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Postoperative Circadian Disturbances

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THIS THESIS IS BASED ON THE FOLLOWING PAPERS:

1. Gögenur I, Rosenberg-Adamsen S, Kiil C, Kjaersgaard M, Kehlet H, Rosenberg J. Laparoscopic cholecystectomy causes less sleep disturbance than open abdominal surgery. Surg Endosc 2001; 15: 1452-5.
2. Gögenur I, Rosenberg-Adamsen S, Lie C, Rasmussen V, Rosenberg J. Lack of circadian variation in the autonomic nervous system after major abdominal operations. Eur J Surg 2002; 168: 242-6.
3. Gögenur I, Achiam MP, Sølving P, Eversbush A, Rosenberg J. Disturbed core body temperature rhythm after major abdominal surgery. J Sleep Biol Rhythms 2004; 2: 226-8.
4. Gögenur I, Ocak U, Altunpinar Ö, Middleton B, Skene D, Rosenberg J. Disturbances in melatonin, cortisol and core body temperature rhythms after major surgery. World J Surg 2007; 31: 290-8.
5. Gögenur I, Middleton B, Kristiansen VB, Skene D, Rosenberg J. Disturbances in melatonin and core body temperature circadian rhythms after minimal invasive surgery. Acta Anaesthesiol Scand 2007; 51: 1099-106.
6. Gögenur I, Burgdorf S, Middleton B, Rasmussen LS, Skene D, Rosenberg J. Impact of sleep and circadian disturbances on cognitive function after major surgery. J Pineal Res 2007; 43: 179-84.
7. Gögenur I, Wildschiøtz G, Rosenberg J. Circadian distribution of sleep phases after major abdominal surgery. Br J Anaesth 2008; 100: 45-9.
8. Gögenur I, Kücükakin B, Bisgaard T, Kristiansen VB, Hjortsø NC, Skene DJ, Rosenberg J. The effect of melatonin on sleep quality after laparoscopic cholecystectomy: A randomized placebo-controlled trial. Anesth Analg 2009; 108:1152-6.
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INTRODUCTION

Introduction of minimally invasive surgery and enhanced recovery programs have resulted in improved postoperative subjective complaints and reduced morbidity [1,2,3,4]. Despite essential improvements in pre-, intra- and postoperative care, patients still have short and long-term subjective complaints, as well as serious morbidity and mortality after surgery [5,6,7,8]. Thus, many patients have subjective discomfort with reduced general well-being, increased fatigue, pain, cognitive and sleep disturbances for a variable period after surgery [9,10,11,12,13,14,15,16].

It is known, that disturbances in the circadian regulation of hormone secretion, the sleep-wake cycle and the tone in the autonomic nervous system substantially influences subjective comfort and morbidity [17,18,19,20,21]. It is also well established that the response to medical treatment (e.g. chemotherapeutic agents [30], neuromuscular blockade agents [23], epidural local anaesthetics [24]) varies considerably throughout the day. The administration of chemotherapeutic agents to patients with metastatic colorectal cancer at certain times of the day, instead of continuous infusion, dramatically reduces toxicity and improves the oncostatic effect [25]. It has also been proven that there is a circadian peak of the presentation of symptoms and diseases at certain times of the day [26,27,28]. The morning excess of cardiovascular events and stroke has been known for a long time [29,26,27,28]. Studies in patients after major surgery have also shown that specific days after surgery and also specific times of the day after surgery are connected with increased cardiovascular events [30,31,32,33] and sudden unexpected death [34]. It is not known if the initiation or the pathophysiological background for this peak of clinical events at certain times of the day is due to circadian rhythm disturbances in release of hormones, changes in the tone of the autonomic nervous system or circadian variation in blood viscosity. A first step to clarify this, is to investigate if and how circadian rhythms after surgery are disturbed. A major determinant of the postoperative recovery, morbidity and mortality is the magnitude of the surgical trauma. It has not been established if there are dose-response relationships between the magnitude of surgery and postoperative circadian disturbances.

The aim of this thesis was to describe circadian disturbances in relation to surgery and to examine the effectors on the circadian disturbances with special emphasis on differences between minimal invasive surgery and major surgery. It was also aimed to examine if there was a correlation between markers of the circadian rhythms examined and postoperative subjective discomfort and cognitive function. Finally, we wanted to examine whether substitution of a central circadian regulatory hormone, could affect subjective discomfort parameters after surgery.

METHODS FOR ASSESSING CIRCADIAN RHYTHMS

Circadian rhythms are regulated from the central nervous system, more specifically from a collection of neurons in the hypothalamus called nucleus suprachiasmaticus (SCN) [35,36,37]. This circadian pacemaker is in continuous contact with the environment through numerous afferent and efferent connections [38,35]. Through these connections, the pacemaker regulates several body functions including the sleep-wake cycle, alertness, cognitive function, hormone secretion, temperature regulation, immune function and autonomic nervous system tone [39,40,41,42,36,43,44,37,45]. It is not possible to examine the pacemaker directly in clinical studies for obvious reasons; hence, it is important to have reliable surrogate markers of the pacemaker activity.

In order to establish if a change in the rhythm is endogenously generated or a result of a change in the environment, or if it is a result of both, the gold standard is “constant routine” protocols [46]. In these constant routine protocols, all the possibly known confounders are kept constant, so that participants are required to remain awake, maintain a constant posture, is placed in constant lightening conditions (usually dim light (< 10 lux)), and receive isocaloric meals every hour for at least 25 hours. Another way to assess changes in the circadian rhythm is by “forced desynchrony” experiments [47]. In these studies, the study subjects live a 20-hour or 28-hour day for a minimum of 12 days. In this way it is possible to differentiate the effects on the sleep-wake cycle and the circadian pacemaker. It is not possible to do strict constant routine or forced desynchrony experiments in patients after surgery because of the need for strict temporal isolation facilities. Therefore there are needs for reliable surrogate parameters for assessing changes in the circadian rhythm. The optimal marker of circadian function and pacemaker activity should be a non-invasive method with low variability due to the method of analysis. Based on these considerations, markers of the circadian rhythm can be measured in blood (e.g. melatonin, cortisol, TSH) [48,49,50,51,52], in urine or saliva (6-sulfatoxymelatonin) [53,54,55,56] by measurements of core body temperature [88], by analysis of activity pattern [57,58,59,60,61,62], by measurements of the tone in the autonomic nervous system (heart rate variability) [63,41,64] or by measuring the sleep-wake cycle [42,65,37].

Melatonin

Melatonin (N-acetyl-5-metoxytryptamin), the main hormone of the pineal gland, is secreted during the dark phase of the day [66,19,67]. The hormone is secreted with a strict circadian rhythm generated from the nucleus suprachiasmaticus and primarily synchronised to the environment by influence of light [68,69]. Thus, the timing of the melatonin rhythm is considered the most reliable marker of the circadian clock. Melatonin can be measured in blood [48,70,51] and its metabolite 6-sulfatoxymelatonin (aMT6s) can be measured in urine and saliva [53,54,55,56].

Plasma melatonin and urine aMT6s measurement: laboratory analyses

Blood samples should be taken hourly at least during the evening and the morning hours and the night. Plasma samples for melatonin measurement are collected in heparinized tubes, centrifuged within few minutes and plasma separated immediately and stored at -200 C [71].

Urine samples are collected in 10 ml dry plastic tubes. The total production of urine in the measurement period is measured and a sample is taken for storage in -200 C. Collection periods should not exceed four hours, except during sleep where longer periods can be accepted, and the total measurement period should be 24 h or more [72].

The gold standard for measuring melatonin is by gas-chromatography-mass-spectrometry (GCMS) as described by Lewy and Markey [51]. In recent years radio-immuno-assays (RIA) have been developed, and these have in several studies been validated using GCMS [48,70]. The most widely used method for routine measurements are now RIA’s.

Plasma melatonin and urine aMT6s measurement: Rhythm analyses

The circadian rhythm of plasma melatonin or urine aMT6s can be assessed by cosinor analysis [73,74]. In cosinor analysis the data are fitted to a model sine curve using the least squares method, and the curve with the lowest residual error is selected as the one which best describes the data [73,74]. From this curve, it is possible to determine the acrophase time (peak time), mesor (mean value) and amplitude of the rhythm. Another method for assessment of the phase of the melatonin rhythm, is by measuring melatonin onset (Melon50%) and offset (Meloff 50%), by the mid-range crossing method [75]. Melon50% represents the time where the melatonin curve have reached 50 % of the maximum level, starting from the baseline. Meloff50% represents the time where the melatonin curve have descended to 50 % of the maximum level. The acrophase time represent the time of peak between the Melon50% and Meloff50% [75].

Sleep-wake cycle

One of the most accepted models for the regulation of human sleep is proposed by Borbelly and colleagues [76,77,78]. In this model for sleep regulation they suggest that sleep is regulated by a homeostatic process (process S, sleep drive) and a circadian process (process C, circadian drive). The characteristics of process S is an accumulating sleep drive during the day, which results in sleep in the evening, and a concurrent reduction in the sleep drive during the night. The circadian process C is suggested to increase during the sleep state ensuring a continued sleep despite a diminishing homeostatic need for sleep during the end of the sleep cycle. The circadian wake drive builds up during the day and is maximal during the hours just before sleep, when the homeostatic sleep drive is near to its peak. The circadian process is independent of the sleep and waking [76,77-79,80]. The sleep wake cycle can be assessed by different methods among which the gold standard for sleep measurement is polysomnography [81].

