Review Article

Postoperative sleep disorders and their potential impacts on surgical outcomes

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Abstract

   Postoperative sleep disturbance is a common occurrence with significant adverse effects on patients including delayed recovery, impairment of cognitive function, pain sensitivity and cardiovascular events. The development of postoperative sleep disturbance is multifactorial and involves the surgical inflammatory response, the severity of surgical trauma, pain, anxiety, the use of anesthetics and environmental factors such as nocturnal noise and light levels. Many of these factors can be managed perioperatively to minimize the deleterious impact on sleep. Pharmacological and non-pharmacological treatment strategies for postoperative sleep disturbance include dexmedetomidine, zolpidem, melatonin, enhanced recovery after surgery (ERAS) protocol and controlling of environmental noise and light levels. It is likely that a combination of pharmacological and non-pharmacological therapies will have the greatest impact; however, further research is required before their use can be routinely recommended.

Keywords: postoperative, sleep disturbance, surgical outcomes

Introduction

   Sleep disturbance is a common occurrence in post-surgical patients, particularly in those admitted to the intensive care unit (ICU)[1–2]. The significance of studying postoperative sleep disturbances is highlighted by poor sleep being a frequent complaint of patients who have recovered from critical illness[3–4]. Postoperative sleep disturbance occurs due to the complex interactions of numerous factors, many of which can be attenuated. If not managed, postoperative sleep disturbance can lead to delayed recovery and increased morbidity. While postoperative sleep disturbance itself is well recognized, its adverse effects on patients are not. Perioperative management of patients is a relatively neglected field of research. Through raising the awareness of this topic, we hope to stimulate interest and research into this important area. In this article, we reviewed sleep disturbance after surgery, as well as its preventative measures and proposed many more new perspectives for future studies.

Natural sleep pathway

   Sleep is a process in which rest and recovery occurs

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in addition to information processing and memory. Sleep can be divided into rapid eye movement (REM) and non-rapid eye movement (N-REM) sleep. N-REM can be further subdivided into N1, N2, and N3. Each stage differs in their electroencephalogram (EEG), electromyogram (EMG) and electrooculogram (EOG). Sleep begins with N-REM at N1 (light sleep). This light sleep stage accounts for 5%–10% of total sleep in adults, N2 accounts for 45%–55%, and N3 for 15%–25%. N3, the most restful stage, is also called deep sleep or slow wave sleep (SWS). REM sleep accounts for 20%–25% of total sleep in adults, whereas N-REM sleep accounts for the rest. One 90-minute cycle goes from N1, N2, N3, N2 and then REM (*Fig. 1*).

Influence of surgery on postoperative sleep

Severe sleep deprivation following surgery has been well characterized in terms of changes of the sleep cycle[5]. Polysomnographic studies have shown disturbances, including decreased total sleep time by up to 80%[5–6], fragmented sleep and either a decrease or complete loss of REM and N3 sleep[5,7–9]. The absence of rapid eye movement can be explained by pain triggered by inflammation[10]. Changes in the state of consciousness by becoming withdrawn or hyperaware due to the presence of a foreign environment can also contribute[11]. A study conducted by Chung *et al* observed postoperative sleep changes in obstructive sleep apnea (OSA) and non-obstructive sleep apnea (non-OSA) patients. They found that the sleep efficiency, REM sleep and N3 sleep were affected on the first night after the surgery. REM sleep was reduced in both OSA and non-OSA by 18% and 20% respectively but improved back to baseline by night seven[12]. Some studies found that REM sleep was completely absent on the first postoperative night
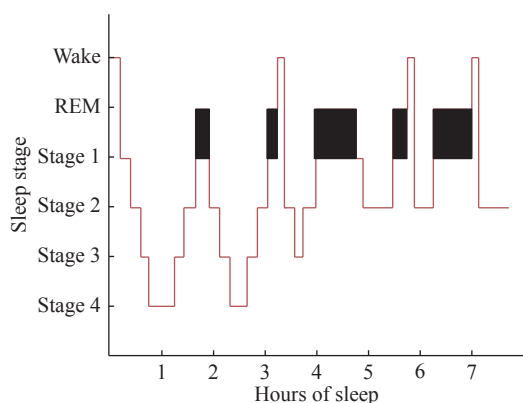

Fig. 1 **A hypnogram of a typical young adult.** N1=stage 1, N2=stage 2, and N3=stage 3+stage 4.

and remained reduced on the second and third nights as well[5–6,13]. SWS was depressed by 10% on the first night postoperatively and was back close to the baseline by night three. One study showed complete absence of SWS during the first two nights after surgery[6,14]. Interestingly, Chung *et al* noticed a rebound effect on REM sleep where an increase of 4% above the baseline occurred on night seven[12].

Surgical inflammatory response

The inflammatory response following surgery is complex and involves both the innate and adaptive immune system[15]. Major surgical trauma is thought to be accompanied by a period of postoperative immunosuppression, which predisposes to infection[15–16]. The postoperative inflammatory response causes neuroinflammation[17] and it is likely that this contributes to the postoperative sleep disturbances that surgical patients experience. Tumor necrosis factor (TNF) and interleukins are mediators of the inflammatory response which have been best described[18]. TNF and interleukin-1 (IL-1) have been most studied in relation to sleep. Injection of exogenous TNF or IL-1 is able to induce all the symptoms associated with sleep deprivation[19–20]. Administration of IL-1 into the lateral ventricle of rabbits resulted in the suppression of REM sleep, increased non-REM sleep and hyperthermia, which is similar to the changes observed in postoperative patients[21–22]. The sleep disturbance observed was attenuated by the pre-treatment with a IL-1 receptor antagonist[22]. Interleukin-6 (IL-6) is also implicated in sleep regulation. Circulating IL-6 levels at night have been correlated with quality of sleep with its high levels associated with a disrupted and that superficial sleep whilst its low levels were associated with a good and deep sleep[23]. Some cytokines involved in the surgical inflammatory response likely play a role in the disturbance of postoperative sleep. Laparoscopic surgery induces a less potent surgical inflammatory response than open surgery[24]. This may help explain why fewer changes in EEG-sleep pattern were observed after laparoscopic cholecystectomy[6].

