Effects of the heart-lung machine on melatonin metabolism and mood disturbances

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Abstract

Objective: Cardiothoracic surgery using the heart-lung machine (HLM) provokes a pronounced endocrine-metabolic response leading to circadian rhythm disturbances that affect postoperative morbidity. Focus has been laid on changes in melatonin metabolism. The effects of an extra-corporal artificial circulation have not been adequately addressed. Methods: Seventeen patients scheduled for open heart surgery using the HLM were compared with 15 patients undergoing major surgery without cardiopulmonary bypass (non-HLM). Late afternoon and night urinary 6-sulfatoxymelatonin were measured at baseline, immediately after the operation and on return to the normal ward. Mood disturbances were assessed at baseline and final sampling times using a standardized questionnaire (arbitrary units). Results: Vital signs were comparable between groups. The difference (delta) between day and night melatonin levels was similar at baseline (HLM group 1.1 ng/ml, non-HLM group 1.4 ng/ml, \( p = 0.25 \)). Immediately following surgery melatonin day—night deltas were unchanged to baseline (HLM 1.0 ng/ml, non-HLM 1.4 ng/ml, \( p = 0.67 \); non-HLM 0.8 ng/ml, \( p = 0.46 \)) but at final sampling normal circadian melatonin profile was abolished (\( -0.3 \text{ ng/ml,} \ p = 0.001 \) and 0.0 ng/ml, \( p = 0.07 \)). However, this effect was not different between the two studied groups (\( p = 0.17 \)). No mood disorders were detectable at baseline (HLM 8.0 vs non-HLM 7.0, \( p = 0.97 \)) and no changes occurred after surgery (7.0 vs 6.5, \( p = 0.33 \)). Overall, patients with a worsening psychological score had pronounced postoperative washout of afternoon—night melatonin delta (\( p = 0.04 \)). Conclusions: We found no relevant influence of the HLM on perioperative circadian melatonin profiles. Additionally, no alterations in mood assessment before and after surgery were observed. However, worsening of psychological score was associated with a pronounced disruption of the normal circadian melatonin profile.

Keywords: Heart-lung machine; Melatonin; Mood disorders; Circadian rhythm disorders; Heart surgery

1. Introduction

Studies that have examined various selected aspects of the circadian system have documented relevant postoperative changes in the regulation of melatonin production [1–3]. Melatonin is produced by the pinealocytes in the nucleus suprachiasmaticus in a circadian pattern. While during daytime bright light attenuates synthesis, darkness allows plasma melatonin levels to increase rapidly and peak during night time. Under stable conditions melatonin appears to influence non-vital functions including sleep regulation, waking patterns, body temperature and modulation of mood and vigilance [4]. However, the role of melatonin under stressful situations is not fully understood and may be underestimated.

Abbreviations: BMI, body mass index; Delta, the difference of melatonin between day and night levels; HADS, hospital anxiety and depression score; HLM, heart-lung machine; ICU, intensive care unit; Non-HLM, non-heart-lung machine; SAPS, short acute physiology score.

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Melatonin itself may upregulate Interleukin 2, 6 and 8, TNF-alpha and interferon-gamma and as such may counteract stress induced immunosuppression and hypothetically even worsen the inflammatory response [5,6]. In critically ill patients a sustained melatonin day—night rhythm seemed to be associated with a shorter stay on the intensive care unit (ICU) and better prognosis [7]. Furthermore, ICU associated psychosis was observed more frequently when the normal melatonin circadian pattern was disrupted [3]. A relevant interplay between melatonin homeostasis and mood disturbances, seasonal depression in particular, has been shown repeatedly [8]. Of importance, depression and anxiety have been found to be important predictors of future cardiovascular events [9].

