Chapter 6

The effects of day-time light treatment on sleep, sleep propensity, drowsiness, melatonin and depressive symptomatology in hemodialysis patients, a pilot study

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Abstract

In this open-label cross-over pilot study the effects of daytime bright light therapy on sleep, average sleep propensity, drowsiness, melatonin and depressive symptomatology in hemodialysis patients are explored. Thirteen patients received 2 hours of bright light treatment during in-hospital hemodialysis treatment 3-5 times per week for 3 weeks. Results were compared with a 3-week control period without bright light treatment. Sleep parameters were recorded with actigraphy. Melatonin concentrations were measured in saliva to determine dim light melatonin onset. Daytime sleep propensity, drowsiness and depressive symptomatology were scored with the Epworth Sleepiness Scale (ESS), Karolinska Sleepiness Scale (KSS) and the 6-item Hamilton Depression Scale (HAM-D6) respectively. Total sleep time tended to be longer with light exposure, 383 ± 125 versus 342 ± 105 minutes, p=0.07. Afternoon light tended to advance the timepoint of sleep onset compared with morning light: mean ± sd advance of 52.6 ± 57.7 minutes with afternoon light versus a delay of 11.5 ± 13.9 minutes with morning light (p=0.07). No changes in dim light melatonin onset were found. Average sleep propensity tended to improve from ESS score 11.9 ± 4.2 to 10.9 ± 4.1, p=0.06. Overall, drowsiness during hemodialysis was lower with light exposure. Mean KSS score was 1.18 point higher without bright light compared to light exposure 95% CI [0.51;1.85], p=0.001. No effect on depressive symptomatology was shown. In conclusion, there were no significant effects on nighttime sleep quality, evening melatonin concentrations and depressive symptomatology. In contrast to our current understanding of human circadian biology, light treatment in the (late) afternoon tended to have advancing effects on sleep onset. Light immediately decreased feelings of drowsiness and probably reduced daytime sleep propensity.
Introduction

Many physiological processes show circadian rhythmicity: fluctuations of bodily functions that recur in a cycle of about 24 hours. These intrinsic rhythms stay present with a near-to-24-hour period even in constant conditions without time cues from the environment. In real life the rhythms are synchronized to external clock time by environmental cues to keep in synchrony with the earth’s 24-hour light/dark cycle. The main environmental cue that serves as a Zeitgeber (‘time giver’) is light. Desynchronization between the external environment and endogenous rhythms can result in negative health effects, such as depression and physical morbidity.(1)

The melatonin rhythm is recognized as the most robust signal available for studying circadian rhythms in humans.(2) Its secretion shows a clear rhythm with low daytime levels and high nighttime levels. Melatonin’s main function is to mediate nighttime signals to the body. These signals, which are generated at night, are differently read in nocturnal animals and humans. In that sense, melatonin does not appear as the universal hormone of sleep. However, through indirect effects, melatonin is involved in sleep-wake regulation.(3) For humans, the night corresponds to the rest phase. An increase of melatonin correlates with sleep propensity and onset of sleep.(4) The onset of melatonin production, measured under dim-light conditions in serum or saliva (dim-light melatonin onset; DLMO), is used as a marker of an individual’s circadian phase.(5)

