Revised (DRS)- 1998 score.(16, 45) A trajectory of scores would be most informative but showed unfeasible because of relatively short delirium episodes. Therefore, we decided to use the total amount of prescribed haloperidol. Haloperidol is a clinically more relevant outcome measure as side effects of this drug are more prevalent in patients on higher (cumulative) doses. Because the duration of most delirium episodes was one or two days and our protocol prescribed twice daily 0.5 mg doses, we chose a cut-off of \( \geq 3 \) mg of total use of haloperidol as an indicator of severity.

In conclusion, our study shows that in elderly patients undergoing acute surgery for hip fracture, perioperative melatonin supplementation is not effective in decreasing the incidence of delirium. However, melatonin reduced the number of patients who had a long lasting episode of delirium and thereby reduces the duration of unpleasant delirious experiences for these patients. Future research should focus on different patient populations receiving melatonin in case of delirium presence and compare its potential effects head-to-head to antipsychotics in delirious hip fracture patients. Furthermore, melatonin supplementation should be investigated in other populations with circadian sleep-wake rhythm disturbances and a high incidence of delirium, such as ICU patients. Additional studies should also focus on variations in melatonin levels and different doses of melatonin.
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Reference List

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