The impact of sleep deprivation on surgeons' performance during night shifts

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THE 4 ORIGINAL PAPERS ARE

1. Amirian I, Danielsen AK, Rosenberg J. Perception of fatigue among surgeons during night shifts. Ann R Coll Surg Engl (Suppl) 2013;95:1-5.
2. Amirian I, Andersen LT, Rosenberg J, Gögenur I. Laparoscopic skills and cognitive function are not affected in surgeons during a night shift. J Surg Educ 2014;71:543-50.
3. Amirian I, Andersen LT, Rosenberg J, Gögenur I. Working night shifts affects surgeons' biological rhythm. Submitted.
4. Amirian I, Mortensen JF, Rosenberg J, Gögenur I. Admission medical records made during night time have the same quality compared with day and evening time records. Dan Med J 2014, in press.

INTRODUCTION

During the last 10-15 years increased focus has been on patient safety and adverse events in relation to medical and surgical treatment. As the first country in the world, Denmark introduced all adverse events to be reported nationally by law in 2004 (5). In a pilot study from 2001 the incidence of all adverse events in Denmark were estimated to be 9% of all in-hospital admissions, where of 40% of the events were assessed to be preventable (6). The adverse events resulted in prolonged admission time up to an average of 7 days per admission. A systematic review from 2008 found the median incidence of adverse events to be 9% of in-hospital admissions based on 8 international studies; of these 44% were estimated to be preventable (7). More than half of patients subjected to adverse events (56%) did not experience a disability or experienced minor disabilities, whereas 7.4% of events were lethal. The majority of the adverse events were in relation to surgical treatment (40%) or medication (15%) (7). Thus, the largest proportion of the in-hospital adverse events was related to operation.

The adverse events that result in patient injury are serious, and initiatives that aim at reducing the risk of patient harm during admission by strengthening hospital systems, are worked on continuously. However, the influence of physicians´ shift work on the risk of adverse events in patients remains controversial. Factors such as working hours per week and consecutive work hours influence the performance in physicians' shift work (8,9). In Scandinavia physicians typically work 37-48 hours per week in average over 4 weeks; in the UK it is 48 hours per week (the general EU maximum) and in the USA the work hour restriction is 80 hours per week. In Scandinavia shift work is of 16-24 hours of duration, which means that the physicians have the day off after a night shift. Similar to Scandinavia, the UK has a maximum of 16 hours of work in a 24-hour period. In USA physicians used to work extended shift, meaning that their consecutive work hours typically were 32 hours or more, and opposed to that extreme Holland has a maximum of 8 work hours.

The extended work hours combined with a workload of 80 hours per week in USA resulted in chronic sleep deprivation in residents. The chronic sleep deprivation combined with work during the circadian night has been known to affect physicians' performance during night shifts (8, 9). Extended work hours and night time work have not only been known to affect patient safety, but also affects the health of the physicians themselves, by increased risk of percutaneous injuries; with even more frequent injuries during night time (10). In addition, the risk of motor vehicle crashes when driving home from work was increased in American residents (11). The long work hours and strain during shift work is known to increase stress in physicians, especially on night shifts, yet the long-term consequence on their health is not yet clarified (12,13). In shift workers the risk of myocardial infarction and ischemic stroke is increased, thus shift work is associated with serious vascular events (14). Therefore, working night shifts may have greater consequences on surgeons' health than we know.

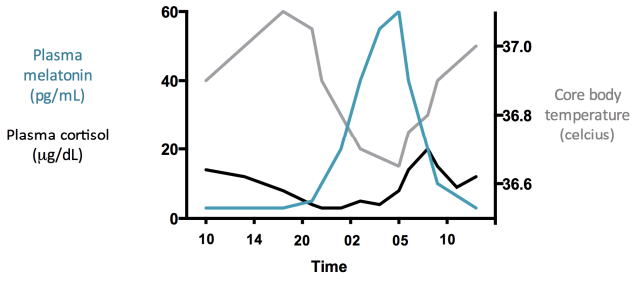
BACKGROUND

CIRCADIAN RHYTHM

As the earth rotates around its own axis and orbits the sun, a 24-hour cycle of light and dark is created, leaving all organisms on the planet earth with an intrinsic clock; an endogenous oscillation of approximately 24 hours; namely the circadian rhythm (15). Although being an endogenous timing system, the circadian rhythm is also affected by external factors, called zeitgebers (16).

The word zeitgeber is German and means "time giver" and examples of zeitgebers are the light/dark cycle, scheduled sleep, food, exercise and social interactions. The circadian pacemaker is formed by the cells of the suprachiasmatic nuclei (SCN) in the hypothalamus and connected to retina in the eye by a pathway called the retinohypothalamic tract (16-18). This connection between the eye and the SCN makes light the most important zeitgeber of the circadian pacemaker (16-18). Through many afferent and efferent connections the SCN regulates the sleep/wake cycle (18-20), the immune system (21-23), the autonomic system (24-26), cognitive function (19,27,28) and temperature (29,30). The circadian pacemaker can be monitored by using different surrogate markers as melatonin (31,32), cortisol (16,33,34), core body temperature (29,35) and sleep/wake cycle (36,37). Melatonin is a hormone synthesized in the pineal gland and known to be one of the most important endogenous circadian regulators (32,38,39). In a normal circadian rhythm the secretion of melatonin commences at 20:00-23:00 hours, peaks between 02:00-04:00 hours and then declines in the morning around 08:00-10:00 hours (32,39,40). The core body temperature reaches a minimum around 05:00 hours (around the circadian trough) and peaks at 17:00, also following a circadian rhythm (16). The assessment of cortisol rhythm is also an expression for the circadian rhythm, yet its pattern differs from melatonin (41). In humans, cortisol levels peak approximately 30 minutes after wakening in the morning and are higher during the activity period, which is day time, than during evening hours (16,33). The lowest cortisol levels are seen during night hours (16). The endogenous rhythm of melatonin, cortisol and core body temperature are presented in figure 1.

Figure 1 The endogenous rhythm of melatonin, cortisol and the core body temperature. Adapted from (16,38,42).

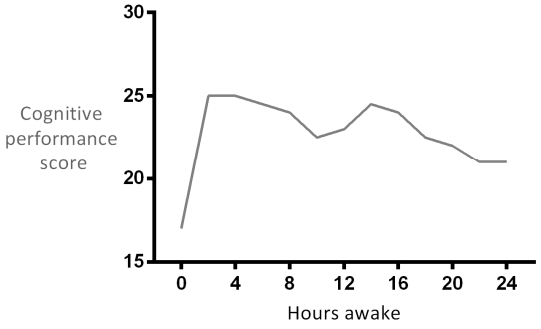


SLEEP DEPRIVATION AND COGNITIVE FUNCTION

Different models have been proposed to explain the regulation between sleep and wake cycle (43). One of the most acknowledged models is the two process model of sleep regulation, presenting a sleep-dependent homeostatic process (Process S) and a sleep-independent circadian process (Process C) (44,45). Process S is dependent on prior sleep and waking, thus showing a rise during waking and a decline during sleep. Process C is under control of the circadian pacemaker that controls sleep and wake rhythm. The timing of sleep and waking is thus determined by an interaction between Process S and Process C, and sleep is thought to occur when the homeostatic and circadian drive to sleep intersect.

Sleep is known to have a restorative effect. Poor and disturbed sleep has a negative impact as it is associated with fatigue, sleepiness, and an increased sensibility to pain stimuli (46-48). Furthermore, sleep deprivation and disturbances in the synchrony of circadian rhythm and the sleep-wake cycle reduce cognition (19,27). Cognition has a natural fluctuation during the 24-hour day (19,28) (figure 2). It is reduced immediately after waking due to sleep inertia, then improves over 2-4 hours of wakefulness and remains high during the first 8 hours. Hereafter a small reduction is seen in the afternoon and then cognition is improved again and remains stable until habitual bedtime. The afternoon peak in cognition strongly interferes with sleep. If wakefulness is prolonged after the habitual bedtime, deterioration is seen in cognition with impairment in the early morning hours, around the circadian nadir (19,28,49). The homeostatic and circadian systems work together to apply their influence. Cognitive speed, alertness, performance, memory and mood degrades with time awake and follows the circadian pattern (19,49). This means that even after several days of sleep deprivation a slight increase in cognition is seen during day time compared with night time (49).

Figure 2 The 24-hour variation in cognitive performance. Cognition is impaired by sleep inertia immediately after waking, improves over the day, with a small afternoon reduction and then improves again until bedtime. Adapted from (19).



SHIFT WORK

In work places where 24-hour coverage is needed, shift work is applied. Shift workers often work in 3-shift systems; night, morning, and afternoon. The challenge in working night shifts is that the shift workers are exposed to work at the circadian nadir, which then displaces sleep to day time; this interferes with the homeostatic and circadian regulation of sleep (50). Working night shifts result in greater loss of overall sleep time. Shift workers experience premature and spontaneous sleep termination in their sleep after a night shift, often having their sleep reduced by approximately 2-4 hours (49,50). Thus, shift workers report sleep disturbances more often than day workers. Alertness and performance reach their nadir at night, inducing attentional gaps and work related accidents that pose a safety risk to the shift workers themselves (40,50). Shift work is associated with increased risk of ischaemic stroke, myocardial infarction (14) and cancers (51).