Remarkably, in patients with chronic kidney disease (CKD) nocturnal melatonin levels decrease as kidney function worsens.(6) CKD is a progressive loss of renal function that might lead to the necessity of dialysis or renal transplantation. Hemodialysis (HD) treatments remove excess fluids and waste products from the patients blood. They are generally given in a dialysis center 3 times per week during 3-4 hours. Also in many HD patients, nocturnal melatonin levels are severely reduced.(7,8) In addition, or perhaps as a consequence of reduced melatonin levels, these patients frequently suffer from nighttime sleep problems(9) and excessive daytime sleepiness, which have a negative impact on their vitality, general and psychological health.(10,11) Although a direct correlation between nocturnal melatonin levels and sleep quality has not been established, it is known that melatonin reinforces the nocturnal decrease of central body temperature which facilitates sleep propensity. There is a clear relationship between the duration of sleep and melatonin secretion. Suppressed melatonin levels due to nighttime light exposure enhances alertness.(3) Therefore the low melatonin levels in HD patients may lead to reduced sleep stimuli. Administration of exogenous melatonin to HD patients has shown some short-term beneficial effects on sleep, but no long-term effects occurred.(8,12)
Since melatonin treatment has not shown adequate treatment results and light is the main Zeitgeber for circadian control, in this pilot study we aim to explore the effects of bright light treatment on sleep in HD patients. Light can influence timing of sleep and wakefulness when given at the right time of day. These time dependent effects of light exposure have been expressed in a ‘phase response curve’ (PRC).(13) The chronotherapeutic effects of light are used in the treatment of psychiatric and certain sleep disorders.(14) However, in this study light therapy is given during HD treatment, ie between 8 am and 6 pm, depending on the individual’s HD regime. This period of day involves the least responsive part of the PRC. No phase shifting effects of light in this study are therefore expected. Instead, here we intend to amplify the light-dark cycle by giving a strong light pulse during the day. Daytime light exposure has already been shown to positively affect nighttime sleep. Whole-day bright light exposure improved sleep efficiency and total sleep time in dementia.(15) In younger individuals, bright light during working hours directly improved performance and alertness as well as perceived nighttime sleep quality. (16) The opposite, underexposure to natural light during working hours correlated with nighttime insomnia and daytime sleepiness complaints.(17)

Light has some immediate activating effects. When administered either during day or night, it immediately decreases feelings of sleepiness and fatigue.(18) Since HD patients often doze off during HD treatment, bright light exposure could hypothetically raise alertness at the time of HD treatment, thereby increasing the build-up of sleep pressure during the day (14), which might facilitate falling asleep at night.

In this study we questioned whether an effect of bright light therapy during daytime in-hospital HD treatment can be expected on sleep duration, sleep quality and timing of sleep onset. In addition, we investigated the effects of bright light therapy on daytime sleepiness, DLMO and depressive symptomatology.

Materials and Methods

Study design
In this open-label cross-over pilot study HD patients were randomized to receive light treatment first or to the control period first (figure 1). The institutional review board approved the protocol (ClinicalTrials.gov: NCT01064544). Written informed consent was obtained from all patients. The study was conducted according to the Declaration of Helsinki.
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FIGURE 1. Study design
Patients were randomized to group A who received 3 weeks of light treatment first followed by a 2-week wash out period and a 3-week control period or to group B who started with the control period, followed by 3 weeks of light treatment. Light treatment was given for 2 hours during hemodialysis sessions, depending on the patients individual HD scheme 3-5 days per week.
ESS = Epworth Sleepiness Scale; HAM-D6 = 6-item Hamilton Depression Scale; KSS=Karolinska Sleepiness Scale

Setting and participants
The study was conducted from January to April 2010 at the dialysis ward of Meander Medical Centre, Amersfoort, The Netherlands. Patients aged 18-85 years and undergoing in-hospital-HD treatment were eligible for inclusion. Table 1 shows the inclusion- and exclusion criteria.

TABLE 1. Inclusion and exclusion criteria

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| - In-hospital hemodialysis treatment  
- Age 18-85 years  
- Subjective complaints of sleep disturbances | - Serious co-morbidity that impairs participation according to the investigators (e.g. neurologic, psychiatric, blindness)  
- Use of melatonin or hypnotics  
- Use of photosensitizing drugs  
- Travel more than 1 time zone within the week prior to the start of the study |

Light treatment
During their usual HD treatment sessions, patients were exposed to Energy Light type HF3319 (Philips, Eindhoven, The Netherlands) for 3 weeks. In-hospital HD treatment is given 3-5 times a week, either in a morning or afternoon shift. Therefore light treatment was given 3-5 times a week, either in the morning or afternoon. Patients are asked for
their individual preference of morning or afternoon HD treatment, but in practice the availability within the ward’s schedule is decisive. The Energy Light was placed at 60 cm from the patient’s eyes, where the light intensity was approximately 2500 Lux. The exposure time per session with this light strength was 2 hours, as recommended by the manufacturer. Exact timing of light treatment depended on the dialysis regimen of the patient and was generally between 8 and 12 am or between 2 and 6 pm. During the control periods, patients were exposed to their usual conditions with indoor lighting and daylight that fell through windows of the room. Energy Light devices are freely available on the consumer market and comply with all applicable safety standards for light sources.