Polysomnography

Polysomnographic recording includes continuous electroencephalography (EEG) with scalp-electrodes, electromyography (EMG) with electrodes over specific muscle groups and electrooculography (EOG) with electrodes detecting eye-movements [81]. Originally, polysomnography was done by stationary recording devices and measurement could therefore be difficult in certain patient groups. The development of newer ambulatory polysomnography devices, which enables the patient to move freely, has expanded the possibilities for polysomnographic recordings to include surgical patients, giving the possibility to do 24 hour recordings. The polysomnographic recording is scored according to the criteria set by Rechtschaffen and Kales [81]. This method is technically demanding, and there is need for substantial technical assisting resources, because the entire scoring is made manually epoch by epoch (epoch length 20-30 sec) [81]. Thus, a single night recording will typically take one to two hours of analysis depending on the complexity of the recording. Because of these factors other methods for sleep analysis have been developed. Actigraphy and sleep questionnaires are some of the less demanding methods for measuring the sleep-wake cycle.

Actigraphy

An advantage of actigraphy compared with polysomnography, is the possibility for continuous recordings of the sleep-wake cycle for several days and even months [57,82]. Actigraphy is measured by a small wrist born device on the non-dominant arm. Wrist movements are continuously translated into an electronic signal through the displacement of a piezoelectric transducer. Hereby the signal is recorded when movement occurs in all three dimensions. Activity counts are then provided on a minute-by-minute basis for example by the so-called zero-crossing mode (ZCM) [83,84]. In the ZCM the number of times per minute where the activity crosses zero activity is registered. These data are then downloaded to a program where the final data analysis is made. We used the Cole and Cripke-algorithm for sleep analysis [85]. In this algorithm there is a weighted sum of the activity in the minute recorded, the preceding four minutes and the following two minutes. In addition there are several rescoring rules [85]. There are high agreement rates (about 95%) and a correlation coefficient of 0.81 for total sleep time in the ZCM method compared with PSG [84]. Actigraphy has also been validated in surgical patients [83]. Here, an agreement between actigraphy and self-reported activity registration of 80% was found, and for sleep the agreement was 77% [83]. Depending on the software used, one can also obtain data for sleep onset time, sleep efficiency, wake duration after sleep onset as well as the number of awakenings.

Activity rhythm

The use of actigraphy has also been utilized in circadian rhythm analysis of activity parameters [60,86]. The circadian rhythm of physical activity is highly correlated to endogenous body rhythms [87]. Thus, measures of circadian activity rhythm, correlates to the circadian rhythm of melatonin and core body temperature [59,62]. Due to the possibility of various masking effectors, the analysis of the activity rhythm may not show the rhythm of the endogenous circadian pacemaker precisely [88].

Non-parametric analysis of circadian activity rhythm

Because activity data seldom resemble a sine curve, it is not possible to do the rhythm analysis by cosinor analysis. A validated method for describing rhythmic changes and phase of the circadian activity rhythm is by the so-called non-parametric circadian rhythm analysis [60,86]. This analysis involves an assessment of the stability of the activity rhythm over several days. This parameter called the inter-daily stability (IS), is a degree of resemblance between individual days. The measure ranges from zero to one, with higher values indicating stable rhythm. The intra-daily variability (IV) is a measure of the fragmentation of periods of rest and activity within 24 hours of measurement. This measure ranges from zero to two, with higher values indicating fragmentation of the rhythm. From the activity data it is also possible to assess the amplitude, which is the difference between the activity in the most active 10 hours (M10) and the activity in the lowest five active hours (L5). The relative amplitude is a measure which is obtained by dividing the amplitude by the sum of L5 and M10, and ranges from zero to one with higher values indicating higher amplitude. Finally, it is also possible to obtain the clock-time where the lowest five hours start, and the highest ten hours start (L5-onset time, and M10-onset time, respectively).

Core body temperature

The body temperature is regulated from the hypothalamus within narrow limits by a complex feed-back system. In normal healthy subjects core body temperature is highest in the period between 14:00 and 20:00h and has a well defined minimum at 05:00 h. The core body temperature is regulated around a “set-point” through heat loss and heat gain mechanisms [89]. The most important system is the heat loss mechanism which is regulated through peripheral vasodilation [90,91]. There is an interaction between the circadian thermoregulatory system and the sleep-wake cycle and melatonin production from the pineal gland [92]. In the evening there is a reduction of physical activity, lowered light influence to the SCN and an increase in melatonin production. Melatonin further increases peripheral temperature through vasodilation and the rapid fall in the core body temperature increases sleep propensity [93]. In the morning the reverse process results in rapid increase in core body temperature and reduced sleep propensity. It should be kept in mind that core body temperature rhythm is a result of endogenous and exogenous components and therefore, it is important to be aware of so-called “masking” effectors that can influence or hide the output of the endogenous pacemaker [94,95]. Examples relevant for the surgical patient is blood and fluid loss during surgery, hypothermia during surgery due to low ambient temperature in the operating theatre, physical activity, insufficient nutrition, posture and inflammatory and endocrine responses to surgery. Thus, analysis of core body temperature in relation to surgery should be done cautiously.

Measurement of core body temperature

Body temperature can be measured using a rectal probe, in the mouth (sub-lingual), near the tympanic membrane and intra-aural (infrared thermometry), in the gut (ingestible pill), the axilla, the esophagus and the urinary bladder [96]. Urinary bladder temperature has characteristics similar to those of rectal temperature [97] and studies have shown that temperature changes in the core (measured by a pulmonary artery catheter) is detected earlier in the bladder compared with the rectum [92,97,98]. Another obvious advantage is the use of an indwelling bladder catheter temperature probe in patients undergoing lower rectum surgery with low anastomoses or in patients having abdominoperineal resection (APR).

Heart rate variability

Heart rate is under the control of the autonomic nervous system [99,100]. The heart rate and the duration between individual heartbeats is constantly being regulated on a beat to beat basis but also through long term effects that regulate heart rate over several hours. Because of continuous changes in the vagal/sympathetic balance, the sinus rhythm exhibits fluctuations around the mean heart rate. The main periodic fluctuations are those caused by respiratory sinus arrhythmia, baroreflex-related and thermoregulation-related heart rate variability (HRV). The effects caused by respiratory movements are short term effects affecting the HRV on a beat to beat basis (high frequency effects, vagally mediated) [99]. Thermoregulatory peripheral blood-flow adjustment results in a low frequency change in peripheral vascular resistance with accompanying fluctuations in the HRV with the

Table 1

Overview of clinical studies where melatonin or its metabolite (aMt6s) has been measured in relation to surgery in patients admitted to the general surgical ward after surgery. ** Patients were randomized to either isoflurane or propofol and increased amplitude was only found in the isoflurane group ** Amplitude reduced in patients with no postoperative complications. Amplitude increased in patients with postoperative complications.*
Y, yes. N, No. ↓, reduced. ↑, increased. -, not measured.

	n	Measurement method	Light control	Preop. Measurement	Postop. measurement duration	Circadian disturbance	Amplitude	Phase
Minimally invasive surgery								
Cronin [106]	**7**	**melatonin (plasma)**	**Y**	**N**	**3 days**	**Y**	**Y (↓)**	**-**
Fassoulaki [108]	**13**	**melatonin (plasma)**	**N**	**Y**	**1 day**	**N**	**N**	**-**
Gögenur [72]	**36**	**aMT6s (urine)**	**Y**	**Y**	**5 days**	**Y**	**Y (↓)**	**-**
Gögenur [109]	**12**	**aMT6s (urine)**	**Y**	**Y**	**1 day**	**Y**	**Y (↓)**	**Delay**
Kärkela [111]	**20**	**melatonin (saliva) aMT6s (urine)**	**Y**	**Y**	**1 day**	**Y**	**Y (↓)**	**-**
Ram [115]	**20**	**aMT6s (urine)**	**N**	**Y**	**2 days**	**Y**	**Y (↑)**	**-**
Reber [116]	**32**	**melatonin (plasma)**	**Y**	**Y**	**8 hours**	**Y**	**Y (↑)***	**-**
Major surgery								
Derenzo [107]	**21**	**aMT6s (urine)**	**N**	**N**	**2 days**	**Y**	**Y (↓)**	**-**
Gögenur [71]	**11**	**melatonin (plasma)**	**Y**	**Y**	**2 days**	**Y**	**Y (↑)**	**Delay**
Shigeta [202]	**29**	**melatonin (plasma)**	**N**	**Y**	**1 day**	**Y**	**Y(↓/↑)****	**-**
Vician [118]	**19**	**melatonin (plasma)**	**N**	**Y**	**2 days**	**Y**	**Y(↑)**	**-**

same frequency (low frequency effects, predominantly sympathetically mediated) [100].