Severity of surgical trauma

Postoperative sleep disturbances are correlated to the magnitude of surgery, with major surgery having the greatest sleep disturbance. The suppression of REM sleep and SWS is greater in major surgery (gastrectomy) than in minor surgery (hernia repair)[13]. Patients who underwent open cholecystectomy had

severe sleep disturbances with decreases in REM and SWS[14], whereas patients who underwent laparoscopic cholecystectomy experienced no change in REM sleep and a minor change in SWS[6]. Questionnaires of patients having undergone surgery reveal the highest incidence of postoperative sleep disturbance occurs after major surgery[13,25]. The duration of surgery is also correlated with the degree of postoperative sleep disturbance[13].

Pain

Pain is the most common cause of night-time postoperative disturbance[25–26] and analgesics were the best intervention for helping patients get back to sleep[25]. Opioids are effective at relieving postoperative pain; however, they worsen postoperative sleep through decreasing REM stimulating arousal and awakening responses[9,27–28]. Short-acting opioids are linked to pain-related sleep arousal and the addition of a background opioid failed to improve sleep and was associated with more adverse events[29–30]. The DREAMFAST found that a patient-controlled analgesia combination of alfentanil and morphine providing both rapid and slow acting analgesia did not improve postoperative sleep[31]. When pain is controlled through the use of non-opioids, patients still suffer from sleep disturbance[32].

Anesthesia causing sleep disturbance

Anesthesia has a minor role in the development of postoperative sleep disturbance. Anesthesia causes similar postoperative sleep disturbance patterns, including decreased REM and SWS, decreased total sleep time and increased sleep fragmentation, regardless of whether the anesthesia is regional or general[8,33–34]. Some studies which have reported relative benefits of regional anesthesia on postoperative sleep may be explained through reduced perioperative opioid consumption compared to patients who had general anesthesia[12,35]. Additionally, in healthy volunteers, general anesthesia had no effect on REM sleep and only a minor effect on SWS[36]. Therefore, anesthesia is of minor importance in the pathogenesis of postoperative sleep disturbance when compared to other factors such as the surgical inflammatory response, the severity of surgical trauma and the presence of postoperative pain (**Fig. 2**). Further evidence that anesthesia is not a major factor in the development of postoperative sleep disturbance is that similar changes in sleep occur in non-surgical patients in a variety of pathologies including acute myocardial infarction, acute stroke, heart failure and ICU patients[37–40].

Anxiety

Preoperative and postoperative anxiety has been shown to contribute to postoperative sleep disturbance[26]. Preoperative anxiety can increase perioperative pain, intraoperative anesthetic requirements and patient distress[41]. Postoperative anxiety has been less well studied than preoperative anxiety. Postoperative anxiety has been found to be associated with moderate to intense postoperative pain, American Society of Anesthesiologists (ASA) III physical status, minor psychiatric disorders and preoperative anxiety[42]. Systemic multimodal analgesia and neural-block analgesia have both been found to be protective against postoperative anxiety[42].

Other postoperative factors

Environmental factors are a common cause of sleep disturbance in the hospital setting, particularly in ICU. Environmental factors include noise, light and night-time observations and interventions on patients. Noise
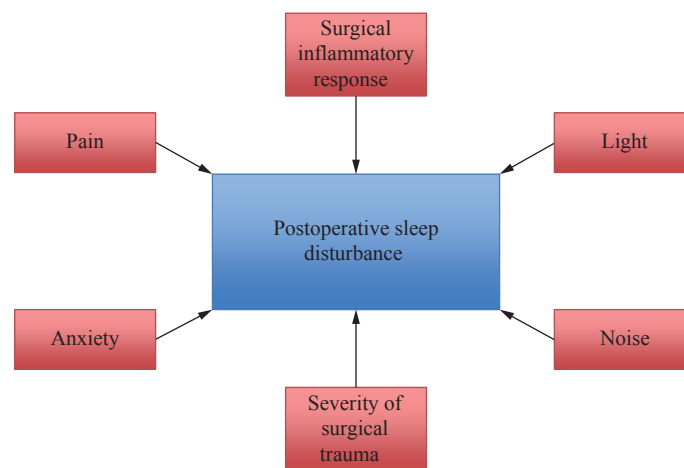

Fig. 2 **The factors contributing to postoperative sleep disturbance.**

is of particular interest, as it is the most commonly cited cause of sleep disturbance in critically ill patients[43–44]. The World Health Organization (WHO) guidelines for noise levels in the ICU state that average levels should not exceed 30 dB during day or night and peak levels at night should not exceed 40 dB[45]. Noise levels in ICU have frequently been shown to exceed these levels, with peak levels often exceeding 80 dB[46–47]. Noise levels in general surgical wards can also exceed 70 dB[48]. Nocturnal light exposure is another factor, which detrimentally affects sleep through disruption of the circadian rhythm. Nocturnal light levels as low as 40 lux are able to disrupt sleep architecture[49]. Nocturnal light levels were measured in 4 ICUs with mean levels of 128 to 1445 lux[46]. These levels are high enough to suppress melatonin secretion and disrupt sleep. Other factors that may adversely affect sleep include the need to use the toilet, nausea and fever[26].

