Insomnia on dialysis nights: the beneficial effects of cool dialysate

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ABSTRACT

Background: Hemodialysis (HD) induces physiological changes that may affect the ability to dissipate heat and adversely affect sleep on the nights following treatment. We studied the effects of altering dialysate temperature on polysomnographic measures of nocturnal sleep and the time course of proximal skin temperature.

Methods: The sample included seven stable HD patients. The three-phase randomized trial was conducted in a research facility. After one acclimatization night, subjects were readmitted in the evening on two additional occasions for 42 hours and received HD the next morning in the warm condition (dialysate - 37° C) and cool condition (dialysate - 35° C) in random order. Continuous proximal skin temperature (axillary, Tax) and polysomnographic measures of sleep were recorded the nights before and after HD was administered.

Results: Highly significant findings included that the course of Tax was markedly affected by the interaction of time and condition. In addition, there was a greater drop of Tax in the early morning following the warm condition than during the baseline nights or in the cool condition. Logistic regression indicated that the odds for the occurrence of sleep and its deeper stages were strongly and positively associated with Tax. Time of sleep onset was earlier in the cool condition (p = 0.032) with trends toward longer total sleep times (p = 0.090) and shorter REM latencies (p = 0.088).

Conclusions: These observations suggest that the use of cool dialysate during HD may improve nocturnal sleep the night following treatment by decreasing sympathetic activation and sustaining the normally elevated nocturnal skin temperature until later into the morning hours.

Key words: Hemodialysis, Dialysate temperature, Sleep disorders, Sleep and dialysis

INTRODUCTION

Fifty to 85% of HD patients complain of insomnia and excessive daytime sleepiness (1-3). Primary sleep disorders such as sleep apnea (SA) (4-6) and periodic limb movement disorder (PLMD) are common, and the prevalence of restless legs syndrome (RLS) is also high (7, 8). Few studies, however, have focused on either the subjective or polysomnographic features of sleep on night before versus night following treatment. The results of those done to date have been equivocal. Nonetheless, dialysis may induce treatment associated sleep changes because of its potential adverse effects on sleep regulatory processes.

According to the Two-Process Model of Sleep Regulation (9), the major mechanisms underlying the regulation of sleep and waking are: 1) a homeostatic process determined by the sleep and waking pattern (Process S); and 2) a circadian process that determines sleep propensity (Process C). The course of Process S is derived from slow-wave-activity (EEG power - 0.75 to 4.5 Hz range) and declines during sleep and increases during waking. Process C is reflected by the rhythm of body temperature (BT). A decline in core BT (increase in skin temperature) is typically associated with and may precede, not only nocturnal sleep onset, but the actual decision to go to bed (10, 11). Furthermore, sleep initiation is hastened and the amount of wakefulness during sleep is decreased when BT is declining at its maximum rate. In contrast, sleep offset and wakefulness are associated with an increase in core BT (decrease in skin temperature).

Our previous work indicated that the heat load induced by HD may play a role in disrupting sleep following treatment as the increase in body temperature (BT) that often results appears
to persist for several hours and may alter the dissipation of heat from the skin that occurs with normal sleep (12). Increases in core BT are thought to derive from increased sympathetic activation and decreased ability to dissipate heat due to the intense peripheral vasoconstriction that accompanies fluid removal (13). A decrease of as little as 1 to 2°C in dialysate temperature helps to reverse these changes by increasing central arteriole and venous tone, venous return, and cardiac output. In this study, we tested the hypothesis that decreasing heat load and improving hemodynamic stability during and after HD by using cool dialysate would facilitate blood flow to the skin during the night, improve heat dissipation, and have other beneficial effects on nocturnal sleep on the night following treatment.