There is a characteristic circadian variation in the autonomic nervous system and thus also in HRV parameters in healthy adults [101,102,64]. It has been shown, that the circadian rhythm in HRV-parameters can be manipulated/modulated by melatonin treatment or bright light therapy [64].

Time domain method

In the time domain method, statistical methods including either the duration of the interbeat intervals or comparisons of the length of the adjacent cycles are used. An example of the methods involving interbeat intervals is the standard deviation of normal to normal (NN) beats (SDNN). The SDNN is usually calculated for the whole 24 hour period and is a measure of overall variance and thus a result of both short term and long term influences on the HR [103]. The root mean square of successive differences (RMSSD) and the proportion of NN-intervals which are more than 50 msec's apart (pNN50) are both examples of measures including the length of adjacent cycles. The RMSSD and pNN50 are both specific markers of the parasympathetic nervous system [103,99].

Frequency domain method

In the frequency domain analysis, the heart rate is analyzed by spectral analysis whereby the variance in heart rate can be expressed depending on its underlying frequency components. Based on this, the frequency bands can be classified according to their underlying power, eg: high frequency (HF) power from 0.15 to 0.4 Hz (vagally mediated); low frequency (LF) power from 0.04 to 0.15 Hz (both vagal and sympathetic influences); and very low frequency (VLF) power from 0.0033 to 0.04 Hz (long-term circadian effects of the thermoregulatory system, the renin-angiotensin system and vasomotor system in addition to influence by vagal and sympathetic nervous activity) [103].

POSTOPERATIVE CIRCADIAN RHYTHMS

Disturbances in the melatonin rhythm after surgery

Melatonin in plasma, urine or saliva have been examined in several studies in relation to surgery [104,105,106,107,108,72,109,71,110, 111,112,113,114,115,116,202,118]. Some of these studies are studies on patients admitted to the postoperative intensive care unit where patients can stay intubated for several days [105,110,112,113,114]. Because of the substantial differences between these patients and patients on a regular surgical ward (medication, light, noise) the mechanisms affecting circadian rhythms are different and thus, these studies cannot be compared directly. In table 1, studies where melatonin disturbances have been examined in relation to surgery and where the patients have been examined in the general surgical ward are displayed.

In the studies where plasma melatonin have been measured in relation to surgery, there have been limitations in the design with either lack of preoperative sampling [106,202], insufficient preoperative samples [116], or insufficient sampling intervals [202,118] making interpretations of amplitude or assessment of phase of the rhythm difficult. In five studies the melatonin metabolite in urine and/or saliva in relation to surgery has been examined [107,72,109,111,115]. A detailed phase assessment could not be performed in any of these studies.

Major surgery and circadian melatonin disturbances

We performed a study on subjects undergoing major surgery for gastrointestinal cancer [71]. Blood samples were taken every hour in a 24 period prior to surgery and 48 hours after surgery. Light exposure was measured and controlled to be < 10 lux in the night-time period (23:00 to 07:00). Compared with preoperatively, the phase of the plasma melatonin rhythm was delayed the first night after surgery, and normalised on the second night after surgery. Basal secretion level of melatonin in the day-time period was reduced immediately after surgery and normalised the second day after surgery [71]. The amplitude and the maximum

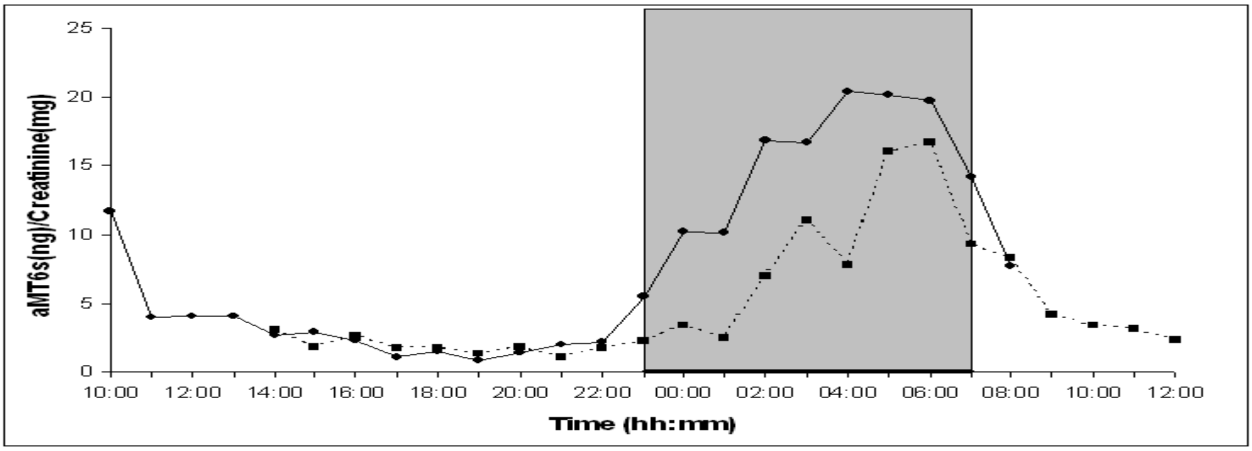

Figure 1
Median values for aMT6s concentrations (ng aMT6s / mg creatinine) before and after surgery. Open circles = preoperative values. Full squares = postoperative values. Shaded area on x-axis represents darkness (23:00 h – 07:00 h).

concentration of melatonin was unchanged the first night after surgery and increased on the second night after surgery. Thus, we showed, for the first time in the literature, that the rhythm of plasma melatonin was delayed the first postoperative night, and normalised on the second postoperative night [71].

Shigetta et al. measured plasma melatonin in 29 patients undergoing major abdominal surgery one day before surgery and on the second postoperative day [202]. They found, that peak concentration was reduced in patients > 80 years old without postoperative complications and that the amplitude was unchanged in patients < 80 years old without complications, compared with preoperatively [202]. The authors did not study the phase characteristics of the postoperative melatonin curve.

The reason for the delay in the onset of the night time increase in plasma melatonin has not been clarified. We found a positive correlation between the duration of surgery and the onset of the night-time melatonin peak on the first night following major surgery, suggesting that either the surgical stress or the time in "lights off" in the day-time may have an impact [71].

We studied 36 patients undergoing major surgery and reported the aMT6s secretion in urine one day before surgery and on the fourth postoperative day [72]. The day-time excretion of urinary aMT6s was increased on the fourth postoperative day and at night-time aMT6s concentration in urine was unchanged compared with preoperatively [72] suggesting that there could be a phase delay in the melatonin rhythm.

Minor surgery and circadian melatonin disturbances

We performed a study where a detailed phase assessment could be made following laparoscopic cholecystectomy [109]. Urinary aMT6s concentration was measured in twelve female patients undergoing laparoscopic cholecystectomy for 24 hours before and 24 hours after surgery [109]. Patients were confined to a single room and light levels were controlled in the night time period (23:00 to 07:00). In a cosinor analysis of the urinary aMT6s-data, a phase delay and a reduction in the amplitude was found the first night after surgery (figure 1). The reduced amplitude in urinary aMT6s have also been found by Derenzo et al. in patients undergoing knee arthroplasty [107]. Preoperative sampling was not made and a detailed phase assessment of the postoperative rhythm could therefore not be made. The authors also investigated whether the reduced amplitude in postoperative aMT6s rhythm was a result of timing or levels of cortisol. There was no consistent relationship between the two rhythms (urinary aMT6s and free cortisol). We also could not find any significant correlation between the phase markers of the plasma cortisol and melatonin rhythm on the first night after major abdominal surgery [71].

Cronin et al. examined in seven women, the hourly melatonin secretion in the period between 22:00 and 08:00 hours, for three days after benign open gynaecological surgery. Plasma melatonin concentrations were significantly lower on the postoperative night compared with the second and third postoperative night [106]. Phase disturbances could not be determined in the study by Cronin et al. because of lack of preoperative sampling [106,202]. In patients undergoing peripheral orthopaedic surgery it was also shown, that urinary aMT6s excretion was reduced compared with preoperatively [111]. No phase assessments could though be made.

