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Long-term effects of melatonin on quality of life and sleep in haemodialysis patients (Melody study): a randomized controlled trial

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Disturbances of sleep–wake rhythm are frequently reported in haemodialysis patients.
- The melatonin rhythm, which plays an important role in synchronization of the sleep–wake rhythm, is disturbed in these patients.
- Short term use of exogenous melatonin resulted in an improvement of sleep quality and melatonin rhythm.

WHAT THIS STUDY ADDS

- In this first long-term study on the effect of melatonin in haemodialysis patients, no improvements on quality of life or on sleep with 12 months use of exogenous melatonin were found.
- Compared with baseline and placebo, in patients who had used melatonin, higher nocturnal melatonin concentrations were reached.

AIM

The disturbed circadian rhythm in haemodialysis patients results in perturbed sleep. Short term melatonin supplementation has alleviated these sleep problems. Our aim was to investigate the effects of long-term melatonin supplementation on quality of life and sleep.

METHODS

In this randomized double-blind placebo-controlled trial haemodialysis patients suffering from subjective sleep problems received melatonin 3 mg day^{-1} *vs.* placebo during 12 months. The primary endpoint quality of life parameter 'vitality' was measured with Medical Outcomes Study Short Form-36. Secondary outcomes were improvement of three sleep parameters measured by actigraphy and nighttime salivary melatonin concentrations.

RESULTS

Sixty-seven patients were randomized. Forty-two patients completed the trial. With melatonin, no beneficial effect on vitality was seen. Other quality of life parameters showed both advantageous and disadvantageous effects of melatonin. Considering sleep, at 3 months sleep efficiency and actual sleep time had improved with melatonin compared with placebo on haemodialysis days (difference 7.6%, 95% CI 0.77, 14.4 and 49 min, 95% CI 2.1, 95.9, respectively). At 12 months none of the sleep parameters differed significantly from placebo. Melatonin salivary concentrations at 6 months had significantly increased in the melatonin group compared with the placebo group.

CONCLUSIONS

The high drop-out rate limits the strength of our conclusions. However, although a previous study reported beneficial short term effects of melatonin on sleep in haemodialysis patients, in this long-term study the positive effects disappeared during follow up (6–12 months). Also the quality of life parameter, vitality, did not improve. Efforts should be made to elucidate the mechanism responsible for the loss of effect with chronic use.

Introduction

Given the increasing prevalence of end-stage renal disease (ESRD) and the associated burden on health status, treatments to improve the clinical outcome and quality of life of haemodialysis patients are urgently needed [1, 2]. Between 50–80% of haemodialysis patients complain of night-time sleep disturbances [3] and about 30% of haemodialysis patients report excessive daytime sleepiness [4, 5], having a negative influence on these patients' vitality and general and psychological health [6, 7]. Improvement of sleeping patterns is associated with a decrease in inflammatory activity and oxidative stress in haemodialysis patients [8]. Despite the broad array of disabling sleep disorders that are identified in ESRD, including sleep apnoea and restless legs, surprisingly little attention is paid to sleep disorders that are caused by dysfunction of the biological clock in these patients [5, 9].

The human biological clock is driven by the master pacemaker that resides in the suprachiasmatic nucleus (SCN) in the brain. It coordinates circadian rhythms, fluctuations of bodily functions that recur in a cycle of about 24 h, such as the sleep–wake rhythm [10]. Biological clock disturbances are not only associated with sleep problems. A number of studies point to the inter-relationship between dysfunction of the biological clock and the development of kidney disease in animals [11–13] and to the development of diabetes [14]. In humans, disturbances of the biological clock, e.g. by working nightshifts, are associated with the development of breast cancer [15] and depression [16].

The pineal hormone melatonin is an important marker of biological clock-time and plays an important role in circadian sleep–wake rhythm. In healthy persons in normal environmental conditions, melatonin secretion shows a clear circadian rhythm with low levels during the day and high levels at night. The increase in melatonin concentration in the evening correlates with an increase in evening sleep propensity and onset of sleep [17–19]. Interestingly melatonin secretion decreases as kidney function declines [20] and in many daytime haemodialysis patients the nocturnal melatonin surge is even absent [21]. Melatonin does not only exert effects on timing of sleep. Blood pressure, like many physiological processes, shows a 24 h rhythm. A 'non-dipping blood pressure profile' [22] which often exists in daytime haemodialysis patients [23] is associated with an impaired nocturnal endogenous melatonin secretion [24].

The alleged association between reduced melatonin secretion and disturbances in sleep and blood pressure regulation in ESRD prompted studies investigating the effect of exogenous melatonin. Previously we reported that short term administration of exogenous melatonin in haemodialysis patients markedly improved subjective and objective sleep parameters [21]. Based on these beneficial effects on sleep of short term use of melatonin and the known influence of sleep problems on quality of life, the present study was designed to investigate the effects of melatonin administration during 12 months on sleep and quality of life in daytime haemodialysis patients who had subjective sleep problems according to the Epworth Sleepiness Scale (ESS) and increased sleep onset latency.

Methods

Study design

The Melody trial is a randomized double-blind placebo-controlled clinical trial conducted in five large regional hospitals in the Netherlands that provide haemodialysis treatment to approximately 500 patients. The institutional review boards approved the protocol of the study (ClinicalTrials.gov: NCT00388661, EudraCT-number 2006–005719-89) and written informed consent was obtained from all patients. The study was conducted according to the Declaration of Helsinki. The study design is shown in Figure 1.