Harmful effects of postoperative sleep disturbances

Effect on postoperative recovery

Postoperative sleep disturbance promotes the development of a catabolic state, which has an adverse effect on postoperative recovery[50–51]. The impact of sleep disturbance has been best characterized in the ICU setting, where it has been associated with delayed recovery, longer hospitalization and prolonged negative effects on patients' health and overall quality of life[2,52–53]. The quality of sleep on the first night postoperatively was found to be an important determinant of duration of hospital stay in patients following abdominal hysterectomy. A high quality of sleep was associated with a shorter hospital stay [(42±16) hours] while a longer hospital stay [(54±10) hours] occurred in those who perceived poor sleep[35]. There have been two studies on patients receiving total knee arthroplasty, which explored the impact of postoperative sleep disturbance on recovery. One study found that postoperative sleep disturbance was an independent predictor of functional impairment at month 3 after the surgery, and the other study found that improved sleep quality through treatment with zolpidem increased patient's recovery and active range of movement after the surgery[54].

Impairment of cognitive function

Postoperative cognitive dysfunction (POCD) is a common occurrence in the elderly, and belongs to disorders which affect orientation, attention, perception and consciousness that develop after surgery. After major surgery, the incidence of POCD is estimated between 7% and 77%[55]. Postoperative sleep disturbance in patients following arthroplasty or non-cardiac surgery is associated with an elevated risk of postoperative delirium. Delirium is very common in ICU patients for a multitude of reasons including postoperative sleep disturbance. Multimodal interventions to prevent delirium in older hospitalized patients, which include minimizing sleep disruption, appear effective in reducing its incidence[56–57].

Influence on pain

Postoperative sleep disturbance has a reciprocal effect on pain. Pain disrupts sleep, and poor sleep increases pain sensitivity[58]. One hour of sleep loss is sufficient to cause altered pain perception[59]. Disturbed sleep in patients prior to breast surgery has been shown to be associated with increased postoperative pain[60]. Studies of burn patients found that nights of poor sleep predicted greater pain and analgesia use the following day, and days with increased pain and analgesia use predicted poor sleep the following night[61–62]. Interventions aimed at improving sleep quality appear to reduce pain symptoms[63–64].

Cardiovascular effects

Chronic poor sleep is a risk factor for both cerebrovascular and cardiovascular disease. Conditions that disrupt sleep include obstructive sleep apnea which predispose to thrombotic events and arrhythmias[65–67]. Sleep deprivation activates the sympathetic adrenergic system, which induces pro-inflammation and blood pressure surges that are associated with accelerated atherosclerosis[68]. A prospective cohort study of 388 patients following percutaneous coronary intervention found an association between the number of symptoms of poor sleep and the occurrence of major cardiac events, including myocardial infarction, repeat revascularization and cardiac death[69].

Preventive strategies

Dexmedetomidine

Dexmedetomidine is a highly selective α_2-adrenoreceptor agonist with sedative, analgesic and anxiolytic properties[70]. Dexmedetomidine is increasingly used for ICU patients[71]. Dexmedetomidine attenuates several factors that contribute to postoperative sleep disturbance including

surgical inflammatory response[72], postoperative pain and increased opioid consumption[72–73]. Dexmedetomidine activates an endogenous sleep-promoting pathway, which is responsible for its sedative properties[74]. Night-time infusion of a sedative dose of dexmedetomidine improved sleep architecture and sleep efficiency[75]. Low-dose dexmedetomidine given to non-ventilated elderly patients in ICU following non-cardiac surgery increased the percentage of stage N2 sleep, sleep efficiency, total sleep time and subjective sleep quality[76]. Long-term follow-up of these patients revealed better cognitive function and quality of life in 3-year survival of the dexmedetomidine group than that of the placebo group[77]. The intraoperative or postoperative use of dexmedetomidine for sedation or postoperative analgesia has been shown to improve postoperative sleep through increasing total sleep time, sleep efficiency and subjective sleep quality in a variety of surgical patients[78–80].

Melatonin

Melatonin is a neurohormone produced by the pineal gland predominantly responsible for the regulation of the circadian rhythm in mammals[81]. Under physiological conditions, melatonin levels exhibit a pattern of a high blood concentration at night and a low concentration during the day. Postoperative sleep disturbance is associated with decreased nocturnal melatonin secretion, which gets normalized after 14 days[82–83]. Meta-analyses have confirmed that exogenous administration of melatonin may be both effective and safe in the management of secondary sleep disorders by increasing the total duration of sleep and reducing sleep latency, whilst keeping sleep architecture intact[84–85]. However, it is important to note that, whilst evidence suggests that melatonin induces sleep and beneficially shifts the circadian phase, there is significant heterogeneity in the studies investigating these effects[86]. In addition, most evidence for the efficacy of melatonin is from postoperative sleep quality questionnaires in adults and children as well as accelerography. In the early postoperative period, melatonin was associated with an improvement in subjective sleep quality and circadian rhythm[87–89]. In addition, a study involving a small sample size of post-prostatectomy patients, pre-operative exogenous melatonin enhanced sleep quality[87], whilst patients following breast cancer surgery also reported an improvement in subjective sleep quality with minimal side effects[90–92]. Overall, whilst there is certainly evidence for the beneficial effects of melatonin in the management of secondary

sleep disorders, particularly from qualitative sources, its precise mechanisms remain to be elucidated.