**SUBJECTS AND METHODS**

**Subject selection**

Patients with major chronic conditions associated with changes in sleep or BT, such as chronic infections, heart failure, chronic lung disease, arthritis, organic brain disease, drug/alcohol abuse, or past psychiatric disorders requiring treatment, were excluded. Because of potential drug-related effects on sleep and wakefulness and thermoregulation, patients routinely taking medications known to modulate central nervous system state or alter BT were also excluded. Finally, potential subjects were screened via a structured interview to exclude those with a previous diagnosis of sleep apnea syndrome, periodic limb movement disorder, and restless legs syndrome. The final sample consisted of seven, clinically stable, well dialyzed HD patients, recruited from University-affiliated dialysis units.

**Design**

The Emory University Institutional Review Board approved the protocol. The three-phase study was conducted in the University’s General Clinical Research Center (GCRC) using a randomized, single-blinded (KPP), crossover design. This facility was selected because it is located in the University Hospital, which has a controlled, consistent environment; the ambient temperature is maintained within a relatively constant temperature of 20 to 22°C and humidity of 45 to 55%. HD was provided in the hospital's dialysis unit, in the same building (two floors up), eliminating the need to expose subjects to any major environmental temperature changes. The independent variable was dialysate temperature, which was administered in two conditions – warm (37°C) and cool (35°C) (14).

The major dependent variables were: 1) axillary skin temperature ($T_{ax}$, a measure of proximal skin temperature) as measured and recorded every minute using the MINI-LOGGER 2000 by Mini Mitter (15); and, 2) PSG measures of nocturnal sleep as recorded by the Oxford Ambulatory Polysomnographic Equipment (MR95 recorder). Tympanic BTs (used as an estimate of core BT – subjects refused direct core measurements) were recorded every 30 minutes using the calibrated instrument available in the GCRC during HD until “lights out”. In addition, the staff recorded the ambient temperature displayed on the room thermometer just before “lights out” and just after “lights on”. Dialysis flow sheets were collected for all subjects to obtain data on intradialytic complaints and blood pressure (BP) measurements. During Phase I, subjects were admitted to the GCRC for one night in order to familiarize them with the study equipment and procedures to reduce first night effects. During Phases II and III (approximately 1 week apart), subjects were readmitted to the GCRC at 18:00 the night before HD and discharged at approximately 12 noon two days later. During these two phases, HD was administered the morning after admission in one of the two conditions, warm condition (dialysate bath temperature 37°C) and cool condition (dialysate bath temperature 35°C) in random order (during Phase II, 4 subjects were in the warm and 3 were in cool condition; during Phase III, this was reversed). The nephrology co-investigator (JLB) randomized the order in which the conditions were delivered and monitored all subjects during treatment. Continuous $T_{ax}$ and PSG recordings were made throughout the nights preceding and following treatment from “lights out” until “lights on” as recording on the PSG equipment event marker (pushed by the subject) and documented by the GCRC nurses. All meals were provided as prescribed by the nephrology co-investigator (JLB); caffeinated (other than one cup of coffee in the morning) and alcoholic beverages were not permitted. In all Phases of the study, subjects slept in hospital gowns and were permitted one sheet and one hospital blanket throughout the night. Following treatment, the equipment was removed and subjects were discharged.

**Measures**

Demographic and clinical information was obtained via chart review. $T_{ax}$ was obtained as a measure of proximal skin temperature, because a recent study showed that mild cutaneous warming of the proximal (including axillary)
area increases sleep propensity (16). The MINILOGGER-2000 from Mini Mitter was used to sample $T_{ax}$ at 1-minute intervals. The recording device weighs 113.4 g and measures 8.51 x 6.10 x 1.60 cm; it has a range of 20 to 42°C, an accuracy of ± 0.1°C at 37°C, and a resolution of 0.04°C at 37°C. Windows-compatible software permits data retrieval and analysis (Mini Mitter Company, 2000). After shaving and cleansing the area with alcohol, a small, insulated temperature sensor (STERI-PROBE, Skin Surface Temperature Probe, No. 499B, Sub-Zero Products, Inc, Cincinnati, OH) was placed high in the axilla of the non-vascular access arm and connected to the recorder, which was then secured in the subject’s pocket.