Setting and participants

Stable haemodialysis patients aged 18 to 85 years with a haemodialysis history of at least 3 months and adequate dialysis efficacy were eligible for inclusion. Patients could participate when they suffered from subjective sleep problems at baseline according to the Epworth Sleepiness Scale (ESS) questionnaire and their mean sleep onset latency measured by means of actigraphy was longer than 15 min. The ESS measures subjective daytime sleepiness and has

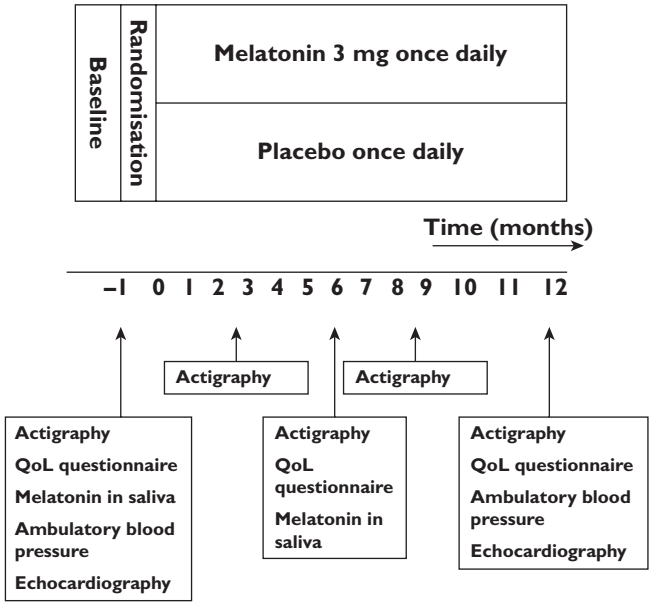

Figure 1

Study design. The study measurements and the dates of measurement are displayed

Table 1
Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age 18–85 years	Current melatonin use
Stable daytime haemodialysis (>3 months)	Known hypersensitivity to melatonin
Subjective sleep problems	Severe psychological or neurological disease
Mean sleep onset latency >15 min	Unstable angina pectoris
	NYHA class IV heart failure
	Pregnancy
	Participation in another clinical trial 1 month prior to the start of this study

been used in haemodialysis patients before [7]. Table 1 sums up the inclusion and exclusion criteria.

Daytime haemodialysis patients were randomized to receive melatonin 3 mg immediate release tablets (Pharma Nord®, Vejle, Denmark) or placebo tablets (Pharma Nord®, Vejle, Denmark) for 12 months. Study medication was prescribed by the participating physicians of the patients. Random allocation of 68 study medication kits was made in block sizes of four. Study treatment was started throughout the year shortly after inclusion of the patient. Patients were instructed to take their study medication at 22.00 h daily. Dialyzate flow, blood flow and dialyzer membrane type were chosen according to standard practice of the participating dialysis centres.

Outcome measures

Quality of life questionnaire The primary outcome measure was defined as an improvement of at least 15 points in the vitality score of the Medical Outcomes Study Short Form 36 (MOS SF-36). The Dutch version of this validated quality of life questionnaire was used at baseline, 6 and 12 months to measure physical, functional, mental and social health [25].

Sleep measurements: actigraphy Secondary outcome measures were reduction in sleep onset latency and improvement of sleep efficiency and actual sleep time. Sleep parameters were investigated by means of actigraphy. Actigraphy is an established sleep monitoring method that records wrist movements and automatically discriminates rest–activity patterns interpreted in terms of sleep and wake periods [26]. Model Actiwatch-L (Cambridge Neurotechnology Ltd®, Cambridge, United Kingdom) actiwatches validated against polysomnography in the haemodialysis population were used [27].

The actiwatch was placed on the wrist of the arm without graft or fistula. Patients were asked to record bed times and rise times on a registration form. Actiwatch Activity & Sleep Analysis version 5.32 was used to score 1 min epochs of actigraphic data as sleep or wake [28]. The following parameters were calculated according to standardized methods [29]: sleep onset latency (SOL), which is the time period between 'lights off' and sleep onset, sleep efficiency (SE), which is the actual sleep time divided by time in bed and is a well recognized measure of sleep quality and actual sleep time (AST), defined as the total duration of recorded sleep periods. Each episode of actigraphy recordings was carried out during 5 consecutive days and nights (Figure 1).

Melatonin rhythm Melatonin concentrations in saliva were measured at baseline and after 6 months both on the night after daytime haemodialysis and subsequent non-dialysis night at 21.00 h, 23.00 h, 01.00 h, 07.00 h and 09.00 h (Figure 1). Patients collected saliva samples by slowly moving a cotton plug (Salivetten®, Sarstedt Numbrecht, Germany) in their mouth for 1 min. They were instructed not to take their study medication on the days of saliva sampling. Five patients in the melatonin group reached melatonin concentraions >50 pg ml^{-1} at 6 months. Since the authors doubt that these reflect endogenous concentrations considering the low baseline concentrations and the melatonin concentrations reached by the other patients in the melatonin group, it could not be excluded that these patients had taken their study medication on the day of saliva sampling despite the instructions. This could not be checked reliably by the investigators, since melatonin concentrations were determined by batch processing, patients had to be asked in retrospect several weeks to months later. The melatonin measurements of these patients were therefore excluded from analysis.