Anesthesia and melatonin disturbances

It has not been investigated whether general anaesthesia per se (without surgery) has an effect on melatonin secretion the first nights after surgery. During general anaesthesia with isoflurane or sevoflurane, plasma melatonin was shown to be increased and decreased respectively in patients undergoing gynaecological surgery [104]. In a study including 8 hours of sampling after open gynaecological surgery in 32 patients, it was shown that both isoflurane and propofol resulted in an increase in melatonin concentrations in the recovery period compared with before anaesthesia and surgery [116]. The patients randomized to propofol had a gradual decrease in the plasma melatonin levels compared with the isoflurane group [116]. Plasma melatonin levels in 13 patients undergoing ambulatory surgery (diagnostic dilatation and curettage of the uterus) with sevoflurane general anaesthesia was though not disturbed [108]. We found a reduction in the plasma melatonin concentration in the immediate period after major surgery, and an unchanged night-time excretion in the first night after surgery, suggesting that the effects of anaesthesia on the melatonin levels was not a major factor [109]. Circulating

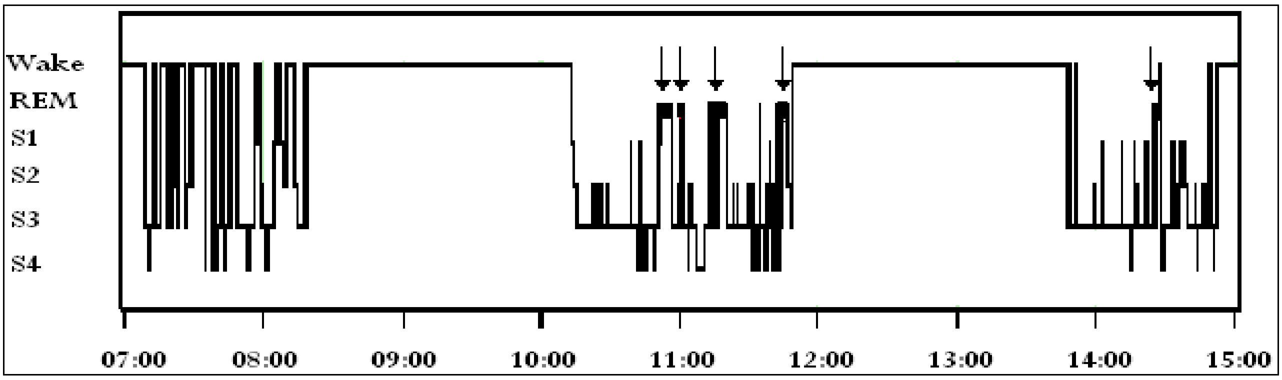

Figure 2a
Postoperative hypnogram (07:00-15:00 h) for a 68 years old female patient who was operated for colon cancer by right sided hemicolectomy. Arrows represent REM-sleep.

melatonin is metabolized in the liver mainly by the cytochrome P450-system (type 1A2) [72] and in the tissues, oxidative pyrrole ring cleavage seems to be the major metabolic pathway [102]. CYP1A2 is not pivotal for the metabolization of the mostly used intravenous and gas-anaesthetics [123,116,214].

In patients undergoing peripheral orthopaedic surgery and randomized to general or spinal anaesthesia there were no differences between the two anaesthetic techniques in the aMT6s secretion in urine or saliva [111].

Disturbances in the sleep-wake cycle after surgery

In order to establish a cause and effect relationship between circadian disturbances in the melatonin rhythm and changes in the sleep-wake cycle, it is necessary to examine surgical patients in "constant routine" or "forced desynchrony" experiments (described above). In this way, it would be possible to differentiate whether the sleep-wake cycle disturbances after surgery are based on factors related to the homeostatic or circadian sleep regulation. However, in order to establish a causal relationship, it is necessary to describe the extent and nature of the sleep-wake disturbances after surgery. Sleep questionnaire-, actigraphy- and polysomnography studies can be used for this purpose [10].

Sleep questionnaire studies

Sleep questionnaire studies examining the sleep-wake cycle with emphasis on the circadian distribution of sleep during the day and night time are preliminary [23,26,103]. We examined the preoperative sleep (one week) and postoperative sleep (four weeks) in a study of 12 patients undergoing laparoscopic surgery, and 15 patients undergoing major surgery [11]. There were no differences in the preoperative total sleep time or day time sleep-duration between the two groups. The patients in the laparoscopy group experienced increased total sleep and day-time sleep in the first week after surgery. In the major surgery group the total sleep time was increased on the first, third and fourth week after surgery, and the day time sleep duration was increased for all four weeks after surgery. Inter-group differences were seen in day-time sleep on the third and fourth week with increased day-time sleep in the major surgery group compared with the laparoscopy group. Thus, we showed that the circadian disturbance of sleep was more prolonged after major surgery compared with laparoscopic surgery [11]. In the only other study where day-time sleep has been assessed after laparoscopic surgery, the authors used a sleep diary, where the patients registered the duration of naps in the day-time period [26]. The authors did not find any significant difference in the sleep duration in any of the seven postoperative days examined, compared with the one week preoperative measurement period [26,11]. The reason for the

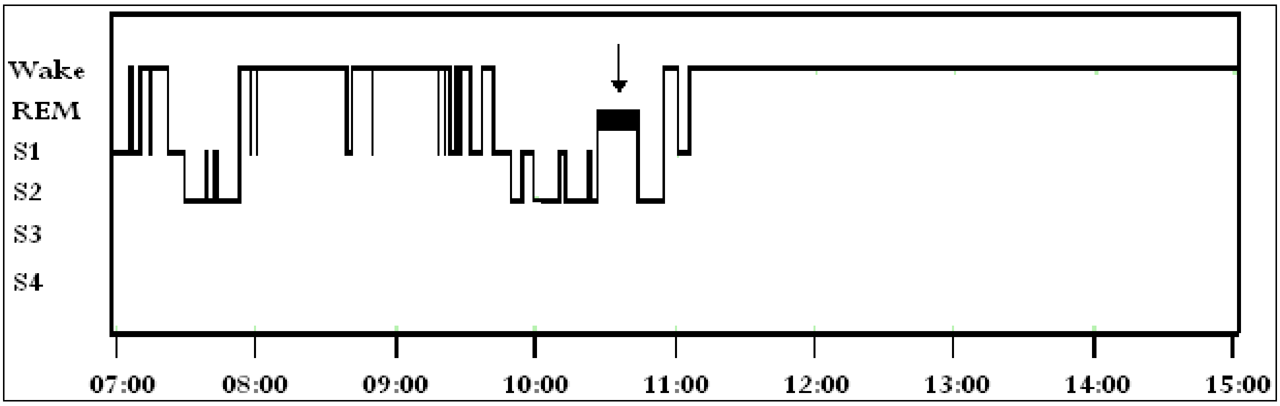

Figure 2b
Postoperative hypnogram (07:00-15:00 h) for a 38 years old male patient who was operated for gastric cancer by subtotal gastrectomy. Arrow represents REM-sleep.

differences in the results may be due to the difference in the measurement method. Thus, we provided the patients with a questionnaire where there was registration slots for 24 hours of sleep divided into 15 minutes duration for each slot. The patients continuously registered sleep in this questionnaire. However, there have been no studies validating questionnaire studies comparing it to the gold standard of polysomnographic recordings in the postoperative period. The possible recall bias which warrants for caution in using questionnaires, may be even more serious after major surgery, where cognitive disturbances are known to occur especially during the first week after surgery [2,72,13,181,193].

Actigraphy studies

The circadian distribution of sleep after laparoscopic surgery or major general surgery can be measured by use of actigraphy [83]. In a study on 76 patients undergoing laparoscopic cholecystectomy and 44 patients undergoing major surgery, we examined the actigraphically determined sleep duration for four days before and four days after surgery [83]. The day-time sleep duration was significantly reduced from day one to day four after laparoscopic cholecystectomy compared with preoperatively, and the night-time sleep was unchanged for the same period. After major surgery the day-time sleep was significantly increased for four days after surgery compared with preoperatively, and the night-time sleep was significantly reduced for the same period compared with preoperatively. In an intergroup comparison, the laparoscopic group had significantly shorter night-time sleep and day-time sleep for the four days after surgery. In the only other study where actigraphically determined sleep has been used after surgery the authors found, that sleep duration was increased on day one, three and five after laparoscopic cholecystectomy compared with preoperatively [26]. In a repeated measures analysis, day-time sleep was found to be significantly increased the first week after surgery [26]. This result is comparable with our questionnaire study [11]. However, in the actigraphy study we found a minor but significant reduction in sleep duration in the day-time after surgery [83]. The discrepancy in the results may be due to considerable inter-individual variation in actigraphy parameters used for determination of day-time sleep. The most ideal measurement method would therefore be polysomnographic recordings of sleep.

Table 2
Daytime (07:00 – 23:00 h) and night-time (23:00 – 07:00 h) HRV parameters (ms2) for the preoperative day (PreD) and postoperative day two (POD2). *VLF: very low frequency power. LF: low frequency power. HF: high frequency power. LF/HF: ratio between low frequency and high frequency power. Data are presented as median (range). a, P < 0.05 for intragroup comparison with the corresponding daytime within the same study day. b, P < 0.05 for intragroup comparison with the corresponding preoperative measurements.*

	PreD		POD2	
	Day	Night	Day	Night
VLF	222.5 (47.4-1721.6)	138.9 (30.0-4976.8)	60.3 (15.9-865.8)^{b}	128 (5.3-1607.1)
LF	131.5 (29.8-1043.8)	90.2 (17.3-1465.2)	24.6 (5.3-850.1)	63.8 (3.5-1300.3)
HF	37.7 (3.5-232.6)	60.3 (5.9-686.6)^{a}	4.8 (0.6-130.3)^{b}	18.8 (0.9-326.2)
LF/HF	4.9 (0.5-10.9)	1.8 (0.2-6.7)^{a}	6.8 (0.3-13.02)^{b}	4.7 (0.7-12.2)^{b}

Polysomnography studies

In a study on 11 surgical patients we assessed sleep by polysomnography for one day before surgery and two days after surgery [91]. The time spent awake, light sleep and in SWS- sleep did not significantly change on the first two nights after surgery compared with preoperatively. The REM sleep duration was though significantly reduced for both nights after major surgery. We found, that the patients had significantly increased REM sleep duration and reduced time awake in the day time on the day after surgery (Figure 2). This was the first description of the polysomnographically determined sleep distribution in the general ward in the day-time after surgery [91]. In the only other study where a continuous polysomnographic measurement were done in the days after surgery, the recordings were made with a stationary PSG-recording device in the intensive care unit environment and the patients underwent a mixture of elective and acute operations, and for both orthopaedic and abdominal surgeries [17].