One of the most hotly debated and polarizing issues in cardiac surgery has been whether on-pump coronary artery bypass grafting was inferior to that performed without the use of the heart lung machine. Even though a large-scale randomized prospective trial is missing, a broad body of data has been gathered suggesting a less favorable early postoperative recovery in the former [10,11]. This period following major surgery is characterized by an endocrine-metabolic and inflammatory surgical stress response inducing sleep and circadian rhythm disturbances which may, at least
2. Methods and materials

This is a randomized prospective observational trial. This study examined pre- and postoperative melatonin levels (urinary 6-sulfatoxy melatonin) and mood responses (hospital anxiety and depression scale (HADS)) in patients undergoing cardiac surgery using the heart-lung machine (HLM) and in a matched patient group undergoing major interventions without cardiopulmonary bypass. Primary endpoints were changes in melatonin profile after surgery compared to baseline (expressed as day/night delta). The secondary endpoints were changes in psychological assessment using a standardized patient questionnaire.

2.1. Study protocol

Patients scheduled to undergo cardiothoracic surgery with the use of cardiopulmonary bypass and patients scheduled for major visceral surgery requiring postoperative stay in the ICU were recruited at the Kantonsspital Luzern, Switzerland between August 2006 and February 2007. Inclusion criteria were age 30—80 years and a minimum hospital stay of 5 days. Exclusion criteria were (1) brain injury/surgery (2) severe renal insufficiency defined as serum creatinine >180 μmol/l, (3) severe liver failure defined as Child—Pugh class B or greater, (4) alcohol abuse and (5) current use of antidepressants or other forms of psychiatric support. Each patient gave written informed consent prior to inclusion. The study was approved by the local ethics committee.

On the day prior to surgery urine was collected and depression/anxiety assessed as described below. The second urinary sample was collected on the same day as the operation if feasible or otherwise on the following day. A final urinary collection and a second psychological testing were made within the first three days after patients returned from the ICU to the regular ward. The recording of vital signs and withdrawal of blood samples were performed at times of urinary collections.

2.2. Melatonin measurements

Plasma halftime of melatonin averages at 0.5–6 min and is rapidly metabolized into 6-sulfatoxymelatonin in the liver. This very stable metabolite is excreted by the kidneys without further changes and correlates closely with plasma melatonin levels [13]. Urine collection was adjusted to local daylight parameters. Urine was sampled two hours before twilight time to assess trough melatonin levels (afternoon collection). Then, 2 h after sunset another 2 h night collection was started to assess peak levels. For each patient twilight time (sun 6 below horizon) depending on the date of operation was calculated using a public meteorology broadcasting system (http://www.sunrisesunset.com). To allow exact temporal collections, a bladder catheter was installed in all patients. Urinary samples were stored at −70 °C and 6-sulfatoxy melatonin was measured using an enzyme-linked immuno-assay from Buhlmann Laboratories (Allschwil, Switzerland). Values of 6-sulfatoxy melatonin are expressed as ng/ml.

2.3. Psychological and physiological assessments

The hospital anxiety and depression score (HADS) has been especially developed to assess psychological stress in hospitalized patients and has been repeatedly validated [14]. A score >11 is considered to indicate anxiety and depression. The questionnaires were answered completely by the patients on the day prior to surgery. This procedure was repeated on the day following the final urinary collection. The simplified acute physiology score II (SAPS II) is designed to uniformly assess critically ill patients and to compare patients in different facilities and to relate scores to prognosis and clinical outcome [15]. According to general guidelines, the score was computed using the most unfavorable parameter during the first 24 h of the ICU stay.

2.4. Statistical analysis

The statistical analyses were performed by a person unaware of the patients’ type of operations and sequence of measurements. Results are presented as medians and interquartile ranges (25th to 75th percentile) unless otherwise indicated. For comparison of inter-group and intra-group differences, Wilcoxon signed rank test and Mann—Whitney test were used as indicated (StatView 3.4, Abacus Concepts). Statistical significance was accepted at $p < 0.05$. For calculation of the sample size we assumed an intergroup difference of 40% a standard deviation 40% of mean and a power of 0.75.