Sleep was recorded using the Medilog 9200 Ambulatory Sleep/Neurology Replay System and Recorder System (Oxford Instruments, Clearwater, FL). This system allows monitoring and recording of up to eight channels of physiological information, plus one additional channel that records digital time to within 1 second accuracy for data retrieval. In addition, a push-button allows the subject to accurately mark the time of “lights out” and “lights on”. The recorder is compact (154 x 112 x 40 mm), lightweight (0.8 kg) and battery powered, and it records information on a mini hard drive. The recordings are played back through the Medilog 9200 Ambulatory Sleep/Neurology Replay System, which enables information stored on the mini hard drive to be scored and analyzed.

A standard montage of electroencephalography (EEG) (C3/A2 or C4/A1 and O2/C3 or O1/C4), monopolar left and right electrooculography (EOG) referenced to the opposite mastoid, surface mentalis electromyography (EMG) was used. Sleep stages were manually scored by blinded investigator (KPP) following standard criteria (17). Nocturnal PSG sleep measures calculated included: total sleep time (TST, minutes); sleep efficiency ($SE = TST/time in bed X 100$); the minutes of TST spent in Stages 1, 2, 3 & 4 (3 & 4 are referred to as slow wave sleep; SWS), and rapid-eye-movement (REM) sleep; latency to three consecutive epochs of sleep (sleep latency, SL, in minutes), and the latency to the first epoch of REM sleep (REM latency, RL, in minutes). Wake after sleep onset (WASO, in minutes) lasting both more and less than 60 seconds were noted in lieu of micro arousals, because of system limitations.

**Data analysis**

Descriptive statistics (mean ± standard error, SE) were used to summarize the demographic, clinical, and PSG measures of nocturnal sleep (Tabs. I and II). Because of this observation and the small sample size, non-parametric tests (Wilcoxin Matched Pairs Sign Rank Test, Mann Whitney U Test, and/or the Kruskal Wallace procedures) were used for group comparisons.

A data file was also compiled for each condition, including the sleep stage for every 30-second epoch and the synchronized $T_{ax}$ between “lights out” and “lights on” of the individual nights. Because there were no statistically significant differences between PSG measures of sleep during the two-baseline nights (Phase I) preceding Phases II and III, these data were pooled. After visual inspection of all nocturnal temperature curves, values below the overall mean minus two standard deviations of $T_{ax}$ (i.e. below 33.1°C) were regarded as outliers and excluded from the analyses. This dataset of multiple data points nested within three nights (the combination of two baseline nights, cool, and warm conditions) with different “lights out” and “lights on” times also nested within subjects, required the use of longitudinal hierarchical random regression analysis (18). These data met the assumptions of normality and homogeneity of variance. In all analyses, hierarchical random regression modeling (i.e., random coefficient analysis) was used to account for the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>7</td>
</tr>
<tr>
<td>Age</td>
<td>46.1 ± 4.2</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3</td>
</tr>
<tr>
<td>Female</td>
<td>4</td>
</tr>
<tr>
<td>Race - African American</td>
<td>7</td>
</tr>
<tr>
<td>Sodium (meq/L)</td>
<td>138.1 ± 1.2</td>
</tr>
<tr>
<td>Potassium (meq/L)</td>
<td>5.0 ± 0.3</td>
</tr>
<tr>
<td>CO2 (mmol/L)</td>
<td>18.7 ± 0.8</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>67.0 ± 6.9</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>14.4 ± 1.2</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>9.6 ± 0.2</td>
</tr>
<tr>
<td>Phosphorous (mg/dL)</td>
<td>6.2 ± 0.5</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>36.8 ± 1.1</td>
</tr>
<tr>
<td>Ferritin (µg/L)</td>
<td>1172.8 ± 316.1</td>
</tr>
<tr>
<td>Iron saturation (%)</td>
<td>23.4 ± 2.9</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>25.1 ± 2.2</td>
</tr>
<tr>
<td>Kt/V**</td>
<td>1.5 ± 0.1</td>
</tr>
</tbody>
</table>

* Values are means ± standard error; SE.