Sampling was performed under semi-constant routine conditions in a dimly lit room (<20 lux) at home [30]. Saliva samples were kept at −18°C until analysis. After centrifugation of the cotton plugs, aliquots of 400 µl of saliva sample were transferred into assay tubes. Melatonin concentrations were measured using the commercially available RIA kit (Bühlmann Laboratories, Schönenbuch, Switzerland) with a detection limit of 0.5 pg ml^{-1}.

Dipping profile of blood pressure Patients were asked to wear an ambulatory blood pressure monitor (SpaceLabs® ItéMedical, Tiel, the Netherlands) for 24 h at baseline and at 12 months. Measurements were taken according to local standards of the participating hospitals. Dipping profile was determined by a decrease in systolic blood pressure of at least 10% during the night compared with daytime systolic blood pressure [22].

Echocardiography At baseline and at 12 months echocardiography was performed according to a standard protocol. The echocardiogram was evaluated by an experienced cardiologist blinded for allocated treatment. The following

standard parameters were assessed to quantify cardiac dimensions: left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD), left ventricular post wall diameter end diastolic (LVPW), left ventricular intraventricular septal end diastolic diameter (LVIVS), left ventricular ejection fraction (LVEF) and left ventricular mass index (LVMI)

Statistics A required sample size of 27 patients per group was calculated based on a clinically relevant difference of 15 points on the MOS-SF36 vitality scale between melatonin and placebo and a standard deviation of 18.9 points based on a previous study (power 0.90, α 0.05) [31]. Since a 25% drop-out rate was expected, the final projected sample size was 34 per group.

Mean values and standard deviations of baseline characteristics, quality of life questionnaire and sleep parameters were calculated. For variables that were non-normally distributed, medians and interquartile ranges were determined.

Sleep parameters were calculated for haemodialysis days and non-haemodialysis days separately.

An intention to treat analysis of quality of life results and sleep measures was performed. Data were analyzed using longitudinal linear regression analysis in SPSS version 19 with the mixed models procedure. This is a sophisticated method suitable for longitudinal data on a time-dependent continuous outcome and several time-dependent and time-independent covariates and factors. The method takes into account that measurements within individuals are more correlated than measurements between individuals. The validity of this method is not hampered by missing values. In the longitudinal linear regression analysis the sleep and quality of life parameters studied were analyzed as dependent variables using study group (melatonin or placebo), time and their interaction as independent variables. This allows for the effect of the intervention to change over time. The effect estimates and their 95% confidence intervals were taken from the model and marginal means per group per time point were calculated and plotted.

Variables that were non-normally distributed were log-transformed before analysis. Their means and confidence intervals were transformed back and then plotted. These can be interpreted as medians and their 95% confidence intervals.

The drop out rate exceeded the predefined expected drop out rate. We therefore performed a *post hoc* sample size calculation on the secondary endpoint sleep onset latency, based on actual study inclusion rate. This calculation was done with a suitable formula for longitudinal data analysis, which takes into account the added information by multiple measurements, while correcting for the higher correlation between multiple measurements in one patient [32].

Results

Sixty-seven daytime haemodialysis patients were included from April 2007 until March 2009, forty-two patients completed the study. Reasons for loss to follow-up are shown in Figure 2.

Clinical characteristics between the melatonin and placebo group at baseline did not differ (Table 2). Some baseline values of quality of life and sleep parameters differed between the melatonin and placebo group and, therefore, we corrected for baseline values in our analyses. Throughout the study no side effects of melatonin were reported.

Quality of life

The primary outcome parameter vitality did not improve with melatonin treatment compared with placebo after 12 months (difference −1.9%, 95% CI −12.6, 8.7). Regarding the other quality of life parameters, physical functioning decreased in the melatonin group compared with placebo after 12 months (difference −11.4%, 95% CI −21.8, −1.1), whereas general mental health increased in the melatonin group compared with placebo after 12 months (difference 9.3%, 95% CI −0.1, 18.7, $P = 0.052$). Emotional role activities and last year's health change tended to improve in het melatonin group (difference 29.8%, 95% CI −1.4, 61.0 after 12 months and difference 14.6%, 95% CI −0.6, 29.8 after 6 months, respectively). However there was a tendency towards decreased physical role activities in the melatonin group after 12 months compared with placebo (difference −22.2%, 95% CI −49.2, 4.8). Other parameters did not significantly improve or worsen with melatonin treatment compared with placebo. The results of all quality of life parameters are shown in Figure 3.

Actigraphy

In Figure 4 the median sleep onset latency, mean sleep efficiency and mean actual sleep time are shown for haemodialysis and non-haemodialysis days separately. There were no significant differences for these parameters between the two groups at baseline. At 3 months, sleep efficiency (difference 7.6%, 95% CI 0.77, 14.4) and actual sleep time (difference 49 min, 95% CI 2.1, 95.9) had improved with melatonin treatment compared with placebo treatment. These effects were not seen on non-haemodialysis days. At 6, 9 and 12 months, no significant differences in any of the sleep parameters between melatonin treatment and placebo were seen.

