

Sleep disturbances and changes in urinary 6-sulphatoxymelatonin levels in patients with breast cancer undergoing lumpectomy

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Background: Sleep disturbances and changes in self-reported discomfort and melatonin secretion are common in the post-operative period. We aimed to study the distribution of sleep stages in the perioperative period and evaluate changes in secretion of the melatonin metabolite aMT6s and subjective parameters of sleepiness, pain, general well-being and fatigue in patients undergoing surgery for breast cancer.

Methods: Twelve patients, 30–70 years, undergoing lumpectomy were included. Polysomnography was performed the night before surgery (PREOP), the night after (PO1) and 14 days after (PO14). Recordings were scored as awake, light-sleep, slow-wave sleep and rapid-eye-movement (REM) sleep. Sleep stages were analysed as % of total sleep time (TST). Self-reported discomfort was assessed using questions about the level of fatigue, well-being, pain and sleepiness. Urinary aMT6s was measured by radioimmunoassay.

Results: There was significantly decreased REM sleep on PO1

(5.9% of TST) compared with PREOP (18.7% of TST) ($P < 0.005$). An increase in light sleep was observed on PO1 (68.4% of TST) compared with PREOP (55.0% of TST) ($P < 0.05$). No significant changes in TST, sleep latency, sleep period or total time awake were found. The observed sleep changes were normalised after 2 weeks. No significant changes were found in pain, well-being, fatigue or sleepiness. Night secretion of aMT6s showed a trend towards a decrease from PREOP to PO1 ($P = 0.09$) and normalisation on PO14 ($P = 0.27$ between PREOP and PO14).

Conclusion: Patients with breast cancer undergoing lumpectomy had significantly disturbed sleep architecture the night after surgery, and these changes were normalised after 2 weeks.

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IN spite of improvements in surgical techniques and anaesthesia care, surgery is still beset with complications because of the overall surgical stress response. One specific result of the stress response is the sleep disturbances observed in the period after both minor and major surgery.^{1,2} The dominant sleep pattern after major non-cardiac surgery is characterised by an almost total elimination of rapid eye movement (REM) sleep, a reduction in the amount of slow-wave sleep (SWS) and an increased amount of light sleep (LS).^{1,3} The sleep disturbances are less predominant after minor non-cardiac surgery with only minor changes in SWS and no changes in REM sleep.^{1,4} To our knowledge, no studies have been done in patients with cancer undergoing minor surgery. It is believed that changes in endogenous levels of the circadian hormone melatonin may influence the development of sleep disturbances in the first nights after surgery.⁵

The potential consequences of this disturbed post-operative sleep are numerous including altered cognitive function, post-operative episodic hypoxaemia, haemodynamic instability, post-operative fatigue, decreased pain threshold, anxiety and depression.^{1,3} Furthermore, an association is well-known between sleep and subjective parameters such as sleepiness, post-operative fatigue and pain, and the objective parameter of melatonin secretion.^{1,2}

Sleep problems are common in patients with cancer^{6,7} and are particularly prevalent in patients with breast cancer.^{6,8} Many patients with breast cancer suffer from reduced sleep quality and approximately 30% of them take hypnotics.^{6,8} Polysomnography (PSG) has previously been used for sleep monitoring in patients with breast cancer,^{9–11} although the sleep pattern has never been investigated in the perioperative period. We hypothesised that sleep disturbances may be present in the

perioperative period, accompanied by possible changes in melatonin secretion and in self-reported discomfort. We therefore aimed to describe the distribution of sleep stages and quantify any possible sleep architecture changes measured by PSG. Furthermore, we aimed to evaluate changes in melatonin secretion and subjective parameters of sleepiness, pain, general well-being and fatigue in patients with breast cancer in the perioperative period.

Methods

All patients entered the study after written informed consent. The study was approved by the Local Ethics Committee and The Danish Data Protection Agency. Furthermore, the study was registered on <http://www.clinicaltrials.gov> (NCT01171508).