Zolpidem

Zolpidem is a short-acting nonbenzodiazepine hypnotic drug. Its primary action is sedation, although weak anxiolytic and anticonvulsive effects have been demonstrated[93]. Zolpidem is less likely to disrupt sleep architecture than benzodiazepines and may raise SWS and REM sleep to normal levels in patients with disturbed sleep[94–95]. Zolpidem administered for 14 days postoperatively improved feelings of sleep quality, reduced pain scores and reduced analgesic use[96]. A recent systematic review found that perioperative use of zolpidem may improve pain control but the evidence is weak and the results are inconsistent[97]. There is some evidence that the use of sedative drugs may increase delirium and confusion especially in the elderly[98].

Enhanced recovery after surgery (ERAS)

ERAS is a multimodal, multidisciplinary approach to perioperative care, which has resulted in substantial improvements in clinical outcomes and cost savings[99]. The ERAS protocol is underpinned by the latest available evidence for optimal recovery after surgery, and is therefore being constantly updated. There are 24 core elements of ERAS[100] (**Table 1**). Some of the elements that ERAS aims to target have been identified as factors that cause postoperative sleep disturbance. Core component of ERAS that will likely have a positive impact on postoperative sleep disturbance include structured preoperative information aimed at reducing anxiety, preoperative prophylaxis against infection, minimally invasive surgical techniques and the use of multimodal opioid-sparing pain management. Studies using ERAS principles have consistently shown reduced length of stay for patients[101–102]. Meta-analyses have confirmed significant reductions of up to 50% in complication rates[103–104].

Non-pharmacological treatments

Ensuring that noise and light levels are kept to a minimum during the night is an important strategy to minimize postoperative sleep disturbance. The evidence for non-pharmacological treatments for postoperative sleep disturbance as assessed in a 2015 Cochrane review has been found to be of low to very low quality[105]. The review found some evidence that the use of eye masks or earplugs may have favorable

Table 1 **The enhanced recovery after surgery (ERAS) protocol**

Preoperative	Intraoperative	Postoperative
Preadmission information, education and counseling	Standard anesthetic protocol	Nasogastric intubation
Preoperative optimization	Intraoperative fluid and electrolyte therapy	Postoperative analgesia
Prehabilitation	Preventing intraoperative hypothermia	Thromboprophylaxis
Preoperative nutritional care	Surgical access (open and minimally invasive surgery including laparoscopic, robotic and trans-anal approaches)	Postoperative fluid and electrolyte therapy
Management of anemia	Drainage of peritoneal cavity and pelvis	Urinary drainage
Prevention of nausea and vomiting		Prevention of postoperative ileus
Bowel preparation		Postoperative glycemic control
Pre-anesthetic medication		Postoperative nutritional care
Antimicrobial prophylaxis and skin preparation		
Preoperative fluid and electrolyte therapy		
Preoperative fasting and carbohydrate loading		

effects on sleep and the incidence of delirium in adults in the ICU setting[105]. A more recent systematic review found that earplugs, eye masks, relaxation training and white noise or music were associated with increased sleep quality, however high quality studies as assessed by the Jadad score were absent[106]. A recent randomized controlled trial found that perioperative psychological support increased the postoperative quality of sleep and quality of life in patients following esophagectomy[107]. Aromatherapy has been shown in a systematic review and meta-analysis to have a beneficial effect on sleep quality[108]. Aromatherapy appears to improve sleep quality in the setting of coronary ICU[109]. Despite all these, more high quality studies are required to definitively test the impact of non-pharmacological treatments on postoperative sleep.

Future perspectives

Further epidemiological research is necessary to quantify the proportion of surgical patients that develop postoperative sleep disturbance. Further research is required to validate the efficacy of the pharmacological and non-pharmacological treatments discussed in this review and beyond. In particular, for the non-pharmacological treatments, recent systematic reviews have found a paucity of high-quality studies. Dexmedetomidine is a promising pharmacological agent that has shown beneficial effects on postoperative sleep disturbance. Further research should aim to optimize the treatment regimen that will allow maximum benefit in reducing postoperative sleep disturbance. It is likely that a combined

approach of pharmacological and non-pharmacological treatment will result in maximal benefit for patients. As further research validates the efficacy of the pharmacological and non-pharmacological treatments discussed, it would be warranted to include these treatments in protocols such as ERAS, in order to further reduce complications and improve recovery after the operation.

Conclusions

Postoperative sleep disturbance is a well-recognized phenomenon. Factors that contribute include the surgical inflammatory response, severity of surgery, type of anesthesia, pain, anxiety, and environmental factors such as nocturnal noise and light. However, the effects of untreated postoperative sleep disturbance are not recognized, which include adverse effects on postoperative recovery, cognitive function, cardiovascular function and pain. Relatively small disruptions to sleep are sufficient to cause these adverse effects. The perioperative management of patients' sleep has been a relatively neglected field of research. Increasing awareness of postoperative sleep disturbance is important to drive research into this important field. Postoperative sleep disturbance is a multi-factorial phenomenon and thus requires a multi-modal prevention and treatment regime. This multi-modal approach should include the alleviation of preoperative anxiety, minimally invasive surgery, effective opioid-sparing postoperative pain management, non-pharmacological approaches such as minimizing night time disturbance, nocturnal light

and noise levels, and pharmacological treatment in which dexmedetomidine appears especially promising. All the pharmacological and non-pharmacological treatments discussed in this review require further high-quality research to validate their efficacy before their routine use can be made possible.

References

[1] Rosenberg J. Sleep disturbances after non-cardiac surgery[J]. *Sleep Med Rev,* 2001, 5(2): 129–137.