In order to provide full 24-hour coverage of medical assistance in hospitals, physicians are submitted to shift work as well. As denoted in the introduction, factors such as working hours per week and consecutive work hours appear to have influence on physicians' performance. Studies have found that residents, who worked extended shifts (more than 24 hours), made more medical errors and had more attentional lapses at night, when chronically sleep deprived (8,9). A study in 2009

found that surgeons who slept less than 6 hours on a night shift and continued to perform elective surgery in day time had an increase of 83% in complications (52). This raised a debate in the United States of America as to how to handle sleep deprivation in surgeons (53,54). Suggestions were made as to obtain patients' informed consent prior to surgery, postpone the operation or to replace the sleep deprived surgeon with a rested colleague. Ethical obligations in sleeping and being rested in order to perform safe surgery were also noted (54). The deterioration in cognition in day time after a night shift is difficult to compensate for, even in physicians that are not chronically sleep deprived, as other studies additionally have found worse post call performance compared with pre call levels (55-59). Other studies have found psychomotor skills to improve after night shifts (60,61) or not to deteriorate (62). In these latter studies we found that the design of the studies may have influenced the results in a manner that made them unreliable. However, surgeons' performance appears to be preserved during the night shift (63-65).

METHODOLOGICAL CONSIDERATIONS

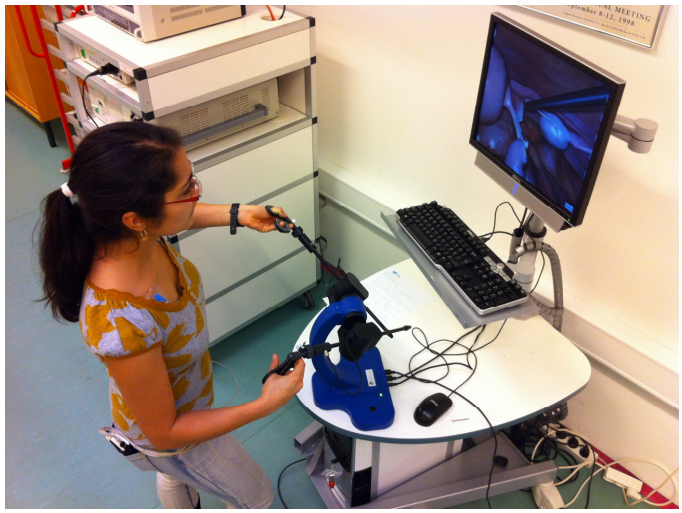
FOCUS GROUP INTERVIEWS

In order to gain understanding of the surgeons' experiences during night shifts, we used qualitative methods, in paper 1 (1), as they are most often used in the study of human thoughts and experiences (66). We conducted focus group interviews with a phenomenological approach. Focus groups are usually groups of 4-12 people aiming to explore specific topics by semi-structured discussions (67). Phenomenology is an interpretive approach that aims for the understanding of an individual's experiences and understanding of a certain phenomenon, more than it aims for causal relationship. The interviews are led by one or two moderators using an open-ended discussion guide in order to allow participants to expand on their experiences (67). The methodological advantage in focus group studies is that participants are able to share experiences and may be inspired to discuss the topics by other participants' statements, as opposed to individual interviews. The interviews were analyzed according to qualitative content analysis (67).

PSYCHOMOTOR PERFORMANCE

We used laparoscopic simulation to assess psychomotor performance in paper 2 (2). Laparoscopic simulation has been widely used in surgeons to assess, improve and to maintain surgical skills (68-70). Furthermore, laparoscopic simulation has been used as a measure of performance after sleep deprivation due to night shifts in surgeons (55-57). We used the ectopic pregnancy procedural module, as this was previously validated for the assessment of surgical skills (71-73) (picture 1). In order to account for an improvement in simulation due to test-retest effect we trained the surgeons in order for them to reach a plateau in laparoscopic skills; the surgeons were trained to a predefined proficiency level by passing the module twice within 5 consecutive repetitions (71,74). We set the primary outcome to time in simulation. The secondary outcomes were set to instrument path length and instrument angular path as a measure of dexterity, and blood loss as a measure of error. The choices made for the parameters were based on previous papers showing an increased time in simulation, unnecessary instrument movement and more errors in sleep deprived surgeons (48,56).

Picture 1 Laparoscopic simulation of the ectopic pregnancy procedural module.



COGNITION

In order to assess attention and concentration in paper 2 (2) we used the d2 test of attention. The d2 test of attention is a validated paper and pencil test for attention and concentration (75). Scoring of the d2 test included: Total number of items processed, which is a quantitative measure of performance on all items processed; errors of omission; errors of commission; total number of errors (the sum of errors of omission and errors of commission); percentage of errors, which reflects performance accuracy; total number of items processed minus errors, which measures the quantity of work completed after a correction for errors, assessing attention and the relationship between accuracy and speed performance; concentration performance, which is the total number of items cancelled out correctly minus the items cancelled out incorrectly, and represents performance speed and accuracy in the overall test; fluctuation rate, which is the maximum amount of items processed minus the minimum amount of items processed, and evaluates performance stability and consistency. The cognitive test has previously been used as a tool in the assessment of cognitive skills in surgeons and nurses during night shifts, as a measure of the effect of sleep deprivation on cognition (76-78).

As a more direct clinical measure of cognition, in paper 2 (2), we created two lists of 10 drugs that the surgeons had to prescribe in the Electronic Patient Medication system, a software program for the prescription of medicine for admitted patients. The lists differed yet they were standardized as the ways of administration were equal. We chose to use electronic medication as a measure of cognition and possible attentional lapses, as error in medication is one of the most common adverse events in hospitals (7).

We wished to examine the impact of sleep deprivation on surgeons' quality of work in night shifts compared to day time work in paper 4 (4). As the medical record is one of the physician's most important work tools we chose to base their quality of work on the quality of their admission medical records. We extracted 1000 admission medical records equally distributed over 4 diagnoses: mechanical bowel obstruction, appendicitis, gallstone, and gastrointestinal bleeding. A checklist with dichotomous outcome (yes/no/) was made for the evaluation of the admission medical records' content. The checklist was based on standard information necessary in the medical records, as not

all information was related to the acute situation the quality of the medical records could be affected by sleep deprivation. In review on malpractice complaints, insufficient medical recording was criticized from the National Board of Patients' Complaints, as they could result in poorer patient outcome (79).

CIRCADIAN MARKERS

In order to assess biological rhythm in surgeons in paper 3 (3) we used two common and non-invasive markers of circadian rhythm; the metabolite of melatonin (aMT6s) measured in urine and salivary cortisol. Melatonin is a hormone synthesized in the pineal gland and known to be one of the most important endogenous circadian regulators (32,38,39). In a normal circadian rhythm, the secretion of melatonin commences at 20:00-23:00 hours, peaks between 02:00-04:00 hours and then declines in the morning around 08:00-10:00 hours (31,39). The urinary metabolite of melatonin is equally rhythmically produced and follows the excretion pattern of melatonin yet with 1-2 hours of delay (32,38). We asked the participants to collect urine for 12 consecutive hours starting at 21:00 hours to 09:00 hours in order to obtain full night time measurements for all 4 days of the study. The salivary assessment of cortisol is commonly used as an estimate for cortisol rhythm and also as a measure for assessing the endogenous circadian rhythm (41). In humans, cortisol levels peak approximately 30 minutes after wakening in the morning and are higher during day time than the evening hours, and at the lowest levels during night hours (16,33). Melatonin secretion is sensitive to daylight and thus decreases when the human eye is exposed to light; cortisol on the other hand is not sensitive to light (15,16,33), which is why both parameters were included.

SLEEP

As the sleep-dependent homeostatic process is a part of the regulation of the sleep-wake cycle, we chose to monitor sleep and wake condition in papers 2 (2) and 3 (3). This was done by the use of wrist actigraphy (picture 2) and sleep diaries. We chose wrist actigraphy as it is validated for the purpose of distinguishing between sleep and wake conditions (80). Moreover, an accuracy of 93% is found between wrist actigraphy and polysomnography and an agreement up to 85% between wrist actigraphy and self reported sleep registration (81). Wrist actigraphy resembles a regular watch and is easy to wear. As the surgeons would wear the wrist actigraphy for 24 hours during the 4 study days they would have to wear them during surgery as well. Before surgical scrub and during surgery the actigraph was mounted on the upper arm, which would not affect data collection during wake time, yet be critical during sleep (82,83). The actigraph was thus returned to the wrist as soon as the surgeons left the operating room. Sleep diaries assessed sleep and wake time the night before the pre call day to the post call day 1. The surgeons noted time in bed, time of sleep, number and duration of wake episodes and time out of bed. This was used to more precisely distinguish between periods of wake inactivity from sleep; to gather information on sleep the night before the pre call day, where the surgeons did not wear an actigraph; and then day time napping.