** Kt/V = a measure of dialysis adequacy.
interdependence of the data points inherent in the hierarchical structure of the dataset (MLwiN software, Centre for Multilevel Modeling, Institute of Education, London, UK). Linear regression was used to determine the effect of dialysate temperature condition on the course of nocturnal T_{ex}. Separate logistic regression analyses were used to determine the effect of dialysate temperature condition on the probability of occurrence of wakefulness, Stage 1, Stage 2, slow wave sleep (Stages 3 and 4) and REM sleep, with presence or absence of that stage at every 30-second interval coded as a dichotomous variable. To determine the predictive value of T_{ex} on the probability of occurrence of both wakefulness and specific sleep stages, separate longitudinal multilevel logistic regression analyses were applied for each sleep stage classification, with the presence or absence of that stage at every 30-second interval coded as a dichotomous variable and T_{ex} as a continuous predictor variable. Optimal regression models were selected using the likelihood ratio chi-square test. Significance level was set at $\alpha = 0.05$.

**RESULTS**

Demographic and clinical features of the sample

The mean (± standard error, SE) age was 46.1 ± 4.2. Three subjects were male and four were female. All were African American. The mean Kt/V was 1.5 ± 0.1 (a measure of dialysis adequacy based on total body water and dialyzer clearance; > 1.2 is acceptable), indicating that subjects were well dialyzed. The mean time when HD was initiated in the warm condition was 09:41 ± 0:07 and the mean termination time was 13:00 ± 00:16. The mean HD initiation time in the cool condition was 10:25 ± 0:37 and the mean termination time was 13:36 ± 0:49. Time differences were not statistically significantly.

The mean ambient temperatures at “lights out” in the warm versus cool conditions were 23.8 ± 0.8 versus 24.0 ± 0.9°C, respectively; the mean ambient temperatures at “lights on” were 25.5 ± 0.7 versus 25.3 ± 0.6°C, respectively. These differences were not statistically significant.

### TABLE II

NOCTURNAL SLEEP PARAMETERS (MEANS ± SE) FOR THE NIGHTS (POOLED) PRIOR TO HD AND THE NIGHTS FOLLOWING THE TWO HD CONDITIONS

<table>
<thead>
<tr>
<th>Sleep parameter</th>
<th>Night before HD Baseline</th>
<th>Night after HD Warm condition 37°C</th>
<th>Night after HD Cool condition 35°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of Sleep Offset</td>
<td>7:43 ± 0:17</td>
<td>07:13 ± 0:15</td>
<td>7:35 ± 0:31</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>16.4 ± 3.0</td>
<td>62.2 ± 33.8</td>
<td>22.1 ± 8.0</td>
</tr>
<tr>
<td>REM latency (min)**</td>
<td>98.7 ± 15.5</td>
<td>119.7 ± 29.6</td>
<td>70.8 ± 5.6</td>
</tr>
<tr>
<td>Stage 1 (min)</td>
<td>55.4 ± 17.7</td>
<td>35.7 ± 8.6</td>
<td>50.7 ± 19.4</td>
</tr>
<tr>
<td>Stage 2 (min)</td>
<td>228.1 ± 22.0</td>
<td>169.8 ± 21.5</td>
<td>164.6 ± 31.3</td>
</tr>
<tr>
<td>Stage SWS (min)</td>
<td>34.8 ± 19.3</td>
<td>47.9 ± 21.0</td>
<td>36.2 ± 21.3</td>
</tr>
<tr>
<td>REM (min)</td>
<td>62.9 ± 10.9</td>
<td>54.3 ± 11.9</td>
<td>56.7 ± 12.7</td>
</tr>
<tr>
<td>NREM (%)</td>
<td>84.3 ± 2.4</td>
<td>83.7 ± 2.9</td>
<td>82.5 ± 2.9</td>
</tr>
<tr>
<td>REM (%)</td>
<td>15.7 ± 2.4</td>
<td>16.3 ± 2.9</td>
<td>17.5 ± 2.9</td>
</tr>
<tr>
<td>Nocturnal Total Sleep</td>
<td>381.2 ± 26.3</td>
<td>307.6 ± 38.4</td>
<td>371.7 ± 25.6</td>
</tr>
<tr>
<td>Time (TST, min)***</td>
<td>74.4 ± 5.7</td>
<td>65.8 ± 10.7</td>
<td>73.5 ± 5.5</td>
</tr>
<tr>
<td>Nocturnal Sleep Efficiency (SE, %)</td>
<td>65.8 ± 10.7</td>
<td>73.5 ± 5.5</td>
<td></td>
</tr>
<tr>
<td>WASO &gt; 120 seconds (minutes)</td>
<td>88.1 ± 32.1</td>
<td>109.3 ± 53.9</td>
<td>85.8 ± 30.4</td>
</tr>
<tr>
<td>WASO &lt; 120 seconds (minutes)</td>
<td>23.5 ± 3.5</td>
<td>24.1 ± 3.1</td>
<td>31.0 ± 7.4</td>
</tr>
</tbody>
</table>