Thus, these studies cannot be compared. The patients in our study were unrestricted in their mobility because of the ambulatory polysomnographic recording device. Thus, the data were not affected by the measurement methods in the day-time. During the night, blood samples were taken through an extended i.v. line to diminish the disturbance for the patients.

In conclusion, we have shown, that patients both after major surgery – but also after laparoscopic surgery – have changes in their sleep-wake cycle, and that this disturbance is more severe after major surgery. It is known that REM sleep is under influence of the circadian pacemaker [45,61]. The characteristic sleep disturbances after major surgery was a lack of REM sleep in the first days after surgery in most patients but also a shift of total sleep time and REM-sleep to the day-time period which we observed in some of our patients [11]. This may be influenced by the central circadian pacemaker. We found, in patients undergoing laparoscopic cholecystectomy, that there was a positive correlation between the aMT6s amplitude and total sleep time on the first postoperative night [109]. We also found, that night time aMT6s excretion was correlated negatively to wakefulness after sleep onset on the fourth night after major surgery [72]. The total 24 hours excretion of aMT6s on postoperative day 4 was also positively correlated to night-time sleep efficiency and negatively correlated to wakefulness after sleep onset [72]. These data suggest that there is a correlation between the excretion of the melatonin metabolite in urine and postoperative sleep parameters [72,109]. However, the exact physiological connection between these correlations has not been clarified in our studies [72,109].

Disturbances in HRV after surgery

In patients undergoing major abdominal surgery, HRV measurement in the perioperative period significantly correlates with short-term and long-term cardio-vascular morbidity and mortality as well as length of hospital stay [75,76,209]. It has also been established that there exists specific circadian peaks in cardiovascular events (sudden unexpected death, myocardial ischemia and pulmonary embolism) after surgery [30,33,34]. It is suggested, that the morning increase in heart rate, blood pressure, vascular tone, blood viscosity and reduction in the fibrinolytic activity, is responsible for this circadian peak in cardiac event [177,178]. It is well established, that the tone in the autonomic nervous system varies considerably during the wake and sleep periods and also during specific sleep stages [6,32,41,47,208,212,222]. Even if there have been several studies describing HRV in relation to general surgery [9,19,69,70,75,76,112,124,149,200,209] there has been no studies to establish the circadian variation in HRV and myocardial ischemia in relation to the sleep-wake cycle.

HRV after major surgery

We performed one study examining HRV in relation to major surgery [90]. The aim was to establish if there was a circadian variation in time domain variables after major surgery [90]. We examined time domain variables (SDNN, RMSSD, PNN50) for a 24 hour measurement period on the second or third day after surgery. There were no circadian variation in the SDNN, RMSSD and pNN50 after surgery. Thus, the expected day-night variation in the autonomic parameters was absent [90]. A limitation of the study was the lack of preoperative measurement and lack of sleep registration. No conclusions could therefore be made regarding the relation of HRV changes to the sleep-wake cycle. Subsequently, we therefore analyzed the HRV and PSG data on 10 subjects with concomitant HRV measurement including measurement of myocardial ischemia (ST-segment deviations) and continuous ambulatory polysomnography [91]. In this analysis we found, that compared with preoperatively, the HRV was disturbed on the second postoperative day with a blunting in the day/night amplitude of frequency domain parameters (table 2). In the 10 patients there were a total of 70 episodes of ST-segment deviations on the postoperative day 2. There was an apparent circadian concentration of myocardial ischemia during the night time period (table 3). This increase was not related to sleep phases. Thus, there were no significant differences in the distribution of myocardial ischemia in the sleep and wake state. It was not possible to find a correlation between the ST-segment deviations and the HRV-parameters. The ST-segment depressions were concentrated in the night time period but there were no difference between the occurrence of ST-depressions during sleep compared with the wake state. Thus, we suggest, that postoperative circadian factors may have a larger impact on the occurrence of ST-segment depressions, than the sleep and wake state per se. In a study on 11 patients after aortic surgery, a reduced circadian variation in frequency domain HRV measures was found, but no correlation between HRV-parameters and the occurrence of myocardial ischemia could be demonstrated [70].

Table 3

ST-depressions measured in the daytime (07:00-23:00 h) versus night-time (23:00-07:00 h) and wake versus sleep on postoperative day two (POD2). *# Data are presented as number of ST-depressions in the measurement period / ST-depressions per hour in the measurement period. ## Data are presented as number of ST-depressions in polysomnographically defined wake and sleep for the whole POD2 measurement period.*

Holter-monitoring and PSG-monitoring was initiated exactly at the same time, ensuring that the time stamps were synchronized myocardial ischemia was defined as reversible horizontal or down-sloping ST-segment depression from baseline ≥ 1 mm or an elevation ≥ 2 mm. For the few ischemic events where there were both wake and sleep periods, the ischemic event was classified as being awake if the dominant (the longest duration) phase was wake. Reversibly, it was classified as being an ischemic event during sleep if sleep was dominating.

Patient number	POD2		POD2	
	Daytime#	Night-time#	Wake##	Sleep##
1	1 / 0.06	2 / 0.25	0.06	0
2	2 / 0.13	3 / 0.38	0.12	0
3	0 / 0	0 / 0	0	0
4	0 / 0	0 / 0	0	0
5	0 / 0	0 / 0	0	0
6	16 / 1	12 / 1.5	1.7	1.5
7	14 / 0.88	8 / 1	0.95	0.65
8	1 / 0.06	11 / 1.38	0.37	0.75
9	0 / 0	0 / 0	0	0
10	0 / 0	0 / 0	0	0

Disturbances in the core body temperature rhythm after surgery

The core body temperature (CBT) is known to be regulated by the central circadian pacemaker in healthy subjects [67,44,217]. The circadian rhythm of the core body temperature is significantly correlated to other endogenous rhythms [46,60,130,217]. An important relationship between the circadian variation in core body temperature and sleep has also been demonstrated. [50,81,132,153,205,95]. Peripheral vasodilatation in the evening with increased peripheral circulation and thus heat diversion from the core to the periphery results in a fall in central core body temperature. This fall in core body temperature have been linked to increased sleep propensity. Thus, there is a tight connection between sleep onset and the core body temperature rhythm [63,64,93,130]. We wanted to examine the core body temperature rhythm after both minor and major surgery.

CBT after minor surgery

We performed a study on patients undergoing laparoscopic surgery. In 12 patients we measured core body temperature the day before laparoscopic cholecystectomy and the day after surgery [109]. Celecoxib 200 mg x 4 was used both preoperatively and postoperatively to minimise the effect of antipyrogenic drugs on the core body temperature rhythm. We showed, that there was a significant shift in the acrophase of core body temperature rhythm with an almost inverse core body temperature rhythm with the lowest temperatures in the afternoon and evening and highest temperature during the night [109].

CBT after major surgery

In 11 patients undergoing major abdominal surgery, we measured core body temperature the day before surgery and on the second postoperative day [92]. We showed, that there was a significant circadian variation in the core body temperature rhythm before surgery with a night-time decrease as expected. On the second postoperative day there was no statistically significant variation in core body temperature. We showed this absent circadian variation by non-parametric repeated measures analysis of variance. No detailed rhythm analyses was performed, thus, the acrophase time and amplitude were not derived [92]. We repeated the study in 11 patients undergoing major surgery with measurement for 1 day preoperatively and for 2 days after surgery [71]. Acetaminophen or NSAID was not used in the perioperative period for pain control. In a cosinor analysis, we found, that there was a significant delay in the temperature acrophase time on the second postoperative day compared with preoperatively [71].

It is difficult to interpret whether the observed changes in core body temperature the first couple of days after surgery are related to an effect on the central circadian pacemaker [109,71,92].

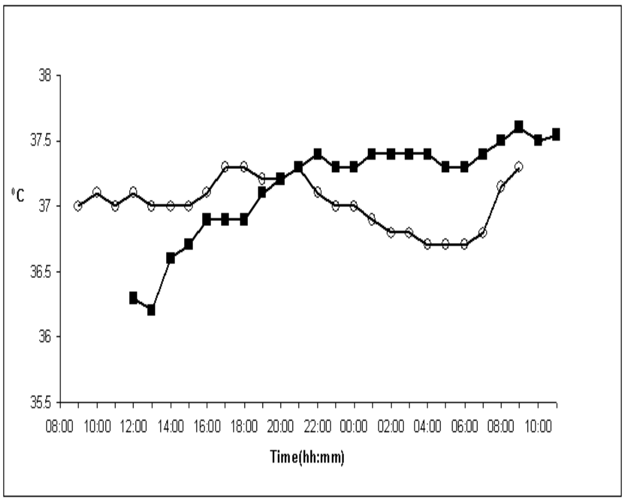

Figure 3a
Core body temperature rhythm before (open circles) and after minimally invasive surgery (filled squares).