Picture 2 Wrist actigraphy, placed on the non-dominant arm.

SUBJECTIVE SCALES

In order to assess surgeons' sleepiness in articles 2 (2) and 3 (3) we used the Karolinska Sleepiness Scale; a validated, 9 grade Likert scale (84,85). Scores of 7-9 in the Karolinska Sleepiness Scale reflect sleepiness and the sleepiness is furthermore reflected in the characteristics of the first stage of sleep (stage 1 Non-Rapid Eye Movement sleep), as electroencephalographic alpha and theta activity, and slow eye movement electrooculographic activity under the condition of open eyes. For subjective evaluations of the surgeons in article 3 we used the Visual Analog Scales (VAS); VAS quality of sleep, VAS fatigue, and VAS general well-being. The scales were created as 100 mm horizontal lines with questions at both ends and the surgeons were instructed to draw a vertical line as an evaluation of their current condition. The VAS scales have previously been used as subjective assessments in relation to circadian rhythm and sleep quality, general well-being and fatigue (86).

STATISTICAL CONSIDERATIONS

In the studies included in this PhD thesis we have used non-parametric statistics for continuous data, after having used the Kolmogorov-Smirnov test for normality. We have thus presented data as median (interquartile range). For paired data we used the Wilcoxon signed rank test for intragroup comparison, and for intragroup repeated measures the Friedman analysis of variance was used. For non-parametric correlation analyses we used the Spearman's rank order correlation. For non-related continuous data the Mann Whitney test was used for intergroup comparison. For the comparison of dichotomous variables we used the Fischers' exact test for dichotomous data and the Chi-square test for categorical variables. In all studies the statistical significance was set to ≤ 0.05. The IBM statistical package for social sciences (SPSS, Chicago, IL, USA) version 19.0 was used for statistical analyses.

HYPOTHESIS AND OBJECTIVE

In the studies included in this PhD thesis we wished to examine the impact of sleep deprivation and circadian rhythm on surgeons' during night shifts. Further we wished to examine the impact sleep deprivation had on surgeons' performance as a measure of how patient safety would be affected and whether their endogenous circadian rhythms were affected.

The objectives of this PhD were to:

1. To illuminate surgeons' own perception of fatigue and the impact they felt it had on their performance.
2. To assess the quality of admission medical records during day, evening and night hours, in order to examine a diurnal variation.
3. To monitor surgeons' performance during night shifts by laparoscopic simulation and cognitive tests in order to assess surgeons' psychomotor performance, dexterity and cognition.
4. To illustrate the effect of a night shift on surgeons' circadian rhythm.

PRESENTATION OF THE INCLUDED PAPERS

Paper 1: Amirian I, Danielsen AK, Rosenberg J. Perception of fatigue among surgeons during night shifts. Ann R Coll Surg Engl (Suppl) 2013;95:1-5 (1).

Objective

The objective of this paper (1) was to provide an understanding of surgeons' perceptions of fatigue and the impact on their work performance during night shifts.

Methods

This qualitative interview study was performed with a phenomenological approach in order to enhance the understanding of the central elements in surgeons' experience of fatigue. At the time of the interviews, all surgeons worked 5-6 single night shifts per month, thus all had experiences to share and were interested in doing so. They shared their experiences and sampling was continued until data saturation was achieved. Results were processed in regard to the consolidated criteria for reporting qualitative research (COREQ) recommendations. The interviews were all conducted by two researchers and each lasted for approximately one hour. A predefined, open-ended discussion guide was made in order to structure the interview session. Interviews were transcribed verbatim, coded by both researchers in parallel processes in order to ensure methodological consensus and subsequently analyzed according to qualitative content analysis.

Results

A total of 13 surgeons out of 44 possible participants were included. The surgeons' variation in age, sex and work experience and their characteristics are shown in table 1. The surgeons described adverse effects of sleep deprivation while on their night shifts and the results were categorized in the following themes: the impact of fatigue on the individual, tasks and busyness, and management of fatigue.

Conclusions

We found that sleep deprivation had an impact on the surgeons and that they were aware of the effect fatigue had on their work performance. As a result, they applied different mechanisms to cope with fatigue. Attending surgeons felt that they had a better overview now, due to more experience and better skills, than when they were residents, despite the fatigue on night shifts.

Strengths and limitations

In this study we need to account for several limitations, although the aim of qualitative studies is not generalizability and reliability in the same sense as in quantitative studies. The overall limitation of qualitative studies is that the results cannot be objectified in the same manner as quantitative studies, as the interview process is related to a specific context and to the participants; and that the researcher is the data-collector as well as the analytical tool.

We chose to place the participants in group interviews in order to have them exchange views and stimulate each other in sharing their perspectives on the subject. This was done as opposed to individual interviews. The disadvantage to group interviews was that despite that two researchers were present in order to make all participants heard; some participants shared their perspective more willingly than others. In quantitative studies a sample size is calculated beforehand and data sampling continues until this sample size has been fulfilled, unless other factors speak for a preterm ending of the study. Guidelines have been made for the appropriateness of participants in focus group studies yet these are guiding principles, as data saturation is the determining factor in qualitative studies (87). In our study we had two groups of 5 residents and attending surgeons and one group of 3 interns. We could have chosen to make another group of interns in order to obtain the same number of interns participating in the study as residents and attending surgeons. Yet during the interview process it became apparent that we did achieve data saturation.

When performing focus group interviews, the researcher constantly has to be aware of the interaction and dynamics of the group. Some participants could have dominated over others during the interview, although groups were established according to the surgeons' working position so that all surgeons shared their experiences with colleagues of equal hierarchy. Only 13 participants agreed to participate out of 44 possible (table 1); thus selection bias might have occurred, which is inevitable in this study design. The participating surgeons might have wished to share their perception of fatigue during night shifts more willingly because they felt a greater impact of fatigue and thus needed to discuss the matter more. The surgeons that did not participate might not have wanted to share their experiences, maybe because they did not perceive fatigue during night shifts as a topic worth discussing. However, we perceived another reason for the lack of participation as difficulties in fitting a busy work schedule with the time to participate. We placed all interviews in the afternoon so that surgeons working day time could participate, yet this prevented surgeons working evening-night shifts or surgeons who had gone home post call from participating. The sessions of the intern residents included only 3 surgeons, which was less participants than a focus group usually should consist of. Thus, another interview with residents could have been performed in order to obtain data from the equal amount of participants as the other two groups. However, the aim of the study was not comparison but generation of varied and nuanced knowledge about experiences. Furthermore, data saturation was reached, which is the overall criteria for the number of participants to include in the study. When translating the quotes from the participants the authors agreed internally upon the translation. In order to ensure correct translation a native speaker could have been asked to translate the quotes back from English to Danish; to ensure a correct understanding of the quotes.

Despite the fact that the focus group interviews were small, data saturation was achieved not only within the groups but also between the groups. A further strength to this study was that all three levels of surgeons working night shifts were included which brought a dynamic to the different perception of fatigue as the attending surgeons could share the difference it made for them to have achieved more experience on their coping with fatigue on night shifts.

Table 1 Characteristics of the focus group participants. Adapted from (1).

	Interns	Residents	Attending surgeons	Total
Women	1	2	2	5
Men	2	3	3	8
Age in years, median (range)	30 (26-30)	34 (29-38)	40 (35-49)	
Years from graduation, median (range)	1 (0.5-1.5)	6 (1-11)	12 (10-21)	
Actual participants/all doctors asked for participation	3/15	5/19	5/10	13/44

Paper 2: Amirian I, Andersen LT, Rosenberg J, Gögenur I. Laparoscopic skills and cognitive function are not affected in surgeons during a night shift. J Surg Educ 2014;71:543-50 (2).

Objective

The objective of this paper (2) was to monitor surgeons' performance during night shifts by laparoscopic simulation and cognitive tests in order to assess their psychomotor performance and cognition.

Methods

A total of 30 surgeons were monitored pre call and on call, during a 17-hour night shift. Laparoscopic simulation was used in the assessment of psychomotor performance and cognition by the d2-test of attention. The surgeons performed the laparoscopic simulation and the d2-test of attention at 08:00 hours pre call and at 04:00 hours on call. Sleep was measured by wrist actigraphy and sleep diary, and sleepiness by the Karolinska Sleepiness Scale.

Results

No difference was found in any of the simulation parameters. Maximal sleepiness was seen during the night shift at 04:00-08:00 hours ($p<0.001$) (figure 3). The surgeons slept significantly less on call 51 (32-152) minutes than pre call 390 (358-419) minutes ($p<0.001$). The d2 test of attention showed significantly improved values on call compared with pre call.

Conclusions

Sleep deprivation during a 17-hour night shift did not impair surgeons' psychomotor or cognitive performance while on call.