Melatonin in saliva

Figure 5 shows mean melatonin concentrations in saliva on a haemodialysis day and on a non-haemodiaysis day. At baseline, a clear nocturnal melatonin rise was absent in all patients. After 6 months of melatonin treatment, nocturnal melatonin concentrations had significantly increased in

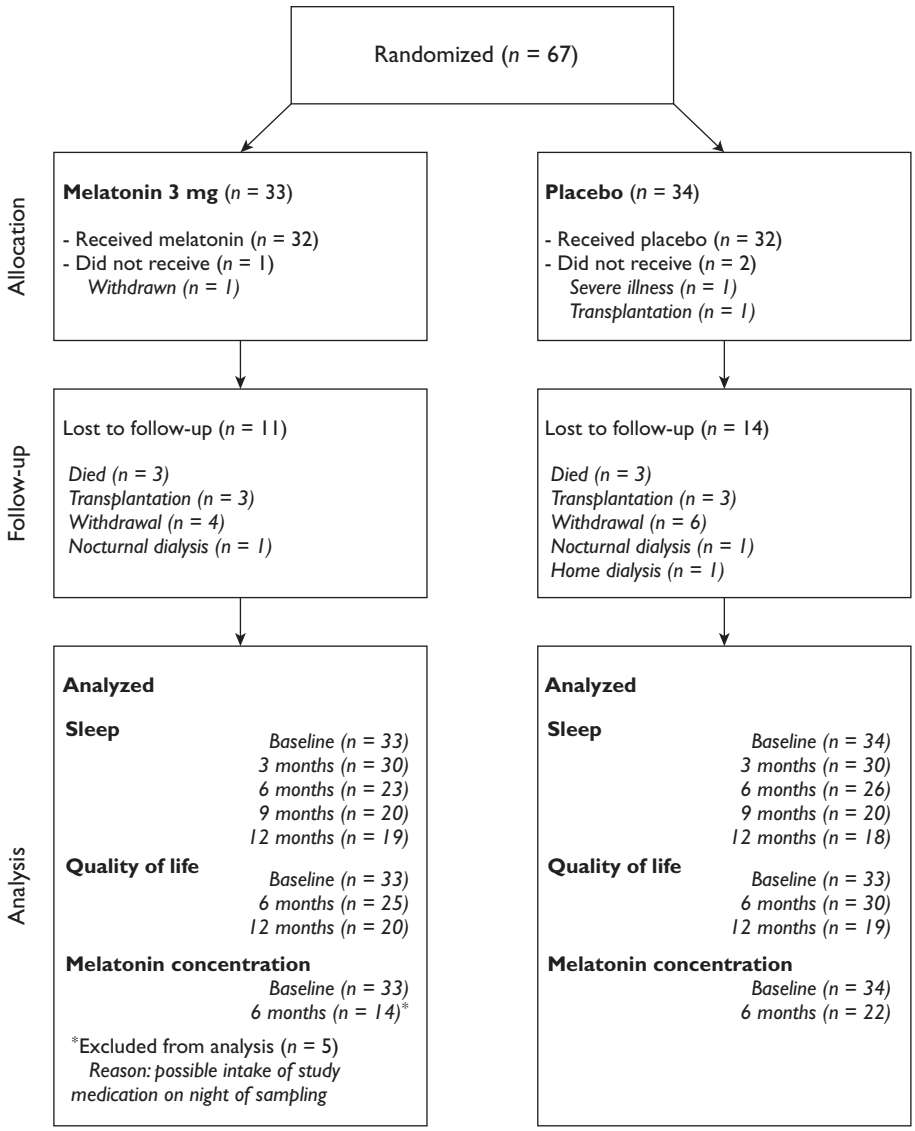

Figure 2
Study profile

the melatonin group compared with the placebo group at all measured time points as well as exposure to melatonin over the entire night on both haemodialysis and non-haemodialysis days after correction for baseline using general linear methods. Melatonin concentrations at 6 months in the placebo group did not differ significantly from baseline values.

Melatonin concentrations of patients that were left out of Figure 5 are shown in Table 3.

Dipping profile of blood pressure and echocardiography

Data collection of ambulatory blood pressure measurements was hampered and therefore analysis of blood pressure effects of melatonin could not be performed. Data on blood pressure measurements at both baseline and 12 months were available in only 13 (39%) patients in the melatonin and 14 (41%) patients in the placebo group. In the melatonin group six patients exhibited a dipping profile and seven patients exhibited a non-dipping profile at baseline. In the placebo group these were five and nine patients, respectively. No obvious intra-individual change in dipping status was observed at the end of the study. Although melatonin supposedly has blood pressure lowering effects [24, 33], we were not able to show changes in nocturnal blood pressure dipping profile since the number of patients was too small to draw definite conclusions due to drop-out. In addition no changes in cardiac dimensions measured by echocardiography were seen (data not shown).