Inclusion criteria were women with breast cancer, diagnosed by triple test, in the age between 30 and 70 years, American Society of Anesthesiologist physical status I–III, and scheduled for a lumpectomy. Exclusion criteria were patients with known sleep apnoea syndrome, pre-operative treatment with beta-adrenergic blockers, known diabetes mellitus, known pre-operative depressive illness or dementia, previous or other current cancer, medically treated sleep disorders (insomnia, restless legs, etc.), shift-work, consumption of more than 50 g of alcohol daily, pre-operative treatment with psychopharmacological drugs, hypnotics, opioids or anxiolytics, predicted bad compliance, pregnancy/nursing, pre- or post-operative complications or events that were expected to increase morbidity or pain the first post-operative days, faecal or urine incontinence, or a pre-operative mini-mental state examination¹² score < 24.

The study consisted of three monitoring periods with the first monitoring being between 19:00 h to 07:00 h the evening before surgery (PREOP), the second in the same time period the evening after surgery (PO1) and the third in the same time period 14 days after surgery (PO14). For these three monitoring periods, patients were admitted to the hospital and stayed in a private room in the patient hotel and did not require any intense monitoring or nursing interventions on any of the monitoring nights. The patient hotel is a facility for patients not needing monitoring or nursing interventions. Thus, it is calm and private, with no disturbances from noise, light or surveillance.

For objective sleep measurements, polysomnographic monitoring was made. A PSG (Embla A10, Medcare Flaga, Reykjavik, Iceland) recording was

made by four channel bipolar electroencephalography (C4-A1, C3-A2, O2-A1, O1-A2), two channel electrooculography and bipolar electromyography (submental).¹³ Gold cup-electrodes (10 mm EEG Electrodes, Medcare, Thornton, CO, USA) were used at O1, O2, A1, A2, C3, C4 and at the electromyography and electrooculography positions according to Rechtschaffen and Kales¹³ after proper skin preparation. All the electrode wires were collected in a bundle and connected to the recording system with the possibility to disconnect from this to walk freely and go to the bathroom.

One experienced scorer blinded for the day of measurement, scored the patient's sleep in 30-s epochs. To determine sleep latency, total sleep time (TST) and wake after sleep onset (WASO), patients had written down in sleep diaries when they turned the lights out and tried to go to sleep and what time they woke up in the morning. The recordings were scored as awake, N1 (stage 1), N2 (stage 2), N3 (stage 3) and REM sleep according to the standard criteria.¹³ For simplicity, N1 and N2 were combined and interpreted as LS and N3 as SWS. The software platform used for manual scoring was Remlogic 3.0 (Embla, Natus Medical Incorporated, Denver, CO, USA).

Self-reported discomfort was assessed using questions about the level of fatigue, general well-being and pain. Assessments were made on the pre-operative morning and every day until the morning after PO14. Fatigue was scored on a 10-point ordinal scale (1 = fit and 10 = very fatigued), as described previously.¹⁴ General well-being was assessed by a visual analogue scale (VAS) scale (0 mm = extremely well and 100 mm = extreme malaise). Pain at rest was also assessed by using a 100-mm VAS ranging from no pain to worst conceivable pain. Patients rated their sleepiness on a 9-point scale (Karolinska Sleepiness Scale, KSS)¹⁵ with the following steps: 'extremely alert' (score = 1), 'alert' (score = 3), 'neither alert nor sleepy' (score = 5), 'sleepy – but no difficulty remaining awake' (score = 7), 'extremely sleepy – fighting sleep' (score = 9). The steps in-between had a scale value but no label.

During the three monitoring periods in the patient hotel, patients were also instructed in urine collection from 19:00 to 23:00 and 23:00 to 07:00 to measure aMT6s levels. A 10-ml sample was taken from each of the collection periods and stored at –20°C until analysis. Urinary aMT6s was measured by radioimmunoassay, as described previously.¹⁶ A light intensity reading (lux) was made at 'lights out' (Elma 1335 luxmeter, Elmanet, Greve, Denmark) to make sure light exposure at the level of gaze did not

exceed 10 lux, and patients were instructed to wear a sleep mask.