Strengths and limitations

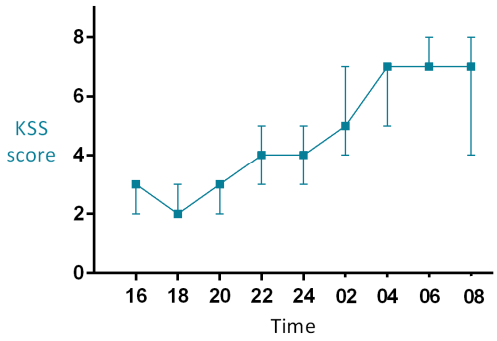
Our primary outcome in this study was time in laparoscopic simulation. We wished to use a reliable and validated module as our primary outcome, which is why we chose the ectopic pregnancy module (71-73). Our reservations with the ectopic pregnancy module was that it only took 2-3 minutes to perform and we wished to obtain simulation for more than 8 minutes in order obtain the effect of sleep loss on dexterity (62,88). Other simulation modules, as the appendectomy and cholecystectomy module were available. Yet none of the modules were validated at the time we initiated the study. To obtain a degree of fatigue during the procedure we chose to repeat the module for 30 minutes, which might have induced a routine in performance that made the surgeons less capable of making errors. The ectopic pregnancy module was not clinically relevant to the surgeons in the department of general surgery in their present clinical job. Had the appendectomy module been validated previously it would, in terms of relevance, have been a better module. The benefit of using the ectopic pregnancy module was that none of the surgeons had previously worked with the module before giving all the surgeons the same starting point with respect of experience. It was also an advantage with respect of equal instruction for all participants. Despite this, the attending surgeons might have had an advantage in participating in the study with laparoscopic simulation as their laparoscopic experience was greater than that of interns and residents. However, intragroup comparisons were made for interns, residents and attending surgeons and no difference was found.

The d2 test was used for assessment of cognition as it previously had been used to assess the impact of sleep deprivation on cognition in physicians and nurses (77,78). The test could measure cognition on several levels as it, apart from error, could assess performance accuracy and concentration performance. Our results showed significant improvement for all measures but one, when pre call values were compared with on call values and. This could be due to a test-retest effect, which is previously described in a clinical setting, where surgeons were tested more than once (76).

The medicine lists used in prescription of medicine in the Electronic Patient Medication system were standardized to the amount of drugs and ways of administration, yet they were not previously validated. No difference was found in time and error for prescription on the pre call day compared with the on call day and this could be due to the fact that the test was not sensitive enough. In order to use a similar measure in other studies, a prior validation should be performed.

The strengths of this study are that the primary outcome was based on a previously validated and well examined module in a laparoscopic simulator. Despite that the d2 test of attention pointed towards test-retest effect the impact of sleep deprivation did not surpass the ability to perform the tests.

Figure 3 The development of sleepiness on call from 04:00 hours to 08:00 hours on the Karolinska Sleepiness Scale (KSS). The median pre call score was 4, at 08:00 hours. Squares represent median. Whiskers represent the interquartile range. P-value < 0.001 (Friedman test). Adapted from (2).



Paper 3: Amirian I, Andersen LT, Rosenberg J, Gögenur I. Circadian disturbances in surgeons working night shifts. Submitted (3).

Objective

Chronic sleep deprivation in medical residents is known to affect performance, increase the risk of medical errors and compromise residents' own safety, when combined with work during the night. The aim of this paper was to examine the circadian rhythm and sleep-wake cycle in surgeons working night shifts.

Methods

The surgeons were monitored prospectively for 4 days: pre call, on call, post call day 1 and post call day 2. For the assessment of the circadian rhythm the urinary metabolite of melatonin (aMT6s) and cortisol in saliva were measured. Sleep and activity was measured by actigraphy and by the use of sleep diary. With regard to the surgeons' subjective conditions the Visual Analog Scales (VAS) for fatigue, general well-being, quality of sleep and Karolinska Sleepiness Scales (KSS) were used.

Results

A statistically significant difference ($p<0.05$) was found in the values of aMT6s and cortisol (figure 4). The primary difference was between the on call values and the pre call values for aMT6s and cortisol; values were normalized on post call day 1. Increased sleep time was seen during the day on call prior to work start and on post call day 1 compared with pre call and post call day 2. No correlations were found between the VAS scales, KSS and the circadian markers and ($p>0.05$ for all comparisons).

Conclusions

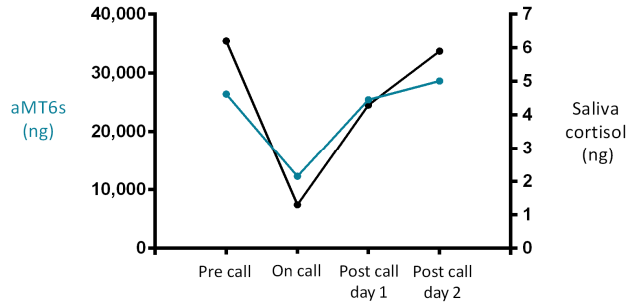
Surgeons' circadian rhythm was affected by working night shifts and their sleep pattern resembled that of shift workers on post call day 1.

Strengths and limitations

The overall limitation in using melatonin as a marker of circadian rhythm is that it is highly sensitive to light. To strengthen measures of circadian rhythm it is useful to have additional markers, in our case we chose both melatonin and cortisol. In order to obtain the aMT6s in concentration we weighed the urine production. In the beginning we did not calibrate the electronic pair of scales before using it and found that the scales measured incorrectly somewhere after the first urine samples. To assure correct data we excluded urine samples from the first 9 participants, that all had been measured with the incorrect pair of scales. We purchased a new pair of scales and measured the following samples with the new pair of scales that was calibrated each time before use. In order to assess the circadian rhythm the urinary metabolite of melatonin was used in 12-hour collections. Thus, the melatonin production was assessed collectively over 12 hours, which gave an insight of overall melatonin production per night. As we did not perform day time urine collection we were not able to assess more detailed disturbances in the circadian rhythm. A disturbed circadian rhythm could be shown in an increased day production of melatonin on the post call days. The saliva cortisol levels during the study presented a natural circadian rhythm, yet a limitation to these findings are that cortisol levels were only measured once a day and thus a more detailed assessment was not provided. In order to obtain a more detailed insight in the circadian pattern of surgeons working night shifts both day time and night melatonin should be measured by at least 4 time points during 24 hours, and furthermore cortisol should be assessed 4 times daily as well (16). With at least 4 time points during a 24-hour period it is possible to make a cosinor analysis with assessment of acrophase time, nadir and amplitude of the rhythm (32). Influences to the circadian rhythm might have been that some surgeons had to work on the pre call day and on post call day 2 whereas others had the day off and were free to sleep in. This was a limitation as it would have been best to standardize work hours for all the participants during the entire measurement period. However, the Department of Surgery employs 80 doctors and it was logistically impossible to standardize work hours for all participants during the entire measurement period.

The strengths of this study were that the surgeons were monitored for 4 consecutive days with two markers of circadian rhythm, both cortisol and melatonin. As the melatonin production is sensitive to light it was important to have another marker as cortisol, which is not sensitive to light (16). Sleep/wake cycle was provided for all 4 days of the study, which gave a valuable insight in the surgeons' sleep/wake cycle combined with the circadian markers.

Figure 4 The development of the urinary metabolite of melatonin aMT6s and cortisol pre call, on call, post call day 1, and post call day 2. Urine was collected from 21:00 to 09:00 on all 4 days. Saliva was collected at 08:00 hours on all 4 days. Blue circles present median for aMT6s ($p=0.001$, Friedman test). Black circles present median for saliva cortisol ($p<0.001$, Friedman test). Adapted from (3).



Paper 4: Amirian I, Mortensen JF, Rosenberg J, Gögenur I. Admission medical records made during night time have the same quality compared with day and evening time records. Dan Med J 2014, in press (4).

Objective

Accurate admission medical records are important as tools of communication in order to ensure patient safety during the hospital stay. Due to sleep deprivation on night shifts, surgeons' performance may be affected. The aim of this study was to assess the quality of admission in medical records, and thereby surgeons' performance, during the day, evening and night hours.

Methods

A total of 1000 admission medical records were collected from 2009 to 2013 and distributed equally on 4 diagnoses: mechanical bowel obstruction, appendicitis, gallstone disease and gastrointestinal bleeding. A pre-defined check list based on Danish standards for medical records was used to assess error in day, evening and night time. Errors were defined as left out information in the following categories of the standard medical records: allergies,

current medication, medical history, systems' review (a review of all organ systems), blood pressure and pulse rate, auscultation of the lungs, cardiac auscultation, evaluation of the abdomen, rectal exploration, and palpation of distal pulses.

Results

In 778 admissions, medical records made at day-evening time, 1183 errors were found, and in 222 medical records during the night time a total of 322 errors were found (figure 5). No significant overall difference in error was found when day-evening values were compared to night time values (p-values for all comparisons > 0.05) apart from the category blood samples (p=0.023). Analyses for subgroups based on the 4 diagnoses showed no difference in day, evening and night time values.