Two group comparisons between warm and cool condition (Wilcoxin Match Pairs-Sign Rank Test).

* $p = 0.032$; ** $p = 0.090$; *** $p = 0.088$. 

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The mean tympanic BT during HD in the warm condition was significantly higher than in the cool condition (36.3 ± 0.1 versus 35.5 ± 0.2; z = -2.4, p = 0.018). Mean tympanic BT, taken every 30 minutes for the period following HD until “lights out” was also significantly higher in the warm condition (36.9 ± 0.1 versus 36.2 ± 0.1; z = -3.18, p = 0.001), demonstrating that tympanic BT continued to remain higher beyond the intradialytic period. There were no reports of shivering noted on the dialysis flow sheets, and none of the subjects withdrew from the study.

Effect of dialysate temperature on the course of proximal skin temperature (T_{ax})

Multilevel regression analyses were used to determine whether dialysate temperature affected the nocturnal time course of T_{ax} during sleep. The grand mean of T_{ax} over all time points and subjects was 35.9 ± 0.2° C (mean ± SE). Figure 1 gives a graphic representation of the best fitting curves following the cool, warm, and baseline conditions. As can be noted, T_{ax} declined more during the night following the warm dialysate than during the baseline nights or the night following treatment with cool dialysate. This greater decline resulted in temperatures below the ranges observed in both the baseline and cool conditions in the early morning. Although the main effect of dialysate temperature on T_{ax} did not reach significance, the course of T_{ax} was significantly affected by the interaction of time and condition for the first, second, and third order terms (all p < 0.000001), showing the greater drop in T_{ax} especially in the early morning following treatment with warm dialysate.

Effect of dialysate temperature and proximal skin temperature on sleep

Multilevel regression analyses were used to determine whether dialysate temperature altered the probability of the occurrence of wakefulness and sleep stages over the course of the night. There was an increased probability of nocturnal wakefulness, especially in the early morning, after receiving the warm dialysate. The (multilevel) overall probability of being awake at any given time of night was p = 0.19, CI = (0.09-0.35), (CI = confidence interval). The odds of nocturnal wakefulness were significantly greater (odds ratio, OR = 1.08, CI = (0.98-1.19), p = 0.12, though this was not significant. Every 1°C increase in T_{ax} increased the odds ratio for the occurrence of wakefulness by 0.40, CI = (0.37-0.45), p < 0.00001. Every 1°C increase in T_{ax} increased the odds ratio for the occurrence of Stage 1 by 1.08, CI = (0.98-1.19), p = 0.12, of SWS by 1.61, CI = (1.41-1.85), p < 0.00001, and of REM by 1.24, CI = (1.15-1.34), p < 0.00001. There were no significant differences in standard PSG measures of nocturnal sleep among the three conditions - baseline, warm, and cool. However, as can be noted, the sleep of subjects during the baseline and cool conditions was very similar and markedly different from sleep in the warm condition (see Tab. I). When two-group comparisons were conducted (Mann Whitney U Test) between the cool and
warm conditions, subjects fell asleep significantly earlier in the cool condition (21:17 ± 2.2 versus 24:15 ± 0:19, z = -1.9, p = 0.032). Although the differences were not significant, subjects in the cool condition tended to have longer total sleep times (37.1 ± 25.6 versus 307.6 ± 38.4; z = -1.4, p = 0.09) and shorter REM latencies (70.8 ± 5.6 versus 119.7 ± 29.6; z = -1.4, p = 0.088). No statistically significant gender based differences in sleep measures were observed within or between the baseline, warm, or cool conditions.