Table 2
Baseline characteristics

	Melatonin	Placebo
Number of patients included	33	34
Number of males (%)	19 (58)	22 (65)
Age (years), mean (SD)	65.5 (11.7)	64.4 (12.0)
Kt V^{-1}* per week, including residual kidney function, mean (SD)	4.1 (0.6)	4.2 (0.7)
Body mass index (kg m^{-2}), mean (SD)	26.3 (4.4)	25.6 (5.4)
Dialysis duration per week (h), mean (SD)	11.2 (1.2)	11.3 (1.9)
Dialysis vintage (months), mean (SD)	30.6 (27.3)	28.3 (22.5)
24 h ambulatory blood pressure		
Systolic(mmHg), mean (SD)	128 (26)	121 (17)
Diastolic(mmHg), mean (SD)	71 (15)	69 (10)
Sleep		
Sleep onset latency on haemodialysis days (min), median (interquartile difference)	23.5 (24.5)	25.2 (33.1)
Sleep onset latency on non-haemodialysis days (min), median (interquartile difference)	20.3 (30.0)	25.0 (31.0)
Sleep efficiency on haemodialysis days (%), mean (SD)	69.7 (16.5)	69.9 (13.1)
Sleep efficiency on non-haemodialysis days (%), mean (SD)	66.3 (19.7)	64.9 (18.1)
Actual sleep time on haemodialysis days (min), mean (SD)	342 (128)	363 (80)
Actual sleep time on non-haemodialysis days (min), mean (SD)	318 (129)	323 (82)
Quality of life		
Physical functioning (%), mean (SD)	44 (25)	45 (28)
Social functioning (%), mean (SD)	55 (22)	58 (26)
Role activities – physical (%), mean (SD)	35 (41)	36 (41)
Role activities – emotional (%), mean (SD)	48 (45)	67 (43)
General mental health (%), mean (SD)	68 (19)	72 (19)
Vitality (%), mean (SD)	49 (16)	48 (22)
Bodily pain (%), mean (SD)	63 (25)	62 (30)
General health perception (%), mean (SD)	36 (17)	37 (20)
Last year's health change (%), mean (SD)	49 (25)	56 (29)

*Kt V^{-1}, index of dialysis adequacy, fractional reduction of urea.

Discussion

This is the first long-term study on the effects of melatonin on quality of life and sleep in haemodialysis patients. In a previous study beneficial short term effects of melatonin were reported, yet in this study we failed to demonstrate that the melatonin effects persist in the long run. This finding is of particular importance since, although hypnotics are frequently prescribed for longer periods of time, few randomized controlled trials address long-term effects and observational studies show that persistent use of hypnotics may be associated with worse outcomes [34].

Vitality measured as part of the MOS-SF-36 quality of life questionnaire was delineated as the primary outcome parameter of the study. No effect of melatonin on vitality was observed in this study. With regards to the other quality of life parameters we did find a positive long-term effect of melatonin on general mental health and tendencies towards improvement of emotional role activities and last year's health change, but on the other hand we found a negative long-term effect of melatonin on physical functioning and a tendency towards decreased physical role activities. Therefore we conclude that with the used dosage regimen of melatonin, it has no substantial positive effect on quality of life. Nevertheless the possibility still exists that melatonin may contribute to improvements in quality of life, since in other patient populations improvements of the MOS-SF36 questionnaire were observed after melatonin treatment [31]. Efforts should now be made to elucidate if the melatonin dosage regimen can be optimized, resulting in improvements on quality of life, e.g. due to better sleep.

In addition, no clinically relevant long-term improvements on sleep were found in the melatonin group although the previously reported short term beneficial effects of melatonin on sleep efficiency and actual sleep time were confirmed after 3 months of melatonin use [21]. However, these findings were apparent only on haemodialysis days.

Due to the higher than the expected 25% drop-out rate, which we accounted for in our projected study size it may be questioned whether the lack of a persisting effect of melatonin on sleep was caused by loss of power of the study or was related to the true absence of a long-term melatonin effect on sleep. In order to estimate attained study power a *post hoc* power calculation was performed. The original power calculation was made on vitality using the standard formula. However since the study consists of a large number of repeated values and the effects of melatonin on sleep were deemed important, a *post hoc* sample size calculation suitable for longitudinal data analysis was performed on one of the sleep parameters, sleep latency. Based on the number of follow-up measurements, intra-individual correlation coefficient and standard deviation of the actual patient data, 28 patients per group were needed to show significantly a clinically relevant 20 min difference in sleep onset latency (power 0.80). This number of patients was only present at baseline and at 3 months. Therefore, since there was a substantial decline in number of participants during the study period, a lack of power could be the reason for the absence of a statistically significant difference in sleep parameters at 6 months and later. However, even though group sizes were too small to conclude definitely on the long-term effect of melatonin on sleep, the courses of the sleep parameters over time in Figure 4 render it unlikely that long-term positive effects of melatonin would have been identified if group sizes had been larger. Selective loss-to-follow-up could obscure such a positive effect (if those on melatonin who benefited stopped participating). This does not seem likely, given the reasons for drop out in Figure 2.

Therefore we question our original hypothesis that melatonin 3 mg administration at 22.00 h daily has a long-term positive influence on sleep. A number of possible