3. Results

3.1. Baseline characteristics

A total of 32 patients, median age 67 years, were recruited. Seventeen patients (six females) underwent surgery with the use of a HLM; five had heart valve replacements, eight had aorto-coronary bypass grafting and four had a combination of valvular and coronary bypass operation. Fifteen patients (four females) underwent surgery without cardiopulmonary bypass (non-HLM group); 10 had major abdominal interventions, four had thoracic interventions and 1 had major head and neck surgery. Overall in the non-HLM group, indication for surgery was malignant disease in eight patients. For both the HLM and non-HLM group, the first median urinary sampling time was 1 day prior to surgery in all patients and post-surgery assessment was on the same day as the operation in the majority of cases ($n = 24$) or on the consecutive day ($n = 8$). Final sampling was done mostly on the third postoperative day (interquartile range day 2—day 4) and accordingly, final HADS assessment on the fourth postoperative day. Baseline characteristics comparing age, vital signs and sleep patterns before hospitalization were similar (Table 1).

in part, be due to the use of cardiopulmonary bypass [10,11]. One small study with 11 patients found deficient melatonin plasma levels in patients undergoing coronary artery bypass grafting operation but unfortunately neither baseline conditions nor a control group had been defined by the investigators [12].
3.2. Perioperative parameters

The overall median hospitalization period was 11 days, operation duration was 3 h 47 min, postinterventional ICU stay was 44 h and intubation period was 13 h. Despite the significantly longer operation duration for the non-HLM patients, their overall hospitalization, ICU stay and intubation periods were shorter when compared to the HLM patient group. The postoperative short acute physiology score between the two groups was not different, indicating similar severity of diseases. For complete comparison of the two groups see Table 2. In the HLM group, median cardiopulmonary bypass time was 99 min and aortic clamp time was 69 min.

3.3. Melatonin and psychological assessment

At baseline (pre-surgery), afternoon and night 6-sulfatoxy melatonin levels were comparable in both groups with the non-HLM patients showing a more heterogeneous distribution (Fig. 1). No differences could be detected when comparing patients with hypertension \((n = 20)\) to non-hypertensive subjects \((1.1 \text{ ng/ml (0.9—1.9)} \text{ vs } 1.1 \text{ ng/ml (0.4—2.2)}\), \(p = 0.37\). Directly after completion of surgery, afternoon—night delta in urinary melatonin was similar to baseline values in both groups indicating preserved melatonin metabolism. Upon final sampling time, a washout or even reversal of the afternoon—night delta in urinary melatonin was found \((p = 0.77)\); these values indicate no relevant signs of depression or anxiety in our patient population at baseline. Individual preoperative and postoperative values of mood assessment are shown in Fig. 3. Median changes in HADS were not significant in HLM \((p = 0.48)\) and non-HLM patients \((p = 0.11)\), and no intergroup difference was found \((p = 0.33)\). Patients with worsening HADS (median 2.0) after surgery were found to have greater changes in melatonin circadian pattern postoperatively as compared to patients with improvement in HADS (median –3.0), \(p = 0.07\) (Fig. 4). We did not find an association between melatonin profiles and gender, age, blood pressure or heart rate (data not shown).

4. Discussion

This study examined the influence of the HLM on melatonin metabolism and mood disturbances. Patients with cardiothoracic surgery using cardiopulmonary bypass were compared to a matched group of patients undergoing major surgery without the use of the HLM. After surgery we saw profound changes in melatonin circadian patterns but there was no difference between the two studied groups. Mood disturbances were comparable in both groups before as well as after the operations. However, a worsening in depression and anxiety was associated with greater changes in melatonin profiles after surgery. We conclude that in patients undergoing major elective thoracic surgery the use of the HLM for coronary artery bypass does not significantly affect melatonin metabolism nor does it cause mood disorders.

Sleep and circadian rhythm disturbances have important effects on postoperative morbidity. Changes in the circadian regulation of melatonin production have been reported to occur following surgery \([1—3]\). Besides the surgical intervention itself, anesthetic procedures, inflammatory states and prevention of bright-light exposure during general anesthesia may also cause alterations in melatonin production. The effects of an extra-corporal artificial circulation,
such as use of the HLM during cardiothoracic surgery, have not been adequately addressed so far.