Patients received pre-medication consisting of a single dose of paracetamol 1000 mg, celecoxib 400 mg and gabapentin 600 mg as analgesics and dexamethasone 8 mg to prevent post-operative nausea. All patients underwent general anaesthesia with intravenous induction with propofol, and propofol and remifentanyl for maintenance. Laryngeal masks were used for all patients, and no neuromuscular blocking drugs were used. All patients received two doses of fentanyl: at the beginning and at the end of anaesthesia. A local anaesthetic, bupivacaine 20 ml 2.5 mg/ml, was injected into the lumpectomy scar. Ondansetron 4 mg intravenously was administered during surgery to prevent post-operative nausea. All patients received standard post-operative care consisting of treatment with paracetamol 1 g \times 4/day and ibuprofen 400 mg \times 3/day for 3 days post-operatively.

All data are presented as median (range), if not stated otherwise. Sleep data are presented in minutes, % of TST, and % or numbers of awakenings/number of REM episodes for the night PREOP, PO1 and PO14. Subjective discomfort and KSS data are presented as median values for the morning after PREOP, PO1 and PO14. aMT6s data are presented in total amount (ng) for the evening (19:00–23:00), night (23:00–07:00) and total collection period (19:00–07:00).

Friedman analysis of variance was used for repeated measures. Intragroup comparisons were performed using Wilcoxon signed-rank tests for all parameters with the following combinations: PO14 vs. PO1, PO14 vs. PREOP and PO1 vs. PREOP. Relationships between variables were quantified using Spearman correlations. For statistical analyses, IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA) was used. A *P*-value of ≤ 0.05 was considered statistically significant. Because of the descriptive, observational design of the study and based on the lack of prior data, a sample size calculation was not made.

Results

Twelve patients were included and completed the study. Patient characteristics and operative data are listed in Table 1. The patients had a median age of 52 years (42–69) and a median body mass index (kg/m²) of 24.4 (20.3–34.1). All underwent a lumpectomy with a median duration of surgery of 90 min (58–185). Two of the 12 patients also had an axillary

Table 1

Baseline and perioperative characteristics.	
Patient characteristics	
Age (years)	52 (42–69)
BMI (kg/m ²)	24.4 (20.3–34.1)
Menopausal status (pre/post)	7/5
ASA physical status class I/II	8/4
Type of surgery (lumpectomy/lumpectomy + axillary dissection)	10/2
Surgery duration (min)	90 (58–185)

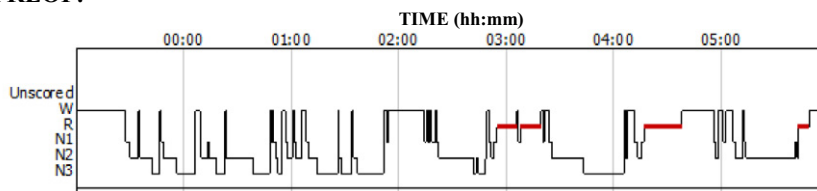
Values are frequencies or median (range). ASA, American Society of Anesthesiologists; BMI, body mass index.

dissection performed. None of the patients experienced any serious post-operative complications, and none of the patients required nursing interventions or monitoring on PO1. One patient was treated with dicloxacillin for a wound infection starting on day PO14, and two patients had seromas that needed drainage on day PO14.

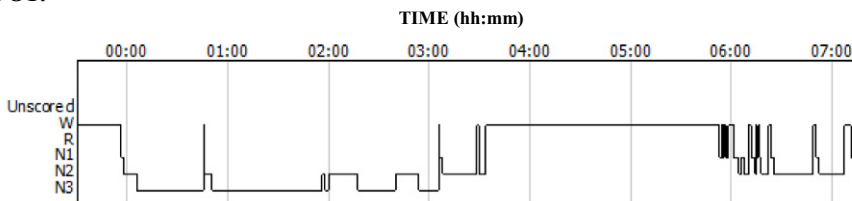
REM sleep in % of TST decreased from PREOP to PO1 ($P < 0.005$) and increased from PO1 to PO14 ($P < 0.005$). Besides experiencing significantly less REM sleep in percentage of TST, patients also had fewer episodes of REM sleep on PO1 compared with PREOP ($P < 0.005$) and more episodes on PO14 compared with PO1 ($P < 0.005$). One patient did not have REM sleep at all the first night after surgery but had 50% of TST in SWS instead and one long awakening of more than 2 h (Fig. 1). LS in % of TST increased from PREOP to PO1 ($P < 0.05$). SWS was unchanged from PREOP to PO1 and decreased from PREOP to PO14 ($P = 0.05$). One patient did not have any SWS on PO1. One patient only had 2.2% SWS on PO1 compared with 15.1% on PREOP and 22.5% on PO14, and yet another patient had 8.7% SWS on PO1 compared with 30.1% on PREOP and 24.8% on PO14. WASO significantly decreased from PREOP to PO14 ($P = 0.05$) and from PO1 to PO14 ($P < 0.05$). Seven of the 12 patients experienced WASO of more than 2 h on PO1, and three of these seven patients experienced WASO of more than 3.5 h. Significantly more awakenings were found on PREOP than PO1 ($P < 0.05$) and on PO14 than PO1 ($P < 0.05$). No significant changes were found in TST, sleep latency, sleep period or total time awake between the three monitoring nights (Table 2).