**Outcome measures**

**Actigraphy**

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.(19) Model Actiwatch-L actiwatches (Cambridge Neurotechnology Ltd®, Cambridge, United Kingdom) validated against polysomnography in the HD population were used.(20) The actiwatch was placed on the wrist of the arm without graft or fistula. Patients were asked to record bedtimes and rise times on a registration form. Actiwatch Activity & Sleep Analysis version 5.32 was used to score 1 minute epochs of actigraphic data as sleep or wake.(21)

The following parameters were calculated by this software program according to standardized methods (22): timing of sleep onset, defined as the the timepoint when the patient first falls asleep; sleep onset latency (SOL), which is the time period between ‘lights off’ and sleep onset; sleep efficiency (SE), which is the total sleep time divided by time in bed, total sleep time (TST), defined as the total duration of recorded sleep periods. Each episode of actigraphy recordings was carried out during 5 consecutive days and nights.

**Melatonin rhythm**

Melatonin concentrations in saliva were measured during one night at baseline and on the last days of the light and control period at 19:00, 21:00, 23:00, 01:00 and 07:00. Patients were instructed to collect saliva samples on the night directly following HD treatment by slowly moving a cotton plug (Salivetten®, Sarstedt Numbrecht, Germany) in their mouth for one minute. Sampling was performed under semi-constant routine conditions in a dimly lit room at home. Patients received oral and written instructions on how to perform the sampling (ie curtains closed, lights dimmed, no alcohol, bananas, caffeine and toothpaste which can all interfere with melatonin analysis). Saliva samples were kept at -20°C
until analysis. Melatonin concentrations were measured with a radioimmunoassay kit (Bühlmann Laboratories, Schönenbuch, Switzerland) with a detection limit of 0.5 pg/ml.

**DLMO calculation**

To calculate the DLMO, it is generally accepted to determine the timepoint at which a melatonin concentration of 3 pg/ml in saliva is reached.\(^{(23)}\) Since melatonin production is relatively low in many HD patients (7,8,24), this threshold might either not be reached at all or relatively late, the latter leading to falsely late DLMOs. Therefore we have decided to calculate the Dim Light Melatonin Onset as the timepoint when 25% of the individually achieved maximal melatonin concentration at any time point of any of the three circumstances (baseline, light and control period) was reached as explained earlier.\(^{(25)}\)

**Sleepiness**

Drowsiness during light exposure was measured by the Karolinska Sleepiness Scale (KSS), measured 30, 60, 90, 120 and 180 minutes after the start of light treatment. The KSS is a 9-point scale based on a self-reported, subjective assessment of the subject's level of drowsiness at the time of measurement. It has been validated against EEG variables. Increasing KSS scores reflect increasing drowsiness.\(^{(26)}\)

A longer-term judgement of daytime average sleep propensity, was measured by the Epworth Sleepiness Scale (ESS). This is a simple self-administered questionnaire that asks subjects to rate on a scale of 0 to 3 their usual chances of dozing off in each of eight different situations. Three questions on sleep onset, nighttime arousals and waking up well rested were added. The ESS has been used in ESRD patients before.\(^{(11)}\)

**Depressive symptomatology**

Depressive symptomatology was measured by the 6-item Hamilton Depression Scale (HAM-D6 questionnaire).\(^{(27)}\)

**Sample size and statistics**

Since no previous results on the effects of light treatment in HD patients have been reported, no appropriate power calculation could be made. Because of the exploring nature of the study, the number of patients included is in the same order of magnitude as included in the study on the effects of melatonin in HD patients.\(^{(8)}\)