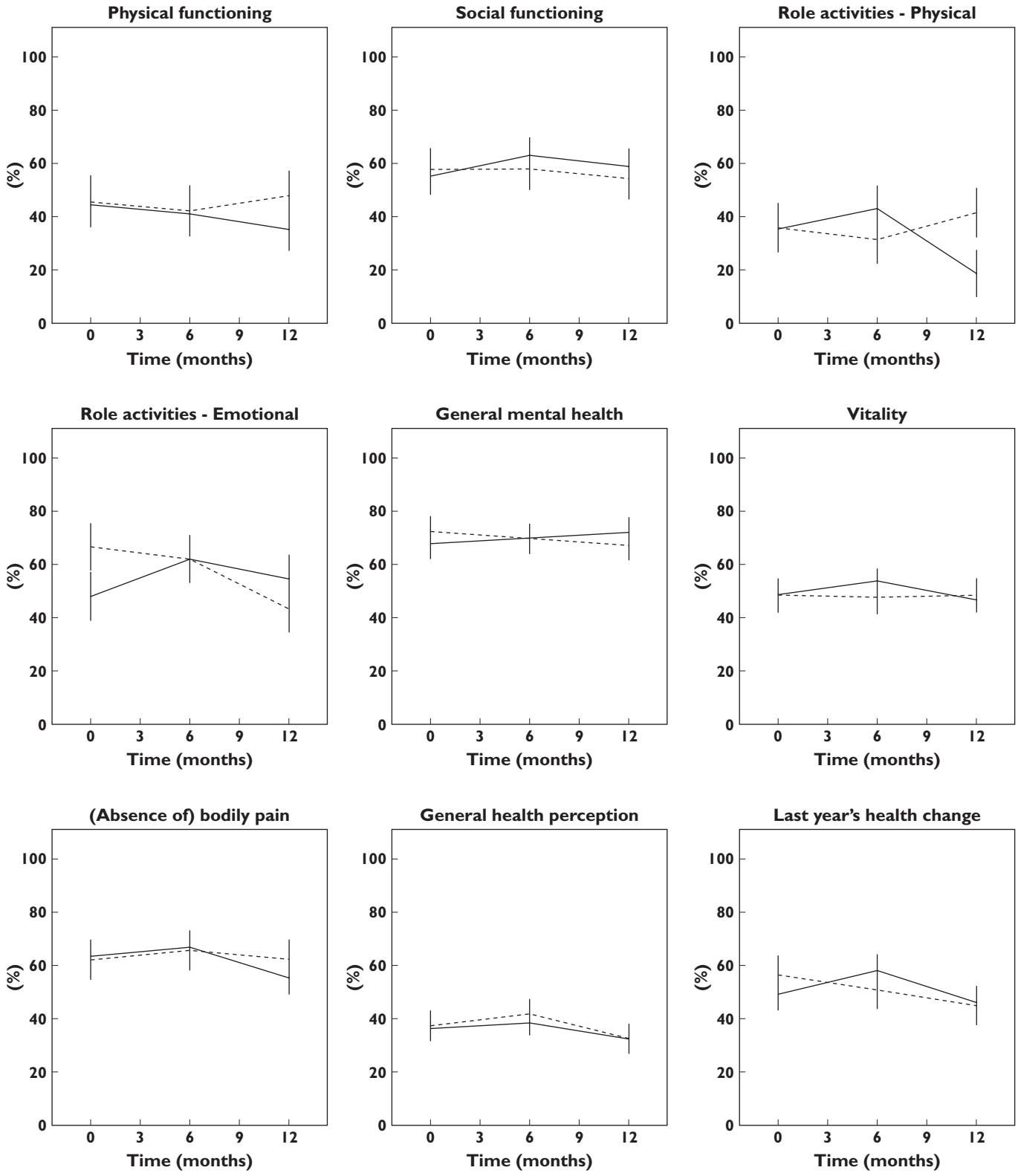

Figure 3

Quality of life. Mean predicted values of MOS-SF results (in %) of quality of life parameters physical functioning, social functioning, role activities – physical, role activities – emotional, general mental health, vitality, bodily pain, general health perception and last year's health change. Higher percentages indicate better quality of life. The horizontal axis reflects the time in months. Solid lines represent the melatonin group, dashed lines represent the placebo group. Vertical lines at the measuring point represent 95% confidence intervals