**DISCUSSION AND CONCLUSIONS**

There are numerous mechanisms via which HD may adversely affect sleep the night following treatment. For example, excessive sleeping both during and after HD, a phenomenon that has long been described, can decrease the underlying homeostatic drive for sleep, causing problems with the initiation of nocturnal sleep and sleep fragmentation. Decrements in central nervous system arousal and overall fatigue associated with the rapid fluid, electrolyte, and acid-base changes and the production of cytokines may also play a role. HD may also influence several circadian variables such as the production of melatonin, social and physical activities, and light exposure – all of which are important circadian cues to help synchronize body rhythms.

Although the effects of dialysis-induced thermoregulatory abnormalities on cardiovascular and intradialytic blood pressure stability have recently been examined (19), the effects of these changes on nocturnal sleep have never been examined. Yet, temperature and sleep are interrelated processes (11, 20) To our knowledge, however, this is the first study to examine the effects of experimentally induced blood temperature changes on these phenomena in chronic HD patients.

A major finding was that, in the warm condition, the interaction of condition and time significantly altered the course of $T_{ax}$. In particular, there was a notable decrease in $T_{ax}$ in the early morning hours in the warm condition. In contrast, in both the baseline and cool conditions, $T_{ax}$ remained higher during this same period. The mechanism underlying these observations may be the same as that believed responsible for the beneficial effects of cool dialysate on intradialytic blood pressure; that is, improved hemodynamic stability via an increase in cardiac output that could facilitate nocturnal shunting of blood to the skin. The higher $T_{ax}$ noted in the baseline condition may have resulted from recovery vascular refilling.

A strong positive relationship was also observed between sleep propensity and $T_{ax}$; a small increase in $T_{ax}$ was associated with decreased probability of being awake and increased probability of being in Stage 2, SWS, and REM sleep. This observation is consistent with a recent study of healthy subjects which showed that very mild warming of the proximal skin area within the thermoneutral zone increased sleep propensity (16). Mild skin warming has also been shown to adversely affect sustained vigilance (16) and promote the deeper stages of sleep. Not surprisingly then the odds of nocturnal wakefulness were significantly higher in the warm condition than in the baseline and cool conditions. There were no significant differences in PSG measures of nocturnal sleep among the baseline, cool, and warm conditions. However, the sleep measures in the baseline and cool conditions were quite similar to each other and different from those characterizing the warm condition. When a two-group comparison of warm versus cool conditions was made, subjects fell asleep significantly earlier in the warm condition and showed a trend toward longer total sleep times and shorter REM latencies. These observations were likely related to factors that increased sleep propensity - the decreased heat load experienced in the cool condition (as reflected in the lower tympanic temperatures following HD), the warmer $T_{ax}$ observed across the night, and the associated increased probability of both sleep and REM sleep in the cool condition. Unfortunately, the small sample limited the power of these analyses to detect other significant differences.

The results of this study suggest that HD may adversely affect sleep the night following treatment, possibly from a treatment associated heat load. The use of cool dialysate may be a reasonable, cost-effective way to reverse this effect. Our results also support the growing body of scientific evidence that skin temperature provides important peripheral signals to central systems that modulate sleep/wake propensity. Further research is warranted to more closely examine this promising sleep promoting intervention. For more details regarding this study, please refer to the original article (21).

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