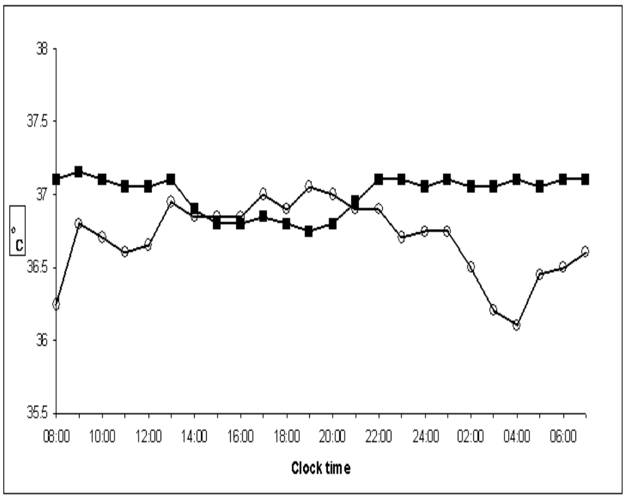

Figure 3b
Core body temperature rhythm before (open circles) and after major surgery (filled squares

Other masking effectors are possible in the peri- and postoperative period (effects of anaesthesia, endocrine response to surgery, inflammatory response to surgery, physical activity). However, based on the consistent findings of a phase delay of the temperature rhythm and melatonin and cortisol rhythms in the first days after surgery [109,71], it is possible, that the observed changes are caused by responses to surgery from the central circadian pacemaker.

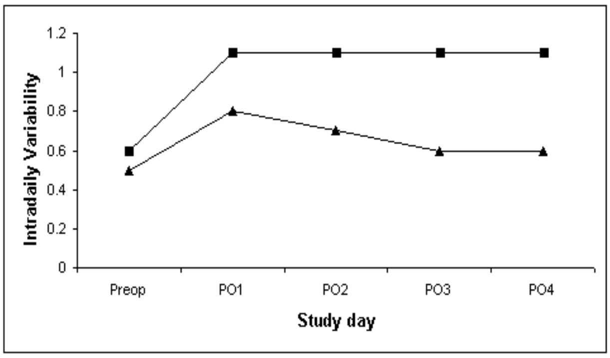

Figure 4a
The actigraphically determined circadian activity parameter intra-daily variability (IV) before and after major abdominal surgery (squares) and laparoscopic cholecystectomy (triangles).

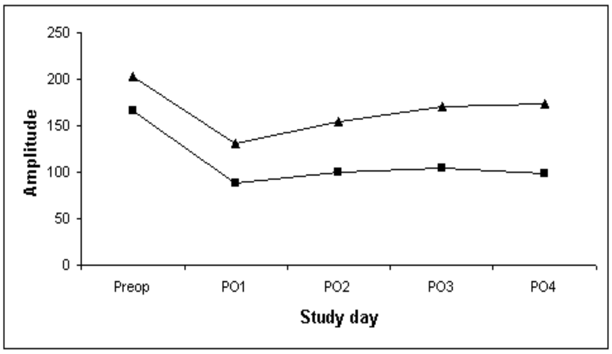

Figure 4b
The amplitude of the actigraphically determined activity rhythm before and after major abdominal surgery (squares) and laparoscopic cholecystectomy (triangles).

Postoperative circadian activity rhythm

The circadian rhythm of physical activity has been shown to be tightly correlated to the activity of the central circadian pacemaker in several studies [57,151,59,62]. A preserved circadian rhythm in motor activity with high amplitude, has been correlated with improved subjective health parameters, morbidity and mortality [163,191]. Thus, in studies on patients with metastatic disease it has been shown, that patients that preserved a marked amplitude in their activity rhythm had better subjective health quality, lower levels of serum cortisol and reduced mortality two years after initiation of chemotherapy [163,191]. Actigraphy has been used in several studies in relation to minor and major surgery to determine sleep [83,26,29,74,72,109,10,12,114,135]. In a study on patients undergoing major surgery and healthy controls it was shown that activity measures were fragmented in the period between the second and fourth postoperative day [83]. In a preliminary study the activity levels were examined in patients undergoing laparoscopic colonic surgery, open colonic surgery with fast-track care principles postoperatively and open surgery with a conventional care program [235]. The authors analysed whether there were a correlation between the activity parameters and the shortened hospital stay in the fast-track and laparoscopic colonic surgery group. There were no apparent correlation between the total activity count and a shortened hospital stay. The authors did not analyse the circadian amplitude in the activity rhythm [235].

Disturbances in the activity rhythm after minor and major surgery

We performed the only study after minor and major surgery where the circadian activity rhythm has been characterised with respect to phase, amplitude and fragmentation [83]. We showed that both patients undergoing laparoscopic surgery and major surgery had a fragmented activity rhythm in the four days postoperative period compared with preoperatively. Thus, both intra-daily stability indicating the stability of the rhythm over several observational days and intra-daily variability measuring fragmentation of the rhythm on a day-to-day basis were disturbed for four days after surgery. The amplitude was reduced for all four post-operative days for both patient groups. These data indicates, that

there are obvious disturbances in the activity parameters both after minor and major surgery, but these are more severe after major surgery indicating a dose response relationship between the surgical stress and the magnitude of circadian activity disturbances (Figure 4 a and b). A limitation of the study is based on the environment of the postoperative measurement of activity rhythms in the laparoscopic group where the postoperative measurement was mainly done in the patient's home environment. Thus, the activity rhythm in the major surgery group could be masked / affected by postoperative care. The patients followed standard peri- and postoperative care principles for patients undergoing major surgery in our department, and we did not intervene with these principles to avoid an additional masking of the activity rhythm. Future studies should correlate circadian activity rhythm parameters with other circadian markers in the postoperative period (plasma melatonin, urine aMT6s or core body temperature rhythm).

CORRELATIONS BETWEEN CIRCADIAN MARKERS AND CLINICAL OUTCOME PARAMETERS

Improvement of postoperative convalescence and recovery has been the focus in several studies [24,120,121]. Convalescence is primarily a measure of the time for the patient to return to work or recreational activities and recovery is primarily the process of returning to a state of health or becoming well. Recovery parameters are important measures because these are major determinants of the patients perceived well-being the days after surgery. Measurements of general well-being, sleep quality and pain by visual analogue scales are frequently used in the evaluation of postoperative recovery [24,27,29,72,234]. Another important parameter which has been used in several studies to assess recovery is measurement of fatigue. It has been shown, that fatigue in the postoperative period is very important for patients recovery [117,126,16]. The background behind fatigue in the postoperative period has not been clarified. It is suggested, that the etiological factors may be different in the immediate and late postoperative periods. Thus, it has been shown that interventions such as laparoscopic surgery [21], and intravenous dexamethasone [27] reduce fatigue in the first days after surgery. For reduction of the late postoperative fatigue preliminary studies have shown, that the supplementation of growth hormone can reduce fatigue [125]. Based on these differential interventions to reduce early or late postoperative fatigue it is possible that the underlying etiological factors are different (e.g. inflammatory cytokines in the immediate postoperative period and loss of lean body mass
and cardio-respiratory dysfunction in the late postoperative period) [16]. An important issue in the evaluation of fatigue after surgery is that the most used fatigue scale by Christensen et al. is a ten point scale which integrates muscular weakness, need for sleep, altered state of mood and concentration [55]. Even if this ten point fatigue scale has been validated in relation to both minimally invasive surgery and major surgery [24,9,29,54,55,199] it is not possible to specifically state what the proportion of sleep or mood disturbances add to the proportion of muscular weakness or vice versa. Thus, the correlation between postoperative fatigue and sleep quality we have shown may be due to this [72].

Correlation between aMT6s in urine and postoperative recovery parameters after major surgery

In a study of 36 patients undergoing major surgery, we examined the urinary excretion of aMT6s before surgery and on the fourth day after surgery [72]. There was a circadian change in the day-evening ratio of aMT6s excretion on the fourth day after surgery compared with preoperatively [72]. There was significantly impaired objective sleep quality, general well-being, fatigue and pain on the fourth day after surgery. However, no correlations were found between any of the aMT6s parameters (day excretion, night excretion or total excretion) and sleep quality, fatigue, general well-being or pain [72]. Although a correlation was not found between the urinary melatonin metabolite parameters and the subjective outcome parameters there was a significant correlation between the total 24 h excretion of aMT6s on the fourth postoperative day, and sleep efficiency and wakefulness after sleep onset. The apparent inconsistency between the correlation between aMT6s excretion and subjective sleep quality and significant correlation to actigraphically determined sleep parameters are not surprising. Studies have shown that there can be positive effects of interventions on objectively measured sleep parameters, but no effect on subjective sleep parameters [101,229].