[2] Friese RS. Sleep and recovery from critical illness and injury: a review of theory, current practice, and future directions[J]. *Crit Care Med,* 2008, 36(3): 697–705.

[3] Freedman NS, Kotzer N, Schwab RJ. Patient perception of sleep quality and etiology of sleep disruption in the intensive care unit[J]. *Am J Respir Crit Care Med,* 1999, 159(4): 1155–1162.

[4] Nelson JE, Meier DE, Oei EJ, et al. Self-reported symptom experience of critically ill cancer patients receiving intensive care[J]. *Crit Care Med,* 2001, 29(2): 277–282.

[5] Aurell J, Elmqvist D. Sleep in the surgical intensive care unit: continuous polygraphic recording of sleep in nine patients receiving postoperative care[J]. *Br Med J (Clin Res Ed),* 1985, 290(6474): 1029–1032.

[6] Rosenberg-Adamsen S, Kehlet H, Dodds C, et al. Postoperative sleep disturbances: mechanisms and clinical implications[J]. *Br J Anaesth,* 1996, 76(4): 552–559.

[7] Dette F, Cassel W, Urban F, et al. Occurrence of rapid eye movement sleep deprivation after surgery under regional anesthesia[J]. *Anesth Analg,* 2013, 116(4): 939–943.

[8] Kavey NB, Altshuler KZ. Sleep in herniorrhaphy patients[J]. *Am J Surg,* 1979, 138(5): 683–687.

[9] Knill RL, Moote CA, Skinner MI, et al. Anesthesia with abdominal surgery leads to intense REM sleep during the first postoperative week[J]. *Anesthesiology,* 1990, 73(1): 52–61.

[10] Onen SH, Onen F, Courpron P, et al. How pain and analgesics disturb sleep[J]. *Clin J Pain,* 2005, 21(5): 422–431.

[11] Dlin BM, Rosen H, Dickstein K, et al. The problems of sleep and rest in the intensive care unit[J]. *Psychosomatics,* 1971, 12(3): 155–163.

[12] Chung F, Liao P, Elsaid H, et al. Factors associated with postoperative exacerbation of sleep-disordered breathing[J]. *Anesthesiology,* 2014, 120(2): 299–311.

[13] Ellis BW, Dudley HAF. Some aspects of sleep research in surgical stress[J]. *J Psychosom Res,* 1976, 20(4): 303–308.

[14] Rosenberg J, Wildschiødtz G, Pedersen MH, et al. Late postoperative nocturnal episodic hypoxaemia and associated sleep pattern[J]. *Br J Anaesth,* 1994, 72(2): 145–150.

[15] Dąbrowska AM, Słotwiński R. The immune response to surgery and infection[J]. *Cent Eur J Immunol,* 2014, 39(4): 532–537.

[16] Marik PE, Flemmer M. The immune response to surgery and trauma: implications for treatment[J]. *J Trauma Acute Care Surg,* 2012, 73(4): 801–808.

[17] Alam A, Hana Z, Jin ZS, et al. Surgery, neuroinflammation and cognitive impairment[J]. *EBioMedicine,* 2018, 37: 547–556.

[18] Lin E, Calvano SE, Lowry SF. Inflammatory cytokines and cell response in surgery[J]. *Surgery,* 2000, 127(2): 117–126.

[19] Kapsimalis F, Richardson G, Opp MR, et al. Cytokines and normal sleep[J]. *Curr Opin Pulm Med,* 2005, 11(6): 481–484.

[20] Krueger JM. The role of cytokines in sleep regulation[J]. *Curr Pharm Des,* 2008, 14(32): 3408–3416.

[21] Kapás L, Hong L, Cady AB, et al. Somnogenic, pyrogenic, and anorectic activities of tumor necrosis factor-alpha and TNF-alpha fragments[J]. *Am J Physiol-Regul, Integr Comp Physiol,* 1992, 263(3): R708–R715.

[22] Opp MR, Krueger JM. Interleukin 1-receptor antagonist blocks interleukin 1-induced sleep and fever[J]. *Am J Physiol-Regul, Integr Comp Physiol,* 1991, 260(2): R453–R457.

[23] Vgontzas AN, Papanicolaou DA, Bixler EO, et al. Circadian Interleukin-6 secretion and quantity and depth of sleep[J]. *J Clin Endocrinol Metab,* 1999, 84(8): 2603–2607.

[24] Kehlet H. Surgical stress response: does endoscopic surgery confer an advantage?[J]. *World J Surg,* 1999, 23(8): 801–807.

[25] Closs SJ. Patients' night-time pain, analgesic provision and sleep after surgery[J]. *Int J Nurs Stud,* 1992, 29(4): 381–392.

[26] Dolan R, Huh J, Tiwari N, et al. A prospective analysis of sleep deprivation and disturbance in surgical patients[J]. *Ann Med Surg (Lond),* 2016, 6: 1–5.

[27] Li Y, Van Den Pol AN. μ-opioid receptor-mediated depression of the hypothalamic hypocretin/orexin arousal system[J]. *J Neurosci,* 2008, 28(11): 2814–2819.

[28] Dimsdale JE, Norman D, DeJardin D, et al. The effect of opioids on sleep architecture[J]. *J Clin Sleep Med,* 2007, 3(1): 33–36.

[29] Parker RK, Holtmann B, White PF. Effects of a nighttime opioid infusion with PCA therapy on patient comfort and analgesic requirements: after abdominal hysterectomy[J]. *Anesthesiology,* 1992, 76(3): 362–367.

[30] George JA, Lin EE, Hanna MN, et al. The effect of intravenous opioid patient-controlled analgesia with and without background infusion on respiratory depression: a meta-analysis[J]. *J Opioid Manag,* 2010, 6(1): 47–54.