Conclusions

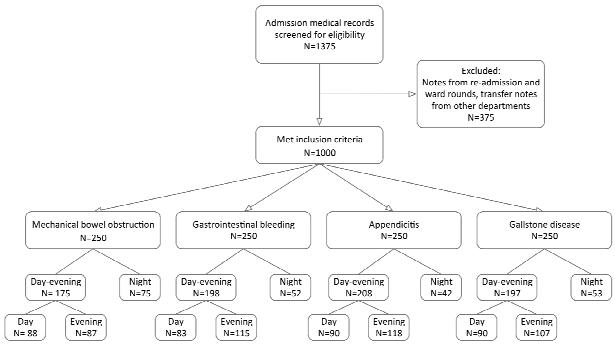
No deterioration was seen at night time in the quality of medical records, yet errors were seen consistently in several categories suggesting poor education of interns.

Strengths and limitations

In this study several methodological limitations need to be addressed. We wished to use the admission medical record as a tool for the assessment of medical records as it is an important part of the surgeons' every day work. As insufficient medical records have been the subject of criticism from the National Board of Patients' Complaints, correct and thorough documentation in medical records is important in ensuring patient safety (79). In order to assess the medical records for errors we developed a check list based on national standards for admission medical records (89). Despite that we sought to standardize the check list by using a dichotomous evaluation of the medical records, the check list was not validated. We found consistent high percentages of error for the following categories rectal exploration, distal pulses, gynecological examination, HCG and hemoglobin across day, evening and night time. These categories were thus not addressed in the primary medical record, but may have been addressed in later notes or on ward rounds by other surgeons, which we did not analyze. Furthermore we assumed that the makers of the medical records were interns, yet we did not have the opportunity to gather information on the subjects writing the medical records. It would have been relevant to know the surgeons' work experience in order to assess if errors in the medical records were associated with years of works experience, as it previously is shown that junior trainees make more mistakes than senior trainees in a simulated ward round setting (90). For the categories HCG and hemoglobin they might have been noted on an emergency room chart used as a tool between the nurses and surgeons at the emergency ward. Nurses sometimes draw venous blood in the process of placing a needle for infusion, in order to assess hemoglobin in patients with gastrointestinal bleeding at an early stage; they are also the ones performing pregnancy tests in urine. As the medical record is the only electronically saved document we found it necessary for the surgeons to note these values in the medical record, also as a legal documentation in case of adverse events or patient complaints.

The strengths in this study were that the methodology in using errors in medical records was useful as a screening tool method in the diurnal variance in performance, despite the limitations mentioned in the above.

Figure 5 A flow chart over the inclusion and distribution of admission medical records.
N represents the number of admission medical records. Day was defined as 08:00-15:59 hours, evening as 16:00-23:59 hours, day-evening as 08:00-23:59 hours and night as 24:00-07:59 hours. Adapted from (4).



DISCUSSION

Surgeons felt that sleep deprivation had an impact on their performance and different mechanisms were applied in order to handle fatigue during night shifts. The circadian rhythm of surgeons was affected by working night shifts and their sleep pattern was similar to that of shift workers. However, sleep deprivation during a 17-hour night shift did not deteriorate surgeons' psychomotor and cognitive performance while being on call and the quality of medical records did not deteriorate at night hours compared with day and evening time.

We gained a greater understanding of how surgeons perceive sleep deprivation on night shifts as we found little presented on the subject in literature (91). It was interesting to see that despite different work tasks in the three groups, all surgeons perceived fatigue during night shifts the same way. They felt that fatigue resulted in less energy, slower work and a reduced cognition, which increased their fear of making errors. This lead them into developing coping strategies to prevent them from making mistakes at work (1). The errors made during night shifts were mainly described as errors in administrative work. The reason for these findings could be that the surgeons work at the circadian night, which induces changes in cognitive performance, as impairment in attention and working memory (40,92). Fatigue was described as worst between 02:00 to 06:00 hours, which can be explained by the fact that alertness, performance and metabolism reaches a low point in the early morning hours, also known as the circadian nadir (2,12,67). However, in urgent situations the surgeons felt alert. The physical impact of fatigue gave the surgeons an experience of hangover or restlessness and a disturbed circadian rhythm in the days after the night shift. This correlates with our finding in paper 3 (3) that working night shifts does affect the circadian rhythm and that sleep before and after the night shifts is changed, resembling that of shift workers (49).

In the existing literature, evidence points towards that surgeons' performance in laparoscopic simulation deteriorates after 24 hours of sleep deprivation (55-59). Some papers have found an improvement (60,61) and one study found no difference (62). In our paper we wished to assess performance during the night shift as emergency procedures also are performed during the night and early morning hours on call. Thus, it is more relevant to perform the measurements while on duty

than after the end of work time. We found no deterioration of psychomotor performance during the night shift, despite that sleepiness significantly increased during the night and peaked in the early morning hours. These findings are supported by a study that measured neurocognitive performance and found that the brain could compensate for less than 24-hours of sleep deprivation (63). This compensation appears also to persist in real life as an American study reviewed all laparoscopic appendectomies and cholecystectomies over 7 years in order to assess if the complication rate was higher for procedures performed at night time (22:00-06:00) versus day time (06:00-22:00) (64). No differences were found in complications, overall morbidity and mortality between day time and night time procedures. The same researchers made a study with a similar design on trauma patients that had acute surgery performed over a 7-year period, where day time procedures (06:00-22:00) were compared with night time (22:00-06:00) (65). Again no differences in complications, overall morbidity or mortality were found between day time and night time procedures. Thus, based on our studies and others it can be concluded that surgeons can compensate for sleep deprivation during a 24-hour period, without staying for post call duty.

As an alternative to submitting surgeons to work hour restrictions, pharmacological performance enhancement with the drug modafinil has been proven useful in increasing certain aspects of cognitive function, in sleep deprived physicians after night shifts (93,94). The improved areas of cognition were improved memory, flexible thinking and decision making. However, no effect of modafinil was seen in psychomotor performance (93) and the physicians reported trouble sleeping on call, if given the opportunity, and at home post call (94). In USA modafinil is licensed for excessive sleepiness due to narcolepsy, obstructive sleep apnea and shift work sleep disorder. As most psycho-stimulants modafinil has a broad side-effect profile (95). Side-effects such as sleep loss, affection of the central nervous system, psychic disorders as anxiety and psychosis are seen (96). The health implications of a long-term use of modafinil on the cardiovascular system are not fully examined, yet it is less addictive than amphetamine (95,96). The use of modafinil as a medium for physicians to take on extended work hours in a safely manner appears completely irresponsible and without regard for the safety and health of the physicians themselves, and the safety of the patients in the long run. The use of modafinil as a neurocognitive enhancer is highly controversial (97).

Despite that surgeons subjectively felt an impact of fatigue on their performance we found no objective measures that proved deterioration in performance or increased error (2,4). By these findings our studies hypothesize that we in Europe have the right work hour regulations for physicians working shifts, as they have the time to recover from sleep deprivation. Other factors need to be taken into account, than the performances of the individual surgeons, as the rates of Danish adverse events in hospitals are comparable internationally (7). In our paper 4 (4) we found that education of young doctors may have an influence on the errors that are consistently made in admission medical records. This was supported by a British study that found twice as many adverse events in junior trainees and senior trainees in simulated ward rounds (90). Many other factors influence patient outcome apart from physicians' individual performance; for instance the training of non-technical skills have proven to ameliorate surgical teams' work behaviors and to improve technical outcomes (98). Furthermore, an observational study found that surgical teams who exhibit less team work behavior have a higher risk of complications and even death (99).

In other studies, increased mortality is seen in patients admitted on weekends compared with weekdays (100,101), and at night time compared with day time (100). A cohort study of 188.212 patients undergoing non-emergent surgery, found that the 30-day mortality rate was higher for patients who were admitted to regular hospital floors on Fridays compared with Mondays through Wednesdays (102). This increase in mortality was not seen in patients who were admitted to the Intensive Care Unit or were discharged postoperatively. This suggests that the team around the patient also has an important influence on patients' outcome.

We found that markers of circadian rhythm were affected in surgeons working night shifts (3). The level of the urinary metabolite of melatonin (aMT6s) decreased markedly on call, which could be due to the fact that melatonin secretion is highly sensitive to light (16). The levels of salivary cortisol however, presented the pattern of a natural circadian rhythm. Furthermore, we found that the surgeons spent the day time prior to the night shift preparing, by sleeping in advance on the on call day. They also recovered from the sleep loss on the first post call day by sleeping when they came home from the night shift and 43% of the surgeons napped in the evening hours. It was interesting to find that this sleep pattern across a night shift resembles to that of shift workers, despite that the surgeons worked night shifts approximately 5-6 times per month. Shift work has serious health consequences; a systematic review and meta-analysis found shift work to be associated with myocardial infarction, and ischemic stroke (14). Furthermore a number of cancer types have been associated with shift work during the night, as non-Hodgkin's Lymphoma (103), breast cancer (104-106), endometrial cancer (107), prostate cancer (108-110), and colon cancer (109,111). In nurses working rotating night shifts increased breast and colon cancer risk was associated with more than 3 night shifts per month for 15 years or more (105,111). The increased cancer risks are associated with suppression of endogenous melatonin due to light exposure.