None of the three self-reported discomfort parameters: pain, fatigue and general well-being; nor sleepiness reported by KSS showed significant changes through the whole time course of the study (Friedman analysis of variance data not shown). No

PREOP:



PO1:



PO14:

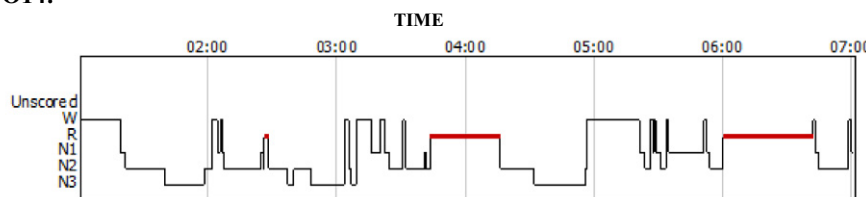


Fig. 1. Pre-operative- (PREOP) and post-operative (PO1 and PO14) hypnograms for a 65 year old woman who was operated for breast cancer by lumpectomy. W, wake; R, rapid eye movement (red line); N1, stage 1 (light sleep); N2, stage 2 (light sleep); N3, stage 3 (slow-wave sleep).

Table 2

Sleep data.				
	PREOP	PO1	PO14	P-value
Sleep latency (min)	23 (4–58)	19 (0–29)	21 (2–107)	
Sleep period (min)	439 (286–491)	434 (352–471)	412 (343–469)	
Number of awakenings	25 (16–38)	23 (5–30)	29 (13–47)	< 0.05* < 0.05†
Awake (min)	106 (64–255)	114 (75–236)	100 (25–184)	
WASO (min)	80 (28–237)	104 (49–216)	54 (21–161)	≤ 0.05‡ < 0.05†
TST (min)	320 (189–428)	332 (182–405)	353 (194–403)	
LS in % of TST	55.0 (43.1–66.1)	68.4 (42.7–94.4)	60.0 (49.3–70.6)	< 0.05*
SWS in % of TST	21.1 (15.1–41.1)	24.5 (0.0–53.8)	20.8 (13.6–26.0)	≤ 0.05‡
REM in % of TST	18.7 (15.6–32.3)	5.9 (0.0–12.8)	20.9 (15.8–25.9)	< 0.005* < 0.005†
REM episodes	7 (3–16)	3 (0–4)	6 (3–13)	< 0.005* ≤ 0.005†

Values are median (range). P-values (Wilcoxon signed-rank test) ≤ 0.05 are shown.

*PO1 vs. PREOP.

†PO14 vs. PO1.

‡PO14 vs. PREOP.

WASO, wake after sleep onset; TST, total sleep time; LS, light sleep; SWS, slow-wave sleep; REM, rapid eye movement.

significant differences in pain, general well-being, fatigue or KSS between the specific median values the morning after PREOP, PO1 and PO14 were found (Table 3).

A significant increase was found between the evening and night values of aMT6s in ng (Table 4).

When comparing PREOP, PO1 and PO14 for aMT6s ng at night and the total amount of aMT6s in ng (evening + night), both analyses showed an increase from PO1 to PO14 ($P < 0.05$). Night secretion of aMT6s showed a non-significant trend towards a decrease from PREOP to PO1 ($P = 0.09$) and a

Table 3

Subjective parameters: pain, general well-being, fatigue and sleepiness (KSS).