[31] Lee A, O'Loughlin E, Roberts LJ. A double-blinded randomized evaluation of alfentanil and morphine *vs* fentanyl: analgesia and sleep trial (DREAMFAST)[J]. *Br J Anaesth,* 2013, 110(2): 293–298.

[32] Cronin AJ, Keifer JC, Davies MF, et al. Postoperative sleep disturbance: influences of opioids and pain in humans[J]. *Sleep,* 2001, 24(1): 39–44.

[33] Lehmkuhl P, Prass D, Pichlmayr I. General anesthesia and postnarcotic sleep disorders[J]. *Neuropsychobiology,* 1987, 18(1): 37–42.

[34] Brimacombe J, Macfie AG. Peri-operative nightmares in surgical patients[J]. *Anaesthesia,* 1993, 48(6): 527–529.

[35] Kjølhede P, Langström P, Nilsson P, et al. The impact of

quality of sleep on recovery from fast-track abdominal hysterectomy[J]. *J Clin Sleep Med,* 2012, 8(4): 395–402.

[36] Moote CA, Knill RL. Isoflurane anesthesia causes a transient alteration in nocturnal sleep[J]. *Anesthesiology,* 1988, 69(3): 327–331.

[37] Giubilei F, Iannilli M, Vitale A, et al. Sleep patterns in acute ischemic stroke[J]. *Acta Neurol Scand,* 1992, 86(6): 567–571.

[38] Broughton R, Baron R. Sleep patterns in the intensive care unit and on the ward after acute myocardial infarction[J]. *Electroencephalogr Clin Neurophysiol,* 1978, 45(3): 348–360.

[39] Hanly PJ, Millar TW, Steljes DG, et al. Respiration and abnormal sleep in patients with congestive heart failure[J]. *Chest,* 1989, 96(3): 480–488.

[40] Richards KC, Bairnsfather L. A description of night sleep patterns in the critical care unit[J]. *Heart Lung,* 1988, 17(1): 35–42.

[41] Caumo W, Schmidt AP, Schneider CN, et al. Risk factors for preoperative anxiety in adults[J]. *Acta Anaesthesiol Scand,* 2001, 45(3): 298–307.

[42] Caumo W, Schmidt AP, Schneider CN, et al. Risk factors for postoperative anxiety in adults[J]. *Anaesthesia,* 2001, 56(8): 720–728.

[43] Drouot X, Cabello B, d'Ortho MP, et al. Sleep in the intensive care unit[J]. *Sleep Med Rev,* 2008, 12(5): 391–403.

[44] Kass JE. To sleep in an intensive care unit, perchance to heal[J]. *Crit Care Med,* 2008, 36(3): 988–989.

[45] Berglund B, Lindvall T, Schwela DH, et al. Guidelines for community noise[R]. Geneva, Switzerland: World Health Organization, 1999: 44

[46] Meyer TJ, Eveloff SE, Bauer MS, et al. Adverse environmental conditions in the respiratory and medical ICU settings[J]. *Chest,* 1994, 105(4): 1211–1216.

[47] Freedman NS, Gazendam J, Levan L, et al. Abnormal sleep/wake cycles and the effect of environmental noise on sleep disruption in the intensive care unit[J]. *Am J Respir Crit Care Med,* 2001, 163(2): 451–457.

[48] Christensen M. Noise levels in a general surgical ward: a descriptive study[J]. *J Clin Nurs,* 2005, 14(2): 156–164.

[49] Chellappa SL, Steiner R, Oelhafen P, et al. Acute exposure to evening blue-enriched light impacts on human sleep[J]. *J Sleep Res,* 2013, 22(5): 573–580.

[50] Adam K, Oswald I. Sleep helps healing[J]. *Br Med J (Clin Res Ed),* 1984, 289(6456): 1400–1401.

[51] Knutson KL, Spiegel K, Penev P, et al. The metabolic consequences of sleep deprivation[J]. *Sleep Med Rev,* 2007, 11(3): 163–178.

[52] Casida J, Nowak L. Integrative therapies to promote sleep in the intensive care unit[M]//Chlan L, Hertz MI. Integrative Therapies in Lung Health and Sleep. Totowa, NJ: Humana Press, 2012: 177-188.

[53] Papathanassoglou EDE. Psychological support and outcomes for ICU patients[J]. *Nurs Crit Care,* 2010, 15(3): 118–128.

[54] Gong L, Wang ZH, Fan D. Sleep quality effects recovery after total knee arthroplasty (TKA) - a randomized, double-blind, controlled study[J]. *J Arthroplasty,* 2015, 30(11): 1897–1901.

[55] O'Keeffe ST, Ní Chonchubhair Á. Postoperative delirium in the elderly[J]. *Br J Anaesth,* 1994, 73(5): 673–687.

[56] Inouye SK, Bogardus Jr ST, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients[J]. *N Engl J Med,* 1999, 340(9): 669–676.

[57] Van Rompaey B, Elseviers MM, Van Drom W, et al. The effect of earplugs during the night on the onset of delirium and sleep perception: a randomized controlled trial in intensive care patients[J]. *Crit Care,* 2012, 16(3): R73.

[58] Chouchou F, Khoury S, Chauny JM, et al. Postoperative sleep disruptions: a potential catalyst of acute pain?[J]. *Sleep Med Rev,* 2014, 18(3): 273–282.

[59] Schuh-Hofer S, Wodarski R, Pfau DB, et al. One night of total sleep deprivation promotes a state of generalized hyperalgesia: a surrogate pain model to study the relationship of insomnia and pain[J]. *Pain,* 2013, 154(9): 1613–1621.