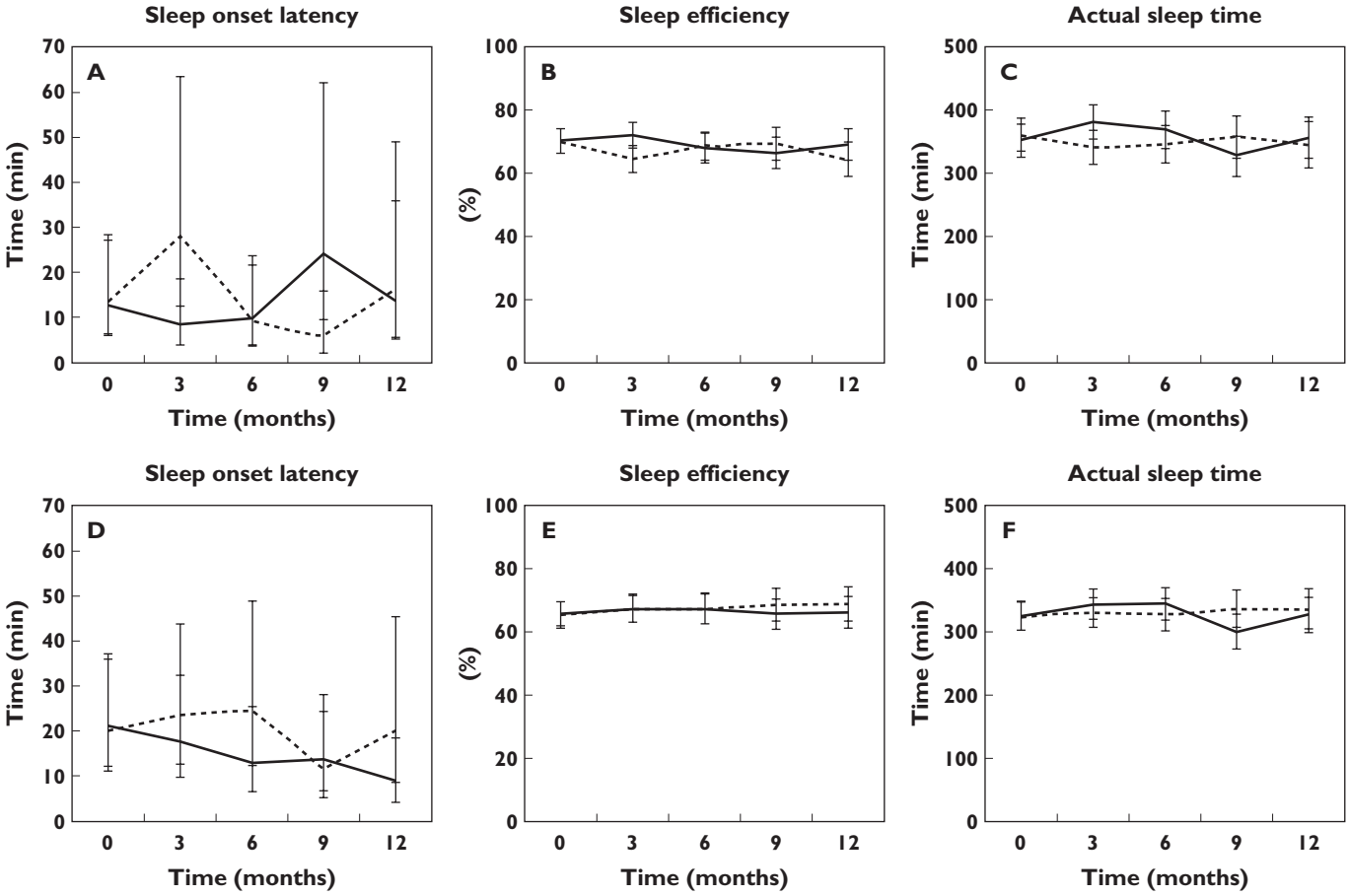

Figure 4

Sleep. Panels A to C: Results of predicted values of median sleep onset latency (A), mean sleep efficiency (B) and mean actual sleep time (C) on haemodialysis days. Panels D to F: Results of predicted values of median sleep onset latency (D), mean sleep efficiency (E) and mean actual sleep time (F) on non-haemodialysis days. Lower sleep onset latency, higher sleep efficiency and higher actual sleep time indicate better sleep. The horizontal axis reflects the time in months. Solid lines represent the melatonin group, dashed lines represent the placebo group. Vertical lines at the measuring point represent the 95% confidence intervals

mechanisms for the decline of effect on sleep exist, including inappropriate melatonin effect or dosing and inadequate time of administration. A possible explanation for the decline in hypnotic effects after 3 months may also be altered melatonin receptor sensitivity or decreased receptor density. Changes in melatonin receptor sensitivity and receptor density have been described before [35]. Indeed, hypnotic effects during 3 months of therapy have been observed in other placebo controlled studies using more traditional hypnotics, such as benzodiazepines [36], but generally the time of use of benzodiazepines for insomnia is restricted, because of loss of effect and occurrence of dependency with time of use. Since continued use of benzodiazepines is associated with an increased mortality rate, it is important to find alternative long-term therapies to treat sleep disturbances [34].

In addition, although melatonin concentrations had risen at night compared with baseline in the melatonin group, the resulting concentration curves were not optimal from a circadian point of view. Melatonin reached maximum concentrations in the early morning instead of midnight on haemodialysis days. In addition melatonin concentrations in the melatonin group were higher than in the placebo group at all time points, including the early evening and morning samples, which suggests higher than desirable daytime melatonin concentrations. This might indicate accumulation of the highly liposoluble melatonin in fatty tissues due to declining clearance and subsequent redistribution from these tissues [37]. It is important to learn more about melatonin accumulation and redistribution from other tissues in haemodialysis patients to be able to explain this different course. One could argue that a prolonged release melatonin formulation instead of an immediate release formulation would have had potential benefits on quality of sleep as described by Lemoine *et al*. in elderly people suffering from insomnia [38]. However, we question the added value in the haemodialysis population. Due to reduced kidney