Another perspective of our findings is the education of the junior surgeons. A British study assessed junior and senior surgical trainees in a simulated ward environment (90). They presented three patient scenarios that were common problems, which the surgeons were expected to be familiar with. They found that senior trainees were more thorough in their assessment of the patients' than the junior trainees. Furthermore the study identified possible adverse events during the ward round and found junior trainees to be responsible for 15 out of 23 events. By ensuring proper education of interns and strengthening their clinical power of judgment, patient safety is also improved. Yet surgical education continues throughout life for surgeons of all levels and not only junior surgeons should be evaluated in their skills. A study evaluated the technical skills of 20 fully trained practicing surgeons in the performance of laparoscopic gastric bypass surgery and found a wide variation in surgeons' technical skills (112). The clinical importance was that surgical skills were a predictor of patients' outcome. The latter two studies elaborate on the importance of one-on-one evaluation of surgeons, or physicians' skills.

Despite that no decrease in surgeons' performances were found in the studies included in this PhD, the surgeons' circadian rhythm was still affected and the surgeons still felt an impact on their performance. We could however, not show a correlation between markers of circadian rhythms and subjective parameters such as fatigue, sleepiness or general well-being. Other studies have found a physiological impact of sleep

deprivation; decreased heart rate variability was seen in surgeons and anesthesiologists as a marker of increased physiological stress during night shifts (13,113). In order to ameliorate the physical impact of fatigue on night shifts it would be interesting to introduce small breaks during the night shift, particularly during the operation. A study in surgeons performing more than 2 hour long operations found that breaks of 20 seconds, where the surgeons stretched arms, neck and shoulders, every 20 minutes, significantly improved muscle strength, precision and fatigue (114). A randomized clinical trial measured the effects of unstructured 5 minute breaks every 25 minutes in surgeons performing complex laparoscopic procedures in children. They found reduced levels of saliva cortisol, a lower count of intraoperative events and increased well-being in the surgeons who were randomized for breaks. The scheduled breaks did not prolong the operation. Further research in similar initiatives to improve the work environment for surgeons and thereby indirectly improve patient safety is needed.

Surgeons working night shifts used day time on the on call day to sleep in advance and subsequently used the first post call day to recover from a nights' sleep loss. We support this method of sleeping in advance, or prophylactic sleep, as nothing is lost from reporting for work in the afternoon of a 17-hour night shift instead of in the morning for a 24-hour night shift, in that way it is avoided to tire out the surgeons cognitively during day time when they have to continue working the evening and night as well. It is established that the majority of shift workers sleep in advance by napping before their first night shift in order to reduce sleepiness during the night shift (49,115,116); napping is known to ameliorate shift work problems in a reliable manner (117).

The assessment of the impact of sleep deprivation on surgeons' performance during night shift is complex and multi-faceted. Surgeons do feel an impact of sleep deprivation during a night shift, and their circadian rhythm is affected. Despite this it appears that they are able to compensate for the sleep loss as no cognitive or psychomotor deterioration was found during the night shift. An important finding was that interns needed better education in writing medical records.

FUTURE STUDIES

The studies included in this thesis have identified several areas that should be studied further.

We have shown that markers of circadian rhythms are disturbed in surgeons. We could not determine whether there were general circadian disturbances as this would require more frequent sampling of the circadian markers in urine or alternatively blood or saliva. To determine whether circadian disturbances do have an impact on psychomotor performance it is necessary to make these investigations in the future.

We showed that there was a low secretion of melatonin during the night on call. Some physicians use self-medication with melatonin in the morning when they go home as a way of achieving better sleep after a night shift and in order to prevent the potential health effects of repeated night shifts. It should be examined in the future, if melatonin administration in the day time after a night shift could restore potential disturbed circadian rhythms, sleep and general well-being (118,119).

Our findings in paper 4 (4) suggested that improvement in the education of interns is necessary. First of all our findings should be validated in the future. Thus, it should be examined if errors in the primary admission record can be tracked further into patient treatment and if this, ultimately, results in reduced patient safety or treatment errors in general. Furthermore we find the British model of simulated ward rounds (90) quite interesting and would suggest that a similar study in simulating admission medical recording was performed in order to assess the ability of writing admission medical records in day time versus night time. This could be a direct estimation of errors.

The last suggestion to future studies regards the impact of fatigue that surgeons felt on their performance. As it has been proved that small breaks have a positive outcome of surgeons' well-being, surgeons' stress and intraoperative events (114,120) we find it interesting to perform similar studies in operations performed at night. As it is shown that surgeons' heart rate variability is reduced during night shifts (13,113), showing a sympathetic dominance of the autonomic nervous system that could be unhealthy, we find it interesting to perform a study that introduces micropauses in operations performed at night time. The aim would be to assess if surgeons' well-being is improved on the post call day, and to examine if a reduction is seen in the sympathetic dominance of the heart rate variability at night.

SUMMARY

The median incidence of adverse events that may result in patient injury is a total of 9% of all in-hospital admissions. In order to reduce this high incidence initiatives are continuously worked on that can reduce the risk of patient harm during admission by strengthening hospital systems. However, the influence of physicians´ shift work on the risk on adverse events in patients remains controversial. In the studies included in this PhD thesis we wished to examine the impact of sleep deprivation and circadian rhythm disturbances on surgeons' during night shifts. Further we wished to examine the impact sleep deprivation had on surgeons' performance as a measure of how patient safety would be affected.

We found that sleep deprivation subjectively had an impact on the surgeons and that they were aware of the effect fatigue had on their work performance. As a result they applied different mechanisms to cope with fatigue. Attending surgeons felt that they had a better overview now, due to more experience and better skills, than when they were residents, despite the fatigue on night shifts. We monitored surgeons' performance during night shifts by laparoscopic simulation and cognitive tests in order to assess their performance; no deterioration was found when pre call values were compared to on call values. The surgeons were monitored prospectively for 4 days across a night shift in order to assess the circadian rhythm and sleep. We found that surgeons' circadian rhythm was affected by working night shifts and their sleep pattern altered, resembling that of shift workers on the post call day. We assessed the quality of admission in medical records as a measure of surgeons' performance, during day, evening and night hours and found no deterioration in the quality of night time medical records. However, consistent high errors were found in several categories. These findings should be followed up in the future with respect of clarifying mechanism and consequences for patient safety.

In conclusion the assessment of the impact of sleep deprivation on surgeons' performance during night shift is complex and multi-faceted. Surgeons do feel an impact of sleep deprivation during night shifts, and their circadian rhythm is affected. Despite this, it appears that the surgeons are able to compensate for the effects of sleep loss. We did not find any results to support that sleep loss results in psychomotor or cogni-

tive deterioration during a 17-hour night shift or that sleep deprivation during a night shift results in reduced patient safety.

LITTERATURE

1. Amirian I, Danielsen AK, Rosenberg J. Perception of fatigue among surgeons during night shifts. Ann R Coll Surg Engl (Suppl) 2013;95:1-5.

2. Amirian I, Andersen LT, Rosenberg J et al. Laparoscopic skills and cognitive function are not affected in surgeons during a night shift. J Surg Educ 2014:71:543-50.

3. Amirian I, Andersen LT, Rosenberg J et al. Working night shifts affects surgeons' biological rhythm. Submitted.

4. Amirian I, Mortensen JF, Rosenberg J et al. Admission medical records made during night time have the same quality compared with day and evening time records. Dan Med J 2014, in press.

5. Bjorn B, Anhoj J, Lilja B. [Reporting of patient safety incidents: experience from five years with a national reporting system]. Ugeskr Laeger 2009;171:1677-80.

6. Schioler T, Lipczak H, Pedersen BL et al. [Incidence of adverse events in hospitals. A retrospective study of medical records]. Ugeskr Laeger 2001;163:5370-8.

7. de Vries EN, Ramrattan MA, Smorenburg SM et al. The incidence and nature of in-hospital adverse events: a systematic review. Qual Saf Health Care 2008;17:216-23.

8. Landrigan CP, Rothschild JM, Cronin JW et al. Effect of reducing interns' work hours on serious medical errors in intensive care units. N Engl J Med 2004;351:1838-48.

9. Lockley SW, Cronin JW, Evans EE et al. Effect of reducing interns' weekly work hours on sleep and attentional failures. N Engl J Med 2004;351:1829-37.

10. Ayas NT, Barger LK, Cade BE et al. Extended work duration and the risk of self-reported percutaneous injuries in interns. JAMA 2006;296:1055-62.

11. Barger LK, Cade BE, Ayas NT et al. Extended work shifts and the risk of motor vehicle crashes among interns. N Engl J Med 2005;352:125-34.

12. Malmberg B, Persson R, Flisberg P et al. Heart rate variability changes in physicians working on night call. Int Arch Occup Environ Health 2011;84:293-301.