[60] Wright CE, Bovbjerg DH, Montgomery GH, et al. Disrupted sleep the night before breast surgery is associated with increased postoperative pain[J]. *J Pain Symptom Manage,* 2009, 37(3): 352–362.

[61] Raymond I, Ancoli-Israel S, Choinière M. Sleep disturbances, pain and analgesia in adults hospitalized for burn injuries[J]. *Sleep Med,* 2004, 5(6): 551–559.

[62] Raymond I, Nielsen TA, Lavigne G, et al. Quality of sleep and its daily relationship to pain intensity in hospitalized adult burn patients[J]. *Pain,* 2001, 92(3): 381–388.

[63] Dimsdale JE, Ball ED, Carrier E, et al. Effect of eszopiclone on sleep, fatigue, and pain in patients with mucositis associated with hematologic malignancies[J]. *Support Care Cancer,* 2011, 19(12): 2015–2020.

[64] Tompkins M, Plante M, Monchik K, et al. The use of a non-benzodiazepine hypnotic sleep-aid (Zolpidem) in patients undergoing ACL reconstruction: a randomized controlled clinical trial[J]. *Knee Surg Sports Traumatol Arthrosc,* 2011, 19(5): 787–791.

[65] Marin JM, Carrizo SJ, Vicente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study[J]. *Lancet,* 2005, 365(9464): 1046–1053.

[66] Kaw R, Chung F, Pasupuleti V, et al. Meta-analysis of the association between obstructive sleep apnoea and postoperative outcome[J]. *Br J Anaesth,* 2012, 109(6): 897–906.

[67] Fassbender P, Herbstreit F, Eikermann M, et al. Obstructive sleep apnea-a perioperative risk factor[J]. *Dtsch Arztebl Int,* 2016, 113(27-28): 463–469.

[68] Faraut B, Boudjeltia KZ, Vanhamme L, et al. Immune, inflammatory and cardiovascular consequences of sleep restriction and recovery[J]. *Sleep Med Rev,* 2012, 16(2): 137–149.

[69] Fernandes NM, Nield LE, Popel N, et al. Symptoms of disturbed sleep predict major adverse cardiac events after percutaneous coronary intervention[J]. *Can J Cardiol,* 2014,

30(1): 118–124.

[70] Mo Y, Zimmermann AE. Role of dexmedetomidine for the prevention and treatment of delirium in intensive care unit patients[J]. *Ann Pharmacother,* 2013, 47(6): 869–876.

[71] Reardon DP, Anger KE, Adams CD, et al. Role of dexmedetomidine in adults in the intensive care unit: an update[J]. *Am J Health Syst Pharm,* 2013, 70(9): 767–777.

[72] Li B, Li YL, Tian SS, et al. Anti-inflammatory effects of perioperative dexmedetomidine administered as an adjunct to general anesthesia: a meta-analysis[J]. *Sci Rep,* 2015, 5: 12342.

[73] Lundorf LJ, Nedergaard HK, Møller AM. Perioperative dexmedetomidine for acute pain after abdominal surgery in adults[J]. *Cochrane Database Syst Rev,* 2016, 2: CD010358.

[74] Nelson LE, Lu J, Guo TZ, et al. The α2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects[J]. *Anesthesiology,* 2003, 98(2): 428–436.

[75] Alexopoulou C, Kondili E, Diamantaki E, et al. Effects of dexmedetomidine on sleep quality in critically ill patients: a pilot study[J]. *Anesthesiology,* 2014, 121(4): 801–807.

[76] Wu XH, Cui F, Zhang C, et al. Low-dose dexmedetomidine improves sleep quality pattern in elderly patients after noncardiac surgery in the intensive care unit: a pilot randomized controlled trial[J]. *Anesthesiology,* 2016, 125(5): 979–991.

[77] Zhang DF, Su X, Meng ZT, et al. Impact of dexmedetomidine on long-term outcomes after noncardiac surgery in elderly: 3-year follow-up of a randomized controlled trial[J]. *Ann Surg,* 2019, 270(2): 356–363.

[78] Shi CX, Jin J, Pan Q, et al. Intraoperative use of dexmedetomidine promotes postoperative sleep and recovery following radical mastectomy under general anesthesia[J]. *Oncotarget,* 2017, 8(45): 79397–79403.

[79] Qin MJ, Chen KZ, Liu TJ, et al. Dexmedetomidine in combination with sufentanil for postoperative analgesia after partial laryngectomy[J]. *BMC Anesthesiol,* 2017, 17(1): 66.

[80] Lu WN, Fu QH, Luo XQ, et al. Effects of dexmedetomidine on sleep quality of patients after surgery without mechanical ventilation in ICU[J]. *Medicine,* 2017, 96(23): e7081.

[81] Claustrat B, Brun J, Chazot G. The basic physiology and pathophysiology of melatonin[J]. *Sleep Med Rev,* 2005, 9(1): 11–24.

[82] Hansen MV, Madsen MT, Wildschiødtz G, et al. Sleep disturbances and changes in urinary 6-sulphatoxymelatonin levels in patients with breast cancer undergoing lumpectomy[J]. *Acta Anaesthesiol Scand,* 2013, 57(9): 1146–1153.

[83] Cronin AJ, Keifer JC, Davies MF, et al. Melatonin secretion after surgery[J]. *Lancet,* 2000, 356(9237): 1244–1245.

[84] Borowicz LM, Goldsborough MA, Selnes OA, et al. Neuropsychologic change after cardiac surgery: a critical review[J]. *J Cardiothorac Vasc Anesth,* 1996, 10(1): 105–112.