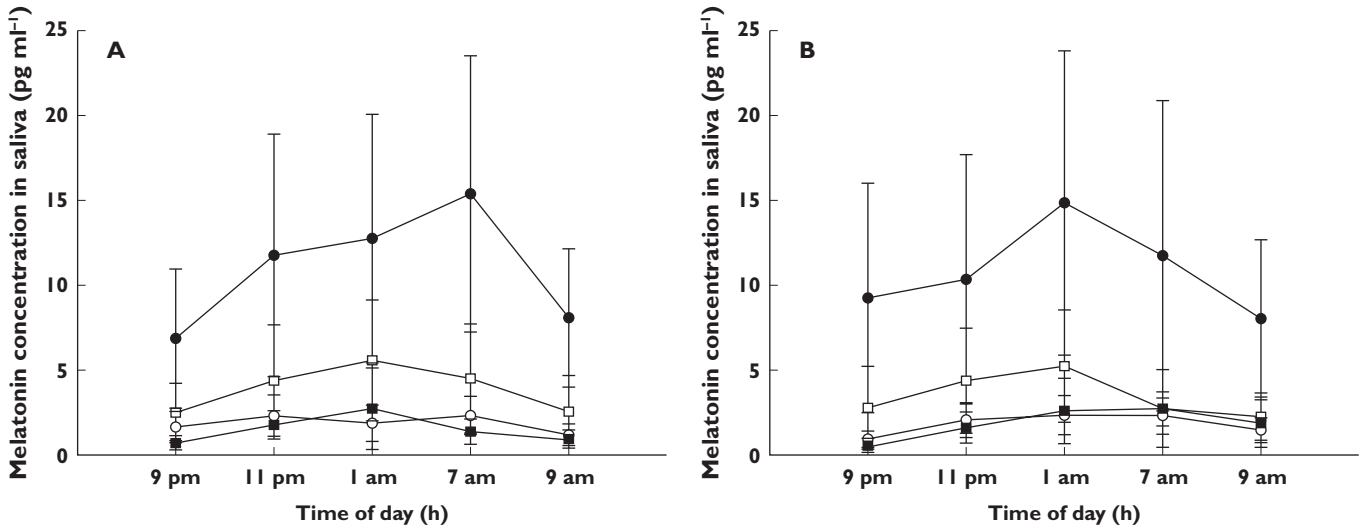

Figure 5

Mean melatonin concentration measured in saliva on the day of haemodialysis (A) and the day without haemodialysis (B). The horizontal axis reflects the time of day in hours and the vertical axis reflects the melatonin concentration in saliva in pg ml^{-1}. Lines with open circles represent the baseline measurements of the melatonin group. Lines with open squares represent the baseline measurements of the placebo group. Lines with closed circles represent the measurements after 6 months of melatonin treatment. Lines with closed squares represent the measurements after 6 months of placebo treatment. Vertical lines at the measuring points represent 95% confidence intervals

Table 3

Melatonin concentrations in saliva (pg ml^{-1}) of patients who were left out of Figure 5

	Haemodialysis day					Non-haemodialysis day				
Patient number	21.00 h	23.00 h	01.00 h	07.00 h	09.00 h	21.00 h	23.00 h	01.00 h	07.00 h	09.00 h
1	7	11.7	>50	43	>50	17.1	>50	>50	23.1	3.7
2	4.7	24.8	27.0	>50	9.6	23.5	28.4	>50	–	11.2
3	13.5	10.8	>50	>50	38.6	28.6	22.6	>50	>50	40.8
4	6.7	11.9	>50	>50	20.7	8.6	10.6	>50	>50	33.2
5	20.7	16.0	>50	31.1	24.6	12.1	10.8	>50	19.4	6.1

function and the dialysis treatment three to four times a week, the pharmacokinetics of melatonin in haemodialysis patients will probably differ from the insomniacs to a certain extent, resulting in a longer elimination half life [39]. From Figure 5 we hypothesize that accumulation within fatty tissue occurs, even with the immediate release formulation that we used. Here we might look at a physiological slow release mechanism, which in our opinion has unfavourable aspects since the difference between the day and night concentrations diminishes, which may negatively influence the opening of the so called 'sleep gate' [40] during the evening and thus may reduce the therapeutic benefit.

With respect to the elevated melatonin concentrations, the decline in physical functioning that we have found is also interesting. These results are consistent with earlier published data from various animal species in which elevated concentrations of melatonin were elicited by melatonin administration at several time points to monitor the effect of melatonin on, among others, locomotor activity. Following melatonin administration, the elevated melatonin concentrations resulted in reduced locomotor activity in the observed animals at all time points [41, 42].

Furthermore, the underlying mechanism for the lack of long-term response to melatonin may well be related to the state of refractoriness to melatonin found in photoperiodic seasonal breeders [43]. For example sheep is a photoperiodic species, in which reproductive activity is sensitive to a change in day length. Melatonin serves as an endocrine code for day length and mimicking a short day pattern by melatonin infusion can result in induction of reproduction. However, the ewes become unresponsive to stimulatory day length after a few months, although circadian melatonin patterns remain constant during this time [44].

Finally, it should be noted that the cause of prolonged sleep onset latency may be multifactorial in this highly complex patient group. The effect of melatonin in haemodialysis patients needs to be optimized and possibly combined with synergistic treatments that add to reinforcement of the circadian rhythm, such as light therapy, cognitive therapy [8], other dialysis regimens [45] and daytime exercise [46].

Future research should focus on optimization of melatonin use. The pharmacokinetics of melatonin in haemodialysis patients should be clarified. In addition to this, other melatonin dosages and dosing strategies (e.g. intermittent use to avoid accumulation) should be investigated. Timing of melatonin administration is also important and should ideally be adjusted to the patient's dim light melatonin onset (DLMO). The DLMO is the time at which the melatonin concentration rises above a certain threshold. This is the best characterization of the 24 h melatonin rhythm. It corresponds to biological clock time and is strongly associated with the circadian sleep–wake rhythm [47]. Usually DLMO will be observed about 2–3 h prior to habitual sleep [48]. With a regular western sleep schedule this will be between 20.00 h and 22.00 h. Since many haemodialysis patients do not show any DLMO at all, we have chosen to administer melatonin 3 mg tablets at 22.00 h. Perhaps for some patients this was not the optimal time of ingestion.

In conclusion, although a previous study endorsed melatonin as a safe and potentially short term drug for sleep improvement in haemodialysis patients, in this study melatonin failed as an effective long-term alternative to treat sleep disorders in haemodialysis patients. Efforts should be made to try and find methods to prolong its positive effects on sleep.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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