Relationship between circadian disturbances and cognitive dysfunction after surgery

Cognitive dysfunction is common after major non-cardiac surgery and may be related to increased morbidity and mortality [140,13,181,192]. The most severe form of cognitive dysfunction after surgery is postoperative delirium. It has been hypothesised, that the occurrence of postoperative cognitive dysfunction increases morbidity and mortality after surgery [140]. In a clinical study of 1064 patients undergoing major non-cardiac surgery it was shown that cognitive dysfunction at hospital discharge and 3 months after surgery were correlated with increased postoperative mortality [159]. The etiological factors contributing to the development of postoperative cognitive dysfunction have not been clarified. Several factors have been suggested such as postoperative hypoxaemia [2], inflammatory and oxidative stress [180], the anaesthetic method [104,182], sleep and circadian disturbances [72]. In geriatric patients a significant correlation between the occurrence of delirium and the 24 hours aMT6s production was found [20]. In patients after thoracic esophagectomy and major abdominal surgery it has been shown, that circadian disturbance in the melatonin rhythm in the postoperative phase was significantly correlated to the occurrence of delirium [112,202]. However, postoperative cognitive dysfunction may have a different pathophysiological background than delirium, and it has not been shown whether an amplitude or phase disturbances in melatonin secretion after surgery is correlated with postoperative cognitive dysfunction. Even if melatonin induces an improvement in verbal memory consolidation in healthy subjects [94] and also has been shown to improve mild cognitive impairment preceeding dementia [79], these positive effects of melatonin treatment have not been demonstrated in a surgical population. A positive correlation has been found between a reduced amplitude in day-evening ratio of saliva cortisol one week after surgery and postoperative cognitive dysfunction [184]. It remains to be shown if there are any association between postoperative

Table 4

Overview of studies where melatonin was administered in the perioperative period.
** Two test performed. ** ED50 and ED90 dose for propofol and thiopental was measured for abolishment of eye lash reflex and verbal response 60 s after administration. *** BIS, Bispectral Index. Y, yes. N, No. ↓, reduced. ↑, increased. →, unchanged. -, not measured.*

	n	Intervention (dose)	Route (melatonin)	Administration in relation to surgery	Type of surgery	Outcome parameter	Effect	Side effect
Acil [5]	66	Melatonin (5 mg) Midazolam (15 mg) Placebo	Sublingual	90 min before general anesthesia	Laparoscopic cholecystectomy	Anxiety Sedation Orientation Neuropsycological test Pain	↓ ↑ → ↓/→* →	→
Capuzzo [49]	138	Melatonin (10 mg) Placebo	Oral	> 90 before general anesthesia	Abdominal, thoracic, vascular, endocrinological, skin	Anxiety Depression Neuropsycological test Pain	→ → → →	-
Caumo [52]	37	Melatonin (5 mg) Placebo	Oral	Night before and 60 min before surgery	Abdominal hysterectomy	Anxiety Pain	↓ ↓	-
Caumo [51]	59	Melatonin (5 mg) Clonidine (100μg) Placebo	Oral	Night before and 60 min before surgery	Abdominal hysterectomy	Anxiety Pain	↓ ↓	-
Gögenur [84]	121	Melatonin (5 mg) Placebo	Oral	3 nights after surgery	Laparoscopic cholecystectomy	Fatigue Sleep General wellbeing Pain	→ → → →	→
Mowafi [164]	40	Melatonin (10 mg) Placebo	Oral	90 min before surgery	Hand surgery	Anxiety Pain	↓ ↓	→
Naguib [167]	75	Melatonin (5 mg) Midazolam (15 mg) Placebo	Sublingual	100 min before general anesthesia	Gynecological laparoscopic procedure	Anxiety Sedation Orientation Psychomotor test Pain	↓ ↑ → ↓/→*	→
Naguib [168]	84	Melatonin (0.05, 0.1, 0.2 mg/kg) Midazolam (0.05, 0.1, 0.2 mg/kg) Placebo	Sublingual	100 min before general anesthesia	Gynecological laparoscopic procedure	Anxiety Sedation Orientation Psychomotor test Pain	↓ ↑ ↓ → →	→
Naguib [169]	200	Melatonin (0,2 mg/kg) Placebo	Sublingual	50 min before general anesthesia	-	Anxiety Sedation Orientation ED_{50} and ED_{90} dose for propofol and thiopental** Pain	↓ ↑ → ↓/↓ →	-
Turkistani [213]	45	Melatonin (5 and 3 mg)	Oral	100 min before surgery	-	Propofol dose before reaching BIS < 45***	↓	→

phase and amplitude circadian rhythm disturbances in the melatonin secretion and cognitive function after surgery.

Correlation between aMT6s in urine and postoperative cognitive dysfunction after major surgery

Cognitive function can be assessed by a validated neuropsychological test battery [183]. The following four neuropsychological tests in combination have been used; cumulative numbers of words were recalled in three trials, and the number of words at delay recalled from the visual verbal learning test [37]; the time and number of errors in part C of the Concept Shifting Test [190]; the time and error scores from the third part of the Stroop Colour Word Interference Test [106]; and the number of correct answers from the Letter Digit Coding Test [143]. Based on these neuropsychological tests, it has been shown that postoperative cognitive dysfunction occurs in 26 % of patients one week after major general surgery and in 11% 3 months after major surgery [13].

In a group of 36 patients undergoing major surgery we found that 50% of the patients had postoperative cognitive dysfunction on postoperative day four [72]. There were significantly worse sleep quality and increased number of night awakenings in the group with POCD compared with the group without POCD. However, no significant differences were found in the night-time, daytime or total aMT6s secretion between the two patient groups. No significant correlations were found in the composite neuropsychological z-score and the aMT6s excretion parameters [72]. As described before we found an increased production of aMT6s in the daytime on the fourth postoperative day, but this cannot be concluded to be a phase disturbance in the melatonin secretion. Thus, we could not conclude anything regarding the phase of the aMT6s rhythm because of lack of sufficient postoperative urine sampling [72]. In the study by Rasmussen et al., where a blunted day and evening rhythm in serum cortisol was proven to be correlated with postoperative cognitive dysfunction, 187 patients were included. Thus, the reason why we did not find a difference may be due to a small study sample, lack of sufficient melatonin sampling and lack of an additional circadian marker [184].

Correlation between postoperative circadian activity rhythm and recovery parameters

We showed that the circadian pattern in the activity rhythm was disturbed after both laparoscopic cholecystectomy and major abdominal surgery [83]. The changes were more severe after major surgery, and the changes affected activity levels in the lowest and highest activity periods of the day and the amplitude of the circadian activity rhythm. We have shown, that measures of non-parametric circadian activity analysis may be a useful tool to assess postoperative recovery and to find differences in the recovery between minor and major surgery [83]. In the same study we showed, that there also was a significant correlation between the inter-daily stability, intra-daily variability and amplitude of the circadian activity rhythm and postoperative recovery parameters (sleep quality, fatigue and general well being) [83].

MELATONIN TREATMENT IN THE PERIOPERATIVE PERIOD

Based on the observed disturbances in the circadian rhythm of melatonin in relation to surgery it has been investigated in preliminary studies whether melatonin could have an effect on subjective recovery parameters in the pre- peri- and postoperative periods (table 4). In a recent meta-analysis of the advantages and disadvantages of sedative hypnotics (not melatonin) it was shown that the numbers needed to treat for improved sleep quality was 13 and the numbers needed to harm for any adverse event was 6 [82]. Melatonin has a very low toxicity, a hypnotic effect comparable to the newly developed hypnotics (zaleplon, zolpidem, zopiclone) and also fewer cognitive side-effects [80,95,172,173,174,201]. Thus, another advantage of using melatonin in the postoperative period would be lower cognitive side effects, and in addition maybe even improved cognitive function [79,94].

In six studies, the anxiolytic effects of melatonin in relation to surgery was studied [5,49,51,52,167,168]. In 5 of the six studies, melatonin was shown to have a significant anxiolytic effect [5,51,52,167,168], and in one study the anxiolytic effect was not different from placebo [49]. No toxic effects were noted in any of the studies.

Melatonin has also been investigated as a treatment for sleep disturbances in patients in the intensive care unit or in the general medical department [11,36,203]. Patients in the intensive care unit had actigraphically determined improved sleep when treated with melatonin [203]. In a recent placebo controlled randomized trial it was shown that 10 mg melatonin administered orally improved sleep quality, measured by the EEG-derived bispectral index, in intensive care unit patients [36]. Melatonin was also more effective than placebo to shorten sleep onset and improve sleep quality and perceived depth of sleep in patients in the medical department [11]. Melatonin did not cause drowsiness or early morning hang-over symptoms compared with placebo [11]. However, melatonin (3 mg oral dose) was no more effective than placebo on observed nocturnal sleep and did not induce any other beneficial effects in tracheotomised intensive care unit patients [109]. There exists only one case report where melatonin was used for prevention of postoperative delirium [100].