	PREOP	PO1	PO14
Pain	1 (0–19)	6 (0–52)	1 (0–46)
General well-being	28 (0–55)	15 (0–71)	7 (0–71)
Fatigue	3 (1–10)	4 (1–10)	4 (1–6)
KSS	3 (1–7)	3 (1–9)	3 (1–5)

Subjective parameters on PREOP, PO1 and PO14. Values are given as median (range).

VAS, visual analogue scale; KSS, Karolinska Sleepiness Scale.

normalisation on PO14 ($P = 0.27$ between PREOP and PO14).

No significant correlations were found between pain, fatigue, general well-being, sleepiness and the objective PSG sleep parameters on PO1 (data not shown). Neither significant correlations were found between the changes from PREOP to PO1 on sleep parameters TST, sleep latency, REM in % of TST, REM episodes and the total production of aMT6s at night (data not shown).

Discussion

The basic findings of our observational study were a high occurrence of disturbed sleep after surgery for breast cancer with decreased REM sleep in % of TST, fewer episodes of REM sleep and increased LS when comparing the first post-operative night with the pre-operative night. These findings of objective sleep disturbances were not reflected in our measurements of subjective pain, general well-being, fatigue or sleepiness. Total amount of the melatonin metabolite aMT6s in urine showed a trend towards a decrease on PO1 compared with PREOP and normalisation on PO14.

Results from previous studies using PSG in patients with breast cancer^{9–11} cannot be compared with our results, as these studies monitored the patients with PSG at least 7 months and up to 3.5 years after the initial diagnosis of cancer.

Our results are in agreement with the general pattern found after major non-cardiac surgery in other studies with an almost total elimination of REM sleep and increased amounts of LS during the first post-operative night.³ In agreement with previous studies,^{17–20} we found fragmented post-operative sleep with long awake periods, although the number of awakenings significantly decreased from PREOP to PO1. The minutes awake were not significantly increased on PO1 compared with

PREOP. WASO significantly varied across the three monitoring nights. In contrast with other studies, we did not find a significant reduction in TST or a marked reduction in the amount of SWS on the first post-operative night.^{17–19,21–23}

Many factors are known to contribute to the development of post-operative sleep disturbances: the magnitude and duration of surgery, opioid administration, post-operative pain, age, the surgical stress response with altered endocrine, metabolic and inflammatory function post-operatively, and the effects of the surroundings.^{1,3,24}

Patients' subjective assessment of pain by VAS only showed a non-significant trend towards an increase on PO1 compared with PREOP, leading us to conclude that pain did not have a major influence on the observed sleep disturbances. With regard to the analgesic treatment of these patients, no opioids were administered for post-operative analgesia. All patients received two doses of fentanyl intra-operatively, but because of the short half-life of this drug, we do not consider the administration of fentanyl to be a disturbing factor in the observed sleep disturbances seen on PO1. Otherwise, only non-steroidal anti-inflammatory drugs, gabapentin and paracetamol were used as analgesics, deviating from the hypothesis that administration of opioids in the post-operative period may be an important factor in the development of these specific post-operative sleep disturbances. Studies on normal adults²⁵ and patients with primary insomnia²⁶ have shown that gabapentin increases SWS, but because this was not what we found in this current study, we do not believe that the administration of gabapentin 600 mg as a single dose had an influence on the observed post-operative sleep pattern. The patients also received a single intraoperative dose of dexamethasone. This could partially explain our findings, as studies in healthy adults have shown increases in SWS and reduction in REM sleep after both pulsatile and continuous infusion of cortisol.^{27,28} Because the biological half-life of dexamethasone is 36–54 h,^{*} we believe that the single dose given intraoperatively could possibly contribute to the reduction in REM sleep the night after surgery. Furthermore, one study in depressed patients²⁹ showed a slight increase in stage 2 sleep and a decrease in REM sleep after administration of 1 mg dexamethasone orally, being a lower dose than given in our study and still con-

*<http://www.medicines.org.uk/emc/medicine/8369> (accessed 15 March 2013).