For all calculations, baseline, light treatment and control period results were calculated for group A and B (figure 1) together. Mean values and standard deviations of patient age, actigraphy parameters, ESS and HAM-D6 results were calculated. Repeated measures
ANOVA was used to assess differences between either baseline, light treatment and control period for the sleep parameters SOL, SE and TST as well as for ESS and HAM-D6 scores. Mean values of SOL, SE and TST were calculated and plotted for HD and non-HD days separately to see possible differences between light treatment days and non-light treatment days. For timing of sleep onset and DLMO, the difference between baseline and the light period as well as the difference between baseline and control period were calculated. Mean values were plotted for the morning and evening shift and HD and non-HD days separately. Differences in timing of sleep onset and DLMO compared to baseline between the morning and afternoon shift were tested with the Student’s T-test.

KSS data were analysed using longitudinal linear regression analysis with the mixed models procedure. The method takes into account that measurements within individuals are more correlated than measurements between individuals. KSS score was chosen as dependent variable and condition (baseline, light treatment, control period) and duration of (absence of) light treatment (30, 60, 90, 120 and 180 minutes) as independent variables. KSS mean values and standard deviations per group per time point were calculated and plotted. A p-value <0.05 was considered statistically significant. IBM SPSS 19 (Chicago, IL, USA) was used for data analysis.

Results

Fifteen patients were included. Thirteen patients completed the study. The study profile, including the reasons for loss to follow-up is summarized in figure 2. Mean age ± standard deviation of the 13 remaining participants was 57.6 ± 17.9 years. There were 11 male and 2 female participants. Seven patients received 2 hours of light treatment in the morning (between 8 and 12 am), six patients received 2 hours of light treatment in the afternoon (between 2 and 6 pm).

Actigraphy

Actigraphy recordings of the control period failed for one patient, therefore this patient could not be included in the repeated measures ANOVA analysis on SOL, SE and TST. No results of non-HD days were available of another participant, since he did not record bedtimes and rise times on these days. In total, actigraphy results of 12 patients were analysed for HD days and of 11 patients for non-HD days. The results of SOL, SE and TST are shown in figure 3. There was no statistically significant difference between baseline, light therapy and control period results for all three sleep parameters. On HD days with
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light treatment, mean SOL was 29.4 ± 25.6 minutes compared to 37.9 ± 39.2 minutes on HD days in the control period. On non-HD days, mean SOL in the light and control period were 43.2 ± 44.8 and 47.6 ± 65.0 minutes respectively.

Mean SE on HD days in the light treatment period was 70.1 ± 15.7% compared to 66.1 ± 19.0% in the control period. On non-HD days in the light period, mean SE was 63.5 ± 20.1% compared to 64.6 ± 21.0% in the control period.

TST tended to be longer on HD days with light treatment than in the control period, 383 ± 125 minutes versus 342 ± 105 minutes respectively, p=0.07. TST did not differ significantly between the light and control period on non-HD days, 299 ± 120 minutes versus 308 ± 121 minutes respectively.
FIGURE 3. Actigraphy results
Mean results of sleep onset latency (minutes), sleep efficiency (%) and total sleep time (minutes) at baseline, with light treatment and in the control period on hemodialysis days and non-hemodialysis days, results of group A and B (figure 1) are grouped together. Light treatment was only given on hemodialysis days. Error bars represent standard deviations.
Timing of sleep onset

Figure 4 shows the differences in timing of sleep onset with light and control conditions compared to baseline.

When all patients were grouped together, no effect of light treatment on timing of sleep onset was observed (figure 4A).

Figure 4B shows the differences in timing of sleep onset for the morning and afternoon groups separately. Afternoon light tended to advance timing of sleep onset more than morning light. On HD days with afternoon light treatment, mean phase advance was 52.6 ± 57.7 minutes, compared to a mean phase delay of 11.5 ± 13.9 minutes on HD days with morning light (p=0.07). On non-HD days (when there was no light treatment), there was no significant difference between morning and evening shift, mean phase advance 5.7 ± 91.3 and 43.6 ± 84.7 minutes respectively.