Baseline (preoperative) urinary melatonin levels in our study tended to be slightly below published values in healthy controls, however the ratio between daytime and night time urinary melatonin were similar (approximately three-fold) [16,17]. After surgery we documented profound changes in urinary melatonin profile towards a levelling off from the normal melatonin circadian rhythm; however, alterations became not evident directly after surgery but on the third postoperative day despite the long periods of operation (median 3:47 h) and artificial ventilation (12:47 h). Our finding of no changes in the cardiopulmonary bypass group R. Chenevard et al. / European Journal of Cardio-thoracic Surgery 34 (2008) 338—343

Intergroup comparison showed no differences between the two studied groups (baseline \( p=0.97 \), back on ward \( p=0.33 \)).

A negative value indicates a lessening amplitude afternoon—night and is opposite to a normal melatonin circadian profile. Our results suggest a more disrupted melatonin homeostasis in patients with a worsened HADS.
immediately following surgery are in accordance with a study investigating extracorporeal circulation in end stage renal disease: serum melatonin concentrations in the blood entering and leaving the hemodialyzer were comparable [18]. Opposite to this, Guo et al. [12] reported suppression of plasma melatonin below detection level during cardiopulmonary bypass operation; this attenuation was temporary and the circadian pattern was quickly restored at day 2 postoperatively; unfortunately, this study lacks a control group and baseline preoperative melatonin concentrations were not assessed. While the majority of authors including ourselves did find a relevant influence of surgery on melatonin profile [1—3], other studies could not show such evidence for an effect [19,20]. It can be argued that possible changes might be affected by the type of operations: Gögenur et al. who studied patients with major abdominal surgery very similar to our control group did showed changes in melatonin metabolism, while in the patient population having open thoracic oesophagectomy studied by Nishimura no alterations were found [20]. However, our results and previously published data do not support an association between the extent of the operative intervention and changes in melatonin profile, since alterations have been shown in both minor (e.g. laparoscopic cholecystectomy) and major abdominal and thoracic operative interventions [21].

To our knowledge, postoperative mood disorders have not been measured concurrently with melatonin profiles. While disturbed melatonin metabolism seems to be linked to seasonal depression [8], knowledge about the interplay and its timing of melatonin and mood disturbances in primarily non-psychiatric disease is very limited. In a previously published study investigating mood disorders after coronary artery bypass grafting depression scores were highest two to three days after surgery [22] very similar to the onset of mental disturbances in intensive care unit psychosis paralleled by abolished circadian melatonin metabolism [3]. In our study final psychological assessment was performed on average three days after surgery and as such we believe that relevant changes would have been detected. Overall we found no relevant changes in mood assessment using HADS and comparing results before and after surgery in either of our patient groups despite the profound alterations in melatonin profile after surgery. In line with our findings, preoperative melatonin application did not reduce anxiety in elderly patients [23], and despite the measurement of very high melatonin concentrations in patients with end stage renal disease, no association with insomnia, delayed sleep onset or night time arousal was found in another study [24]. Interestingly, when comparing patients with worsening of HADS score to those with postoperative mood improvement in our population, the former had greater changes in melatonin circadian profile following surgery. This finding suggests that in some but not all individuals’ disrupted melatonin homeostasis may influence mood disturbances. Of importance, depression and anxiety have been found to be important predictors of future cardiovascular events [9].

4.1. Limitations

For our control group we chose a non-cardiac surgery population. We decided against patients undergoing off-pump aorto-coronary bypass grafting since they are mostly younger, less bypasses are placed and time of surgery is mostly shorter. By avoiding this possible confounder, we are aware that there may exist relevant differences between the two groups studied, hypertension and malignancy in particular [25,26]. Even though we did not find relevant differences in melatonin metabolism for patients with hypertension or malignancies, we cannot exclude such bias since our study was not adequately designed to detect such differences.

Despite recruiting the most patients of all studies investigating melatonin metabolism in surgery (Guo et al.: 12 patients; Gögenur et al.: 11 patients; Karkela et al.: 20 patients) we are aware that the sample size chosen is limited and thus conflicting a type II error cannot fully be excluded. However, the possibility of a falsely neutral finding is low at approximately 5%.

4.2. Conclusions

Postoperative morbidity remains an area of concern. The influence of melatonin is controversial. Our results show no significant influence of cardiopulmonary bypass using the HLM on either melatonin metabolism or on mood disturbances after surgery when compared to a matched patient group.

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