13. Amirian I, Andersen LT, Rosenberg J et al. Decreased heart rate variability in surgeons during night shifts. Can J Surg 2014: in press.

14. Vyas MV, Garg AX, Iansavichus AV et al. Shift work and vascular events: systematic review and meta-analysis. BMJ 2012;345:e4800.

15. Kalsbeek A, van der Spek R, Lei J et al. Circadian rhythms in the hypothalamo-pituitary-adrenal (HPA) axis. Mol Cell Endocrinol 2012;349:20-9.

16. Hofstra WA, de Weerd AW. How to assess circadian rhythm in humans: a review of literature. Epilepsy Behav 2008;13:438-44.

17. Duffy JF, Czeisler CA. Effect of light on human circadian physiology. Sleep Med Clin 2009;4:165-77.

18. Murphy PJ, Campbell SS. Physiology of the circadian system in animals and humans. J Clin Neurophysiol 1996;13:2-16.

19. Wright KP, Lowry CA, Lebourgeois MK. Circadian and wakefulness-sleep modulation of cognition in humans. Front Mol Neurosci 2012;5:50.

20. Mistlberger RE. Circadian regulation of sleep in mammals: role of the suprachiasmatic nucleus. Brain Res Brain Res Rev 2005;49:429-54.

21. Logan RW, Sarkar DK. Circadian nature of immune function. Mol Cell Endocrinol 2012;349:82-90.

22. Coogan AN, Wyse CA. Neuroimmunology of the circadian clock. Brain Res 2008;1232:104-12.

23. Blask DE. Melatonin, sleep disturbance and cancer risk. Sleep Med Rev 2009;13:257-64.

24. Boudreau P, Yeh WH, Dumont GA et al. Circadian variation of heart rate variability across sleep stages. Sleep 2013;36:1919-28.

25. Huikuri HV, Niemela MJ, Ojala S et al. Circadian rhythms of frequency domain measures of heart rate variability in healthy subjects and patients with coronary artery disease. Effects of arousal and upright posture. Circulation 1994;90:121-6.

26. Warren WS, Champney TH, Cassone VM. The suprachiasmatic nucleus controls the circadian rhythm of heart rate via the sympathetic nervous system. Physiol Behav 1994;55:1091-9.

27. Wright KP, Hull JT, Hughes RJ et al. Sleep and wakefulness out of phase with internal biological time impairs learning in humans. J Cogn Neurosci 2006;18:508-21.

28. Blatter K, Cajochen C. Circadian rhythms in cognitive performance: methodological constraints, protocols, theoretical underpinnings. Physiol Behav 2007;90:196-208.

29. Refinetti R. The circadian rhythm of body temperature. Front Biosci (Landmark Ed) 2010;15:564-94.

30. Sarabia JA, Rol MA, Mendiola P et al. Circadian rhythm of wrist temperature in normal-living subjects. A candidate of new index of the circadian system. Physiol Behav 2008;95:570-80.

31. Arendt J. Melatonin and human rhythms. Chronobiol Int 2006;23:21-37.

32. Middleton B. Measurement of melatonin and 6-sulphatoxymelatonin. Methods Mol Biol 2013;1065:171-99.

33. Chung S, Son GH, Kim K. Circadian rhythm of adrenal glucocorticoid: its regulation and clinical implications. Biochim Biophys Acta 2011;1812:581-91.

34. van de Werken M, Booij SH, van der Zwan JE et al. The biological clock modulates the human cortisol response in a multiplicative fashion. Chronobiol Int 2014: in press.

35. Akerstedt T, Froberg JE, Friberg Y et al. Melatonin excretion, body temperature and subjective arousal during 64 hours of sleep deprivation. Psychoneuroendocrinology 1979;4:219-25.

36. Sadeh A. The role and validity of actigraphy in sleep medicine: an update. Sleep Med Rev 2011;15:259-67.

37. Ancoli-Israel S, Cole R, Alessi C et al. The role of actigraphy in the study of sleep and circadian rhythms. Sleep 2003;26:342-92.

38. Benloucif S, Burgess HJ, Klerman EB et al. Measuring melatonin in humans. J Clin Sleep Med 2008;4:66-9.

39. Arendt J. Melatonin: characteristics, concerns, and prospects. J Biol Rhythms 2005;20:291-303.

40. Arendt J. Shift work: coping with the biological clock. Occup Med (Lond) 2010;60:10-20.

41. Harris A, Waage S, Ursin H et al. Cortisol, reaction time test and health among offshore shift workers. Psychoneuroendocrinology 2010;35:1339-47.

42. Rajaratnam SM, Arendt J. Health in a 24-h society. Lancet 2001;358:999-1005.

43. Borbely AA, Achermann P. Concepts and models of sleep regulation: an overview. J Sleep Res 1992;1:63-79.

44. Borbely AA. A two process model of sleep regulation. Hum Neurobiol 1982;1:195-204.

45. Borbely AA. Processes underlying sleep regulation. Horm Res 1998;49:114-17.

46. Chiu YH, Silman AJ, Macfarlane GJ et al. Poor sleep and depression are independently associated with a reduced pain threshold. Results of a population based study. Pain 2005;115:316-21.

47. Schestatsky P, Dall-Agnol L, Gheller L et al. Pain-autonomic interaction after work-induced sleep restriction. Eur J Neurol 2013;20:638-46.

48. Chhangani BS, Roehrs TA, Harris EJ et al. Pain sensitivity in sleepy pain-free normals. Sleep 2009;32:1011-7.

49. Akerstedt T. Shift work and disturbed sleep/wakefulness. Occup Med (Lond) 2003;53:89-94.

50. Akerstedt T, Wright KP. Sleep loss and fatigue in shift work and shift work disorder. Sleep Med Clin 2009;4:257-71.

51. Stevens RG, Hansen J, Costa G et al. Considerations of circadian impact for defining 'shift work' in cancer studies: IARC Working Group Report. Occup Environ Med 2011;68:154-62.

52. Rothschild JM, Keohane CA, Rogers S et al. Risks of complications by attending physicians after performing nighttime procedures. JAMA 2009;302:1565-72.

53. Nurok M, Czeisler CA, Lehmann LS. Sleep deprivation, elective surgical procedures, and informed consent. N Engl J Med 2010;363:2577-9.

54. Pellegrini CA, Britt LD, Hoyt DB. Sleep deprivation and elective surgery. N Engl J Med 2010;363:2672-3.

55. Eastridge BJ, Hamilton EC, O'Keefe GE et al. Effect of sleep deprivation on the performance of simulated laparoscopic surgical skill. Am J Surg 2003;186:169-74.

56. Grantcharov TP, Bardram L, Funch-Jensen P et al. Laparoscopic performance after one night on call in a surgical department: prospective study. BMJ 2001;323:1222-3.

57. Taffinder NJ, McManus IC, Gul Y et al. Effect of sleep deprivation on surgeons' dexterity on laparoscopy simulator. Lancet 1998;352:1191.

58. Kahol K, Leyba MJ, Deka M et al. Effect of fatigue on psychomotor and cognitive skills. Am J Surg 2008;195:195-204.

59. Lingenfelser T, Kaschel R, Weber A et al. Young hospital doctors after night duty: their task-specific cognitive status and emotional condition. Med Educ 1994;28:566-72.

60. Jensen A, Milner R, Fisher C et al. Short-term sleep deficits do not adversely affect acquisition of laparoscopic skills in a laboratory setting. Surg Endosc 2004;18:948-53.

61. DeMaria EJ, McBride CL, Broderick TJ et al. Night call does not impair learning of laparoscopic skills. Surg Innov 2005;12:145-9.

62. Uchal M, Tjugum J, Martinsen E et al. The impact of sleep deprivation on product quality and procedure effectiveness in a laparoscopic physical simulator: a randomized controlled trial. Am J Surg 2005;189:753-7.

63. Leff DR, Orihuela-Espina F, Athanasiou T et al. Circadian cortical compensation: a longitudinal study of brain function during technical and cognitive skills in acutely sleep-deprived surgical residents. Ann Surg 2010;252:1082-90.

64. Yaghoubian A, Kaji AH, Ishaque B et al. Acute care surgery performed by sleep deprived residents: are outcomes affected? J Surg Res 2010;163:192-6.

65. Yaghoubian A, Kaji AH, Putnam B et al. Trauma surgery performed by "sleep deprived" residents: are outcomes affected? J Surg Educ 2010;67:449-51.

66. Starks H, Trinidad SB. Choose your method: a comparison of phenomenology, discourse analysis, and grounded theory. Qual Health Res 2007;17:1372-80.

67. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care 2007;19:349-57.

68. Palter VN, Grantcharov TP. Individualized deliberate practice on a virtual reality simulator improves technical performance of surgical novices in the operating room: a randomized controlled trial. Ann Surg 2014;259:443-8.

69. Maagaard M, Sorensen JL, Oestergaard J et al. Retention of laparoscopic procedural skills acquired on a virtual-reality surgical trainer. Surg Endosc 2011;25:722-7.