[85] Buscemi N, Vandermeer B, Hooton N, et al. The efficacy and safety of exogenous melatonin for primary sleep disorders a meta-analysis[J]. *J Gen Intern Med,* 2005, 20(12): 1151–1158.

[86] Andersen LPH, Werner MU, Rosenberg J, et al. A systematic review of peri-operative melatonin[J]. *Anaesthesia,* 2014, 69(10): 1163–1171.

[87] Borazan H, Tuncer S, Yalcin N, et al. Effects of preoperative oral melatonin medication on postoperative analgesia, sleep quality, and sedation in patients undergoing elective prostatectomy: a randomized clinical trial[J]. *J Anesth,* 2010, 24(2): 155–160.

[88] Gögenur I, Kücükakin B, Bisgaard T, et al. The effect of melatonin on sleep quality after laparoscopic cholecystectomy: a randomized, placebo-controlled trial[J]. *Anesth Analg,* 2009, 108(4): 1152–1156.

[89] Caumo W, Torres F, Moreira Jr NL, et al. The clinical impact of preoperative melatonin on postoperative outcomes in patients undergoing abdominal hysterectomy[J]. *Anesth Analg,* 2007, 105(5): 1263–1271.

[90] Chen WY, Giobbie-Hurder A, Gantman K, et al. A randomized, placebo-controlled trial of melatonin on breast cancer survivors: impact on sleep, mood, and hot flashes[J]. *Breast Cancer Res Treat,* 2014, 145(2): 381–388.

[91] Hansen MV, Madsen MT, Andersen LT, et al. Effect of melatonin on cognitive function and sleep in relation to breast cancer surgery: a randomized, double-blind, placebo-controlled trial[J]. *Int J Breast Cancer,* 2014, 2014: 416531.

[92] Madsen MT, Hansen MV, Andersen LT, et al. Effect of melatonin on sleep in the perioperative period after breast cancer surgery: a randomized, double-blind, placebo-controlled trial[J]. *J Clin Sleep Med,* 2016, 12(2): 225–233.

[93] Tashjian RZ, Banerjee R, Bradley MP, et al. Zolpidem reduces postoperative pain, fatigue, and narcotic consumption following knee arthroscopy: a prospective randomized placebo-controlled double-blinded study[J]. *J Knee Surg,* 2006, 19(2): 105–111.

[94] Monti JM. Effect of zolpidem on sleep in insomniac patients[J]. *Eur J Clin Pharmacol,* 1989, 36(5): 461–466.

[95] Eisen J, MacFarlane J, Shapiro CM. ABC of sleep disorders. Psychotropic drugs and sleep[J]. *BMJ,* 1993, 306(6888): 1331–1334.

[96] Krenk L, Jennum P, Kehlet H. Postoperative sleep disturbances after zolpidem treatment in fast-track hip and knee replacement[J]. *J Clin Sleep Med,* 2014, 10(3): 321–326.

[97] Bjurström MF, Irwin MR. Perioperative pharmacological sleep-promotion and pain control: a systematic review[J]. *Pain Pract,* 2019, 19(5): 552–569.

[98] Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people[J]. *Lancet,* 2014, 383(9920): 911–922.

[99] Ljungqvist O, Scott M, Fearon KC. Enhanced recovery after surgery: a review[J]. *JAMA Surg,* 2017, 152(3): 292–298.

[100] Gustafsson UO, Scott MJ, Hubner M, et al. Guidelines for perioperative care in elective colorectal surgery: enhanced recovery after surgery (ERAS®) society recommendations: 2018[J]. *World J Surg,* 2019, 43(3): 659–695.

[101] Senagore AJ, Whalley D, Delaney CP, et al. Epidural

anesthesia-analgesia shortens length of stay after laparoscopic segmental colectomy for benign pathology[J]. *Surgery,* 2001, 129(6): 672–676.

[102] Delaney CP, Fazio VW, Senagore AJ, et al. 'Fast track' postoperative management protocol for patients with high co-morbidity undergoing complex abdominal and pelvic colorectal surgery[J]. *Br J Surg,* 2001, 88(11): 1533–1538.

[103] Varadhan KK, Neal KR, Dejong CHC, et al. The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized controlled trials[J]. *Clin Nutr,* 2010, 29(4): 434–440.

[104] Greco M, Capretti G, Beretta L, et al. Enhanced recovery program in colorectal surgery: a meta-analysis of randomized controlled trials[J]. *World J Surg,* 2014, 38(6): 1531–1541.

[105] Hu RF, Jiang XY, Chen J, et al. Non-pharmacological interventions for sleep promotion in the intensive care unit[J]. *Cochrane Database Syst Rev,* 2015, (10): CD008808.

[106] de Souza Machado F, da Silva Souza RC, Poveda VB, et al. Non-pharmacological interventions to promote the sleep of patients after cardiac surgery: a systematic review[J]. *Rev Lat Am Enfermagem,* 2017, 25: e2926.

[107] Scarpa M, Pinto E, Saraceni E, et al. Randomized clinical trial of psychological support and sleep adjuvant measures for postoperative sleep disturbance in patients undergoing oesophagectomy[J]. *Br J Surg,* 2017, 104(10): 1307–1314.

[108] Hwang E, Shin S. The effects of aromatherapy on sleep improvement: a systematic literature review and meta-analysis[J]. *J Altern Complement Med,* 2015, 21(2): 61–68.

[109] Karadag E, Samancioglu S, Ozden D, et al. Effects of aromatherapy on sleep quality and anxiety of patients[J]. *Nurs Crit Care,* 2017, 22(2): 105–112.

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