Table 4

aMT6s data.	PREOP	PO1	PO14
aMT6s (ng) Evening 19:00–23:00	1001.3* (336.0–2124.0)	1464.4† (211.6–2811.6)	952.5‡ (470.4–3017.6)
aMT6s (ng) Night 23:00–07:00	10116.3 (2736.0–25907.2)	9747.8§ (2232.0–16321.5)	13841.2 (2208.6–23509.2)
aMT6s (total ng) Evening + night 19:00–07:00	10952.45 (3622.4–26738.8)	11502.4§ (4206.0–16746.5)	15009.6 (3952.8–24379.2)

Values are median (range). *P*-values (Wilcoxon signed-rank test) < 0.05 are shown. Comparisons were made between evening vs. night for PREOP, PO1 and PO14. Comparisons were also made between PO1 vs. PREOP, PO14 vs. PREOP and PO14 vs. PO1.

**P* < 0.005, PREOP evening vs. night.

†*P* < 0.005, PO1 evening vs. night.

‡*P* < 0.005, PO14 evening vs. night.

§*P* < 0.05, PO1 vs. PO14.

tributing to the association that dexamethasone could have an influence on sleep architecture.

The hospital environment was the same for all patients all three nights with a private room in the patient hotel. Thus, differences in measurement environment for the three nights cannot explain the observed sleep disturbances. However, when interpreting the length of WASO, it could seem that an effect of the environment, with a habituation through the three nights, may have been present.

Although we did not find significant changes in the patients general well-being measured by a VAS scale, we hypothesise that the sleep architecture changes we found when comparing PREOP to PO1 could have been even greater if we had chosen not to measure the night before surgery where nervousness because of the upcoming operation most likely was prominent and a contributing factor to disturbed sleep.

The magnitude of surgery has previously been shown to be related to the degree and severity of post-operative sleep disturbances, and therefore, we compared our results with those from other studies in patients undergoing minor surgery. One study⁴ in patients undergoing laparoscopic cholecystectomy showed no changes in REM sleep after this minor surgical procedure, and one study¹⁷ in patients undergoing herniorrhaphy and one study²³ in patients undergoing minor surgery (not specified) showed a decrease in the duration of post-operative REM sleep. The studied patient populations were different, and it is therefore not possible to compare our results directly with these previous studies. The size of the incisions and the anaesthetic- and post-operative pain regimens differed, as did the envi-

ronments of the study with one being in the intensive care unit,²³ and lastly, our study is the only study that involved patients with cancer and the only study including modern multimodal perioperative treatment including gabapentin for analgesia and dexamethasone for preventing post-operative nausea.

Other studies in patients undergoing minor surgery^{30–32} have shown the same decrease in melatonin levels on the first post-operative night as we have, although our decrease was not significant. None of these studies measured melatonin levels 2 weeks after surgery. One study³⁰ found both a delay in the timing of the aMT6s rhythm and a decreased amplitude, although we were not able to investigate this as we did not collect urine for a 24-h period.

There are several potentially important clinical implications and consequences of post-operative sleep disturbances ranging from altered mental status and cognitive dysfunction^{1,33,34} to cardiopulmonary instability with increased risk of hypoxaemia and post-operative cardiac events.¹ As these consequences are serious and cover many aspects of post-operative recovery, it is important to be aware of the risk of developing post-operative sleep disturbances of this magnitude even after minor surgery such as a lumpectomy.

A limitation of our study could be the so-called 'first night effect', as we only measured one night pre-operatively. However, we do not believe that this had a substantial effect on our data based on a previous study that showed that with the same monitoring equipment and experimental setup, a first night effect was not present.²²

Another limitation of our study was the descriptive, observational design, including only 12 patients. We were not able to make a sample size calculation, as no studies investigating post-operative sleep architecture in breast cancer were found. Therefore, we based our sample size on previous studies designed to evaluate post-operative sleep in patients undergoing minor surgery.^{4,17,23}

In conclusion, we found severe REM sleep deprivation together with an increase in LS in percentage of TST on the first night post-operatively, with both of these sleep stages being normalised again 2 weeks after the operation. Patients were also more awake on the first post-operative night compared with their presumed normal sleep pattern obtained 2 weeks after surgery. Subjective discomfort and sleepiness did not show changes reflecting these sleep disturbances. aMT6s in urine showed a trend towards a decrease on the first night post-operatively and a normalisation after 2 weeks.

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