FIGURE 4. Timing of sleep onset
Phase advances (minutes) and phase delays (minutes) compared to baseline are shown for the light treatment period and control period and for hemodialysis days and non-hemodialysis days separately. Results of group A and B (figure 1) are grouped together. Upper panels (A) show mean results for all patients. Lower panels (B) show mean results for morning light and afternoon light separately. Error bars represent standard deviations.
Melatonin

For some patients, no rise in melatonin concentrations was seen between measurements or all measurements were below the detection limit. Therefore only 7 of the 13 participants were included in the DLMO analysis (figure 5). Five patients received light treatment in the morning, 2 patients received light treatment in the afternoon. Relative to baseline, DLMO had advanced 98.2 ± 50.9 minutes with light treatment and 52.0 ± 50.6 minutes in the control period. This reflects a non-significant difference in advance of DLMO within the morning group. With light treatment in the afternoon, the DLMO had advanced 117.0 ± 132.9 minutes compared to baseline versus an advance of 74.5 ± 21.9 minutes in the control period. This also reflects a non-significant difference in advance of DLMO within afternoon group.

**FIGURE 5. Dim Light Melatonin Onset (DLMO)**

Mean DLMO phase shifts compared to baseline are shown for the light treatment period and control period. DLMOs were measured on hemodialysis days. Results for morning light and afternoon light are shown separately. Error bars represent standard deviations.
Sleepiness
Average sleep propensity measured with ESS was $11.9 \pm 4.2$ (n=13) at baseline. This tended to improve to $10.9 \pm 4.1$ (n=13) with light treatment, $p=0.06$. In the control period, patients reported an ESS score of $11.8 \pm 4.7$ (n=13), which was comparable to baseline. Drowsiness, reflected by KSS scores during HD treatment are shown in figure 6. In general, drowsiness increased during HD treatment. Overall, drowsiness was lower with light treatment than without light treatment. Mean KSS scores at baseline and in the control period were 0.92 points 95%CI [0.34;1.50], $p=0.002$ and 1.18 points 95%CI [0.51;1.85], $p=0.001$ higher than with light treatment respectively. The effect of light is mainly seen in the first hour of light exposure, since drowsiness after 30 minutes of light exposure differed from drowsiness scores at 90, 120 and 180 minutes. At these time points, mean KSS differences compared to t=30 minutes were 0.82 95% CI [0.08;1.57], $p=0.03$, 0.83 95% CI [0.06;1.61], $p=0.04$ and 0.90 95% CI [0.06;1.74], $p=0.04$ respectively.

Depressive symptomatology
HAM-D6 score was $2.8 \pm 3.4$ (n=11 at baseline) and $2.5 \pm 3.8$ in the control period. With light treatment, this non-significantly improved to $1.9 \pm 2.1$. 

FIGURE 6. Karolinska Sleepiness Scale (KSS)
Mean KSS scores during hemodialysis treatment. Results of group A and B (figure 1) are grouped together. Higher scores indicate more sleepiness. Light treatment was started at the start of hemodialysis treatment. The x-axis reflects time after start of hemodialysis treatment. The grey line represents the results of the baseline measurements, the dashed line represents the outcome of the light treatment measurements, the black line represents the outcome of the control measurements. Error bars reflect standard deviations.
Discussion

In this pilot study our aim was to explore the effects of 3 weeks of bright light therapy during in-hospital HD treatment on nighttime sleep, daytime sleepiness, DLMO and depressive symptomatology.