70. Larsen CR, Oestergaard J, Ottesen BS et al. The efficacy of virtual reality simulation training in laparoscopy: a systematic review of randomized trials. Acta Obstet Gynecol Scand 2012;91:1015-28.

71. Larsen CR, Grantcharov T, Aggarwal R et al. Objective assessment of gynecologic laparoscopic skills using the LapSimGyn virtual reality simulator. Surg Endosc 2006;20:1460-6.

72. Burden C, Oestergaard J, Larsen CR. Integration of laparoscopic virtual-reality simulation into gynaecology training. BJOG 2011;118:5-10.

73. Aggarwal R, Tully A, Grantcharov T et al. Virtual reality simulation training can improve technical skills during laparoscopic salpingectomy for ectopic pregnancy. BJOG 2006;113:1382-7.

74. Oestergaard J, Bjerrum F, Maagaard M et al. Instructor feedback versus no instructor feedback on performance in a laparoscopic virtual reality simulator: a randomized educational trial. BMC Med Educ 2012;12:7.

75. Bates ME, Lemay EP. The d2 Test of attention: construct validity and extensions in scoring techniques. J Int Neuropsychol Soc 2004;10:392-400.

76. Schlosser K, Maschuw K, Kupietz E et al. Call-associated acute fatigue in surgical residents--subjective perception or objective fact? A cross-sectional observational study to examine the influence of fatigue on surgical performance. World J Surg 2012;36:2276-87.

77. Lehmann KS, Martus P, Little-Elk S et al. Impact of sleep deprivation on medium-term psychomotor and cognitive performance of surgeons: prospective cross-over study with a virtual surgery simulator and psychometric tests. Surgery 2010;147:246-54.

78. Niu SF, Chu H, Chen CH et al. A comparison of the effects of fixed- and rotating-shift schedules on nursing

staff attention levels: a randomized trial. Biol Res Nurs 2013;15:443-50.
79. Nikoghosyan-Bossen G, Hauberg A, Homoe P. Systematic analysis of ear-nose-throat malpractice complaints may be beneficial for patient safety. Dan Med J 2012;59:A4422.
80. Cole RJ, Kripke DF, Gruen W et al. Automatic sleep/wake identification from wrist activity. Sleep 1992;15:461-9.
81. Bisgaard T, Kjaersgaard M, Bernhard A et al. Computerized monitoring of physical activity and sleep in postoperative abdominal surgery patients. J Clin Monit Comput 1999;15:1-8.
82. Van Hilten JJ, Middelkoop HA, Kuiper SI et al. Where to record motor activity: an evaluation of commonly used sites of placement for activity monitors. Electroencephalogr Clin Neurophysiol 1993;89:359-62.
83. Pat Rapp M, Nelson F, Oliver M et al. Comparison of commonly used placement sites for activity monitoring. Biol Res Nurs 2010;11:302-9.
84. Kaida K, Takahashi M, Akerstedt T et al. Validation of the Karolinska sleepiness scale against performance and EEG variables. Clin Neurophysiol 2006;117:1574-81.
85. Akerstedt T, Gillberg M. Subjective and objective sleepiness in the active individual. Int J Neurosci 1990;52:29-37.
86. Gogenur I, Middleton B, Burgdorf S et al. Impact of sleep and circadian disturbances in urinary 6-sulphatoxymelatonin levels, on cognitive function after major surgery. J Pineal Res 2007;43:179-84.
87. Carlsen B, Glenton C. What about N? A methodological study of sample-size reporting in focus group studies. BMC Med Res Methodol 2011;11:26.
88. Pilcher JJ, Huffcutt AI. Effects of sleep deprivation on performance: a meta-analysis. Sleep 1996;19:318-26.
89. Brostrøm S, Saxtrup N. Subjektivt og objektivt - anamnese, undersøgelse og journal. 2011 3.ed. Copenhagen: Munksgaard Danmark.
90. Pucher PH, Aggarwal R, Srisatkunam T et al. Validation of the simulated ward environment for assessment of ward-based surgical care. Ann Surg 2014;259:215-21.
91. Papp KK, Stoller EP, Sage P et al. The effects of sleep loss and fatigue on resident-physicians: a multi-institutional, mixed-method study. Acad Med 2004;79:394-406.
92. Alhola P, Polo-Kantola P. Sleep deprivation: Impact on cognitive performance. Neuropsychiatr Dis Treat 2007;3:553-67.
93. Sugden C, Housden CR, Aggarwal R et al. Effect of pharmacological enhancement on the cognitive and clinical psychomotor performance of sleep-deprived doctors: a randomized controlled trial. Ann Surg 2012;255:222-7.
94. Gill M, Haerich P, Westcott K et al. Cognitive performance following modafinil versus placebo in sleep-deprived emergency physicians: a double-blind randomized crossover study. Acad Emerg Med 2006;13:158-65.
95. Minzenberg MJ, Carter CS. Modafinil: a review of neurochemical actions and effects on cognition. Neuropsychopharmacology 2008;33:1477-502.
96. Proctor A, Bianchi MT. Clinical pharmacology in sleep medicine. ISRN Pharmacol 2012;2012:914168.
97. Sugden C, Aggarwal R, Housden C et al. Pharmacological enhancement of performance in doctors. BMJ 2010;340:c2542.
98. McCulloch P, Mishra A, Handa A et al. The effects of aviation-style non-technical skills training on technical performance and outcome in the operating theatre. Qual Saf Health Care 2009;18:109-15.
99. Mazzocco K, Petitti DB, Fong KT et al. Surgical team behaviors and patient outcomes. Am J Surg 2009;197:678-85.
100. Ogbu UC, Westert GP, Slobbe LC et al. A multifaceted look at time of admission and its impact on case-fatality among a cohort of ischaemic stroke patients. J Neurol Neurosurg Psychiatry 2011;82:8-13.
101. Barba R, Losa JE, Velasco M et al. Mortality among adult patients admitted to the hospital on weekends. Eur J Intern Med 2006;17:322-4.
102. Zare MM, Itani KM, Schifftner TL et al. Mortality after nonemergent major surgery performed on Friday versus Monday through Wednesday. Ann Surg 2007;246:866-74.
103. Lahti TA, Partonen T, Kyyronen P et al. Night-time work predisposes to non-Hodgkin lymphoma. Int J Cancer 2008;123:2148-51.
104. Davis S, Mirick DK, Stevens RG. Night shift work, light at night, and risk of breast cancer. J Natl Cancer Inst 2001;93:1557-62.
105. Schernhammer ES, Laden F, Speizer FE et al. Rotating night shifts and risk of breast cancer in women participating in the nurses' health study. J Natl Cancer Inst 2001;93:1563-8.
106. Hansen J. Light at night, shiftwork, and breast cancer risk. J Natl Cancer Inst 2001;93:1513-5.
107. Viswanathan AN, Schernhammer ES. Circulating melatonin and the risk of breast and endometrial cancer in women. Cancer Lett 2009;281:1-7.
108. Conlon M, Lightfoot N, Kreiger N. Rotating shift work and risk of prostate cancer. Epidemiology 2007;18:182-3.
109. Kloog I, Haim A, Stevens RG et al. Global co-distribution of light at night (LAN) and cancers of prostate, colon, and lung in men. Chronobiol Int 2009;26:108-25.
110. Kubo T, Ozasa K, Mikami K et al. Prospective cohort study of the risk of prostate cancer among rotating-shift workers: findings from the Japan collaborative cohort study. Am J Epidemiol 2006;164:549-55.
111. Schernhammer ES, Laden F, Speizer FE et al. Night-shift work and risk of colorectal cancer in the nurses' health study. J Natl Cancer Inst 2003;95:825-8.
112. Birkmeyer JD, Finks JF, O'Reilly A et al. Surgical skill and complication rates after bariatric surgery. N Engl J Med 2013;369:1434-42.
113. Malmberg B, Kecklund G, Karlson B et al. Sleep and recovery in physicians on night call: a longitudinal field study. BMC Health Serv Res 2010;10:239.
114. Dorion D, Darveau S. Do micropauses prevent surgeon's fatigue and loss of accuracy associated with prolonged surgery? An experimental prospective study. Ann Surg 2013;257:256-9.
115. Akerstedt T, Torsvall L. Napping in shift work. Sleep 1985;8:105-9.

116. Sallinen M, Harma M, Mutanen P et al. Sleep-wake rhythm in an irregular shift system. J Sleep Res 2003;12:103-12.
117. Takahashi M. The role of prescribed napping in sleep medicine. Sleep Med Rev 2003;7:227-35.
118. Cavallo A, Ris MD, Succop P et al. Melatonin treatment of pediatric residents for adaptation to night shift work. Ambul Pediatr 2005;5:172-7.
119. Smith MR, Lee C, Crowley SJ et al. Morning melatonin has limited benefit as a soporific for daytime sleep after night work. Chronobiol Int 2005;22:873-88.
120. Engelmann C, Schneider M, Kirschbaum C et al. Effects of intraoperative breaks on mental and somatic operator fatigue: a randomized clinical trial. Surg Endosc 2011;25:1245-50.