Table 5

Mean of the postoperative sleep quality, fatigue, general wellbeing and sleep diary parameters in the subgroup with pain levels below median for the treatment group. *Values are given as mean SD). Significant differences are indicated for intergroup comparisons. * = P < 0.05, ** = P < 0.01.*

	Subgroup (≤ median pain level)	
	Placebo (n = 30)	Melatonin (n = 29)
Sleep quality (VAS)	35 (16)	24 (15) **
Fatigue (score 1-10)	4.1 (1.7)	3.9 (1.7)
General wellbeing (VAS)	25 (10)	22 (13)
Sleep diary		
Sleep latency (min)	28 (38)	13 (10) *
Total sleep duration	445 (88)	442 (58)
No. awakenings	1.7 (1.0)	2.1 (2.9)
Awakening duration	32 (51)	22 (19)
No. naps	0.7 (0.7)	0.6 (0.4)
Nap duration	43 (34)	45 (38)

Melatonin after laparoscopic cholecystectomy

As mentioned before, melatonin secretion was disturbed after surgery with a phase delay and reduced amplitude on the first night after surgery [109]. It has been suggested that a reduced melatonin amplitude during the night may be associated with sleep disturbances and that melatonin replacement therapy can restore sleep [97,98,136,137]. We hypothesized that pharmacological substitution with oral melatonin would restore the endogenous melatonin levels and improve sleep and secondary fatigue and general wellbeing after surgery.

In a placebo controlled randomized clinical trial we examined the effect of oral melatonin 5 mg for three days after laparoscopic cholecystectomy [84]. 121 patients were randomised to receive either oral melatonin (n = 60) or placebo (n = 61). Primary outcome parameters were sleep quality, general well being and fatigue. Melatonin reduced sleep latency on the first postoperative night compared with placebo, but did not have any significant effects on sleep quality, general well being or fatigue. There were no significant differences in side effects between the two groups [84]. In a subgroup analysis of the patients with lower than median pain, melatonin improved sleep quality in the three days postoperative period and also improved sleep onset time (table 5). This subgroup analyses was though not planned in the power analysis before study initiation. A limitation of the study was that we did not measure the effect of melatonin on a circadian marker, and we did not confirm the diary assessed sleep data with objective measurements by e.g. actigraphy. Another limitation of the study may be that we chose to let the timing of melatonin be based on the individual preference of patients (½ hour before expected bedtime). A preoperative assessment of the dim light melatonin onset would have given the possibility to administer the oral melatonin on an individual basis. However, this was not possible because of the study design and limitations with respect to possibilities for analysis of plasma or urinary melatonin. The apparent effect of melatonin on patients with lower than median pain levels is interesting and in accordance with the literature regarding the aetiology of postoperative sleep disturbances in outpatient populations [42,48,12,14,15]. It has been shown that pain is a major determinant of postoperative sleep disturbances [42,48,74,12,14,15,186], however, there are still a considerable amount of patients who suffers from sleep disturbances the first nights after surgery despite the absence of pain [26,29,12,14,15]. Thus, the administration of melatonin was apparently not “strong enough” to override the sleep disturbing effect of pain in patients with postoperative pain, whereas in patients with less pain, there was a significant positive effect of melatonin on sleep quality and sleep onset time. It could be argued that we did not give the optimal analgesic treatment in relation to surgery and this was the reason for the lack of significant effect in the whole group. It should be investigated in the future whether the addition of melatonin to a procedure specific multi-modal analgesic treatment [122] could improve subjective sleep quality and other recovery parameters in the postoperative phase.

Melatonin after open surgery

In a study by Caumo et al the activity rhythm was analyzed in patients undergoing abdominal hysterectomy [52]. The patients were randomized in two groups receiving 5 mg oral melatonin (n = 17) or placebo (n = 16) the night before surgery and one hour before abdominal hysterectomy. The patients' activity rhythms were assessed before and after surgery. There was a significant effect of melatonin on circadian rhythm the first week after discharge indicating an improved recovery [52]. Based on these data it is possible to conclude that the circadian analyses of activity data after surgery could be used as an objective measure of postoperative recovery and that the circadian activity rhythm can be modulated by chronobiotics [52]. The same group reported in a recent study, that 5 mg oral melatonin administered one hour before abdominal hysterectomy, had a significant anxiolytic effect and analgesic effect compared with placebo [51].

FUTURE PERSPECTIVES

There is a considerable interindividual variation in markers of the circadian rhythm such as excretion of melatonin, cortisol, core body temperature, autonomic nervous system tone, activity rhythm and sleep wake cycle. Postoperatively, there are profound disturbances in these endogenous rhythms. There is need for further investigations in a larger sample of patients where markers of the central circadian pacemaker can be investigated in relation to per- and postoperative interventions. The aim is to explore if modifications of the observed delay in some of the circadian rhythm disturbances we have shown, can result in improved postoperative outcome (recovery, convalescence, morbidity and mortality). In this context there is a need for non-invasive measures of central circadian pacemaker activity which can be utilized in a larger sample of patients. In this context, the use of circadian activity rhythms should be validated in studies combining circadian activity rhythm analysis and other markers of the central circadian pacemaker. It should also be measured if these circadian activity rhythm parameters correlate to postoperative morbidity and/or mortality.

In preliminary studies in patients undergoing general anaesthesia and surgery it has been shown that melatonin has a remarkable effect on preoperative anxiety, but also on pain[51,52]. In one study where melatonin were given one hour prior to surgery, the numbers needed to treat for avoiding one patient with moderate to severe postoperative pain within 24 hours were 2.2 [52]. Thus, it is possible that a major effect of melatonin in the perioperative period is based on the preoperative rather than postoperative administration. It should therefore be investigated in the future, whether melatonin administered before or during minimally invasive surgery or major surgery can improve postoperative recovery and/or morbidity. These effects of melatonin may be due to its potent antioxidative effects rather than its effects on the central circadian pacemaker [133,134].

The pathogenic factors behind the evolvement of postoperative circadian disturbances and the connection between these and postoperative subjective recovery parameters have not been fully elucidated and should be further investigated in the future. It is important to investigate these correlations in a context where modern evidence based multi-modal care principles are included. Thus, it is possible that melatonin after minimally invasive surgery and major surgery will have a positive effect in the patient who is optimally medically prepared and treated with a multi-modal analgesic regimen.

Based on the large interindividual variation in markers of the circadian rhythm of e.g. melatonin it should be investigated whether preoperative establishment of the endogenous melatonin profile may make it possible to rationalize peri- and postoperative pharmacological interventions. Thus, it has been shown that there is a considerable circadian variation in response to analgesic treatment and chemotherapeutic treatment between individuals. In this context, the examination of genes in peripheral tissues including cells in the blood, may add to this picture [105]. There are preliminary studies indicating, that the disturbances in markers of the central circadian pacemaker may correlate to peripheral genetic circadian markers [105]. This is an important area which should be evaluated and further investigated in the future.

SUMMARY

An increasing number of studies have shown that circadian variation in the excretion of hormones, the sleep wake circle, the core body temperature rhythm, the tone of the autonomic nervous system and the activity rhythm are important both in health and in disease processes. An increasing attention has also been directed towards the circadian variation in endogenous rhythms in relation to surgery. The attention has been directed to the question whether the circadian variation in endogenous rhythms can affect postoperative recovery, morbidity and mortality. Based on the lack of studies where these endogenous rhythms have been investigated in relation to surgery we performed a series of studies exploring different endogenous rhythms and factors affecting these rhythms. We also wanted to examine whether the disturbances in the postoperative circadian rhythms could be correlated to postoperative recovery parameters, and if pharmacological administration of chronobiotics could improve postoperative recovery.

Circadian rhythm disturbances were found in all the examined endogenous rhythms. A delay was found in the endogenous rhythm of plasma melatonin and excretion of the metabolite of melatonin (AMT6s) in urine the first night after both minor and major surgery. This delay after major surgery was correlated to the duration of surgery. The amplitude in the melatonin rhythm was unchanged the first night but increased in the second night after major surgery. The amplitude in AMT6s was reduced the first night after minimally invasive surgery. The core body temperature rhythm was disturbed after both major and minor surgery. There was a change in the sleep wake cycle with a significantly increased duration of REM-sleep in the day and evening time after major surgery compared with preoperatively. There was also a shift in the autonomic nervous balance after major surgery with a significantly increased number of myocardial ischaemic episodes during the nighttime period. The circadian activity rhythm was also disturbed after both minor and major surgery. The daytime AMT6s excretion in urine after major surgery was increased on the fourth day after surgery and the total excretion of aMT6s in urine was correlated to sleep efficiency and wake time after sleep onset, but was not correlated to the occur-

rence of postoperative cognitive dysfunction. We could only prove an effect of melatonin substitution in patients with lower than median pain levels for a three days period after laparoscopic cholecystectomy.

In the series of studies included in this thesis we have systematically shown that circadian disturbances are found in the secretion of hormones, the sleep-wake cycle, core body temperature rhythm, autonomic nervous system tone, myocardial ischaemia and activity rhythm after surgery. Correlation exists between circadian rhythm parameters and measures of postoperative sleep quality and recovery. However, oral melatonin treatment in the first three nights after surgery, cannot yet be generally recommended for improvement of sleep quality or other recovery parameters based on the available results. It may be indicated in subgroups or if other perioperative treatment algorithms were used, but this has to be investigated in future trials.

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