Regarding nighttime sleep, no effects on sleep onset latency, sleep efficiency and total sleep time were seen, although TST tended to improve with light therapy. However, we remarkably found that light exposure in the afternoon tended to advance time of sleep onset compared to light exposure in the morning. This was an unexpected but interesting result. Since light was mainly given in the least responsive part of the phase response curve (13) only little, if any, effect of light on phase shifts was expected beforehand. The chronotherapeutic effects of light are well known. Light has phase shifting effects, when applied at the right time of day in relation to the individual’s internal clock time. A shift to an earlier phase following afternoon light exposure is not congruent with the current understanding of human circadian biology. Early morning light generally leads to a phase advance, late evening light causes phase delays.(28) At first sight, the results of this pilot study are contradictory to this. However, timing of light is not the only reported factor to advance time of sleep onset. Zeitgeber strength, i.e. the difference between daytime and nighttime light intensity also influences time of sleep onset. It has been shown that spending more hours in bright light outdoors corresponds to an advance of sleep.(29) Proceeding on this line of thought, we hypothesize that the bright light exposure in the (late) afternoon to our HD patients constituted a large contrast to the low light exposure that followed directly in the evening at home. This could have provided a signal to the SCN that the period of darkness has already begun, resulting in earlier times of sleep onset for the patients with afternoon light exposure compared to morning exposure. The patients that were exposed to bright light in the morning did not experience such an abrupt transition in light intensity in the late afternoon/early evening.

The importance of a large contrast in light exposure not only on sleep, but also on melatonin secretion has already been shown by Jasser et al. Bright light at night is known to suppress melatonin secretion at the moment of light exposure. However, a few hours of dim light adaptation before nocturnal bright light exposure, attenuated this melatonin suppression, emphasizing the importance of contrast in light strength.(30) Also Hébert et al. showed that after dim light exposure during the day, bright light at night had a larger effect on melatonin suppression than when persons had been exposed to bright light during the day.(31) Both studies support the idea that a large contrast between light and dark light exposure is important for the effect on melatonin secretion.
The advancing effect of afternoon light on timing of sleep onset was only seen on the day of light treatment itself (HD days). It did not last to the following non-HD day, when a strong contrast in light strength was not present.

Since timing of sleep onset is correlated with the DLMO (25), we questioned whether DLMO had also been advanced on HD days in the afternoon group compared to the morning group. This could not be confirmed. However, only a small sample of DLMO’s could be calculated due to very low melatonin secretion in the other patients. Therefore we would argue that results remain inconclusive due to low sample size.

The direct activating effects of light were seen on the KSS scores as expected. When exposed to light, patients reported a higher level of alertness, especially during the first 60 minutes of exposure. Also average daytime sleep propensity improved with 3 weeks of light therapy. However, a statistically significant improvement of 1 point on the ESS scale, should not be considered clinically significant. In total, 3 patients changed from the category sleepy to not sleepy from baseline to light following the ESS cut off value ≥10.

There are several limitations to this study. Firstly, for practical reasons and to reduce the experimental load on the patients, light treatment was scheduled during HD treatment times. Therefore the timing of light therapy in relation to the individual’s PRC could not be calculated. In addition, at the start of light treatment, patients were at their peak of kidney failure toxicity. The presence of uraemic encephalopathy and possible interference with the effect of light therapy cannot be excluded. Secondly, light treatment was only given on HD days. The effects of light therapy would possibly have been more distinct had light therapy been given on the non-HD days as well. The experimental design therefore does not comply to accepted chronotherapy guidelines. Ambient room light intensity was not measured. These experiments should be seen as a first effort to study the potential contributions of light treatment in a complicated clinical setting to a group of patients with high morbidity that frequently suffer from sleep disturbances with known reduced melatonin levels. Future research should focus on more frequent light exposure (eg home treatment) in larger groups of patients to study if an earlier sleep onset with afternoon light exposure and possible increased total sleep time can be confirmed. Since light reduces feelings of drowsiness, a nap analysis could be included.

In conclusion, 3 weeks of light therapy during HD sessions seems to have advancing effects on timing of sleep start if administered in the (late) afternoon and possibly lengthens total sleep time. Light has immediate activating effects during HD-treatment.
Chapter 6

Declaration of interest

The authors of this manuscript have no conflicts of interest to disclose.

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References
