ICU

MANAGEMENT & PRACTICE

THE OFFICIAL MANAGEMENT JOURNAL OF ISICEM

VOLUME 16 - ISSUE 4 - WINTER 2016

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DOES DEXMEDETOMIDINE REDUCE DELIRIUM BY IMPROVING SLEEP?

Delirium is a common complication in intensive care unit (ICU) patients and its occurrence is associated with worse outcome (Inouye et al. 2014; Abelha et al. 2013). Sleep disturbances are considered one of the important risk factors of delirium development (Flink et al. 2012). Recent evidence shows that dexmedetomidine, either at sedative or non-sedative doses, can improve sleep quality and reduce delirium. Here we review evidence regarding sleep disturbances, delirium, and the effects of dexmedetomidine in ICU patients.

Normal Sleep and its Importance

Sleep is a naturally recurring state of mind and body, characterised by lowered consciousness, relatively inhibited sensory activity, inhibition of nearly all voluntary muscles and reduced interactions with surroundings. According to polysomnographic study results, sleep is divided into non-rapid eye movement (REM) sleep and REM sleep. Non-REM sleep is further divided into stage 1 (N1, also called light sleep, accounting for 5-10% of total sleep in adults), stage 2 (N2, accounting for 45-55% of total sleep in adults), and stage 3 (N3, also called deep sleep or slow wave sleep [SWS], accounting for 15-25% of total sleep in adults). REM sleep accounts for 20–25% of total sleep in adults.

Normal sleep has a significant circadian rhythm and cycles in the order of N1 → N2 →N3 → N2 → REM. In healthy adults, the duration of each cycle lasts approximately 90 minutes. N3 sleep is a deep stage and is considered the most restful form of sleep. The sleeper is less responsive to the environment and restores the body; night terrors, nocturnal enuresis, sleepwalking and somniloquy often occur in this stage. During the REM sleep stage, high-frequency electroencephalogram (EEG) waves, which are similar to a waking state, appear, but the sleeper is harder to arouse than other stages. Vivid dreams may occur during this stage (McNamara et al. 2010). Lack of REM sleep impairs the ability to learn complex tasks, and deprivation of REM sleep often results in REM rebound, i.e., more REM sleep than usual. Compared with the young, sleep in the elderly tends to show frequent waking, fragmented sleep, decreased N3 sleep and early waking (Elliott et al. 2011).

Sleep in ICU Patients

Sleep is severely disturbed in mechanically ventilated ICU patients (Delisle et al. 2011). Polysomnographic studies performed in mechanically ventilated ICU patients have demonstrated a severe increase in sleep fragmentation, prolonged N1 and N2 sleep, reduced N3 and REM sleep, and an abnormal distribution of sleep, because almost half of the total sleep time occurred during the daytime (Delisle et al. 2011; Cabello et al. 2008). Patients reported little or no sleep, poor sleep quality, frequent awakening, and daytime sleep. They attributed sleep disruption to environmental noise, intrusive treatment, and thirst etc. (Elliott et al. 2011).

Patients also develop significant sleep disturbances immediately after major surgery. Polysomnographic manifestation usually includes severe sleep deprivation, sleep fragmentation, decrease or loss of SWS and REM sleep during the early period after surgery (Aurell and Elmqvist 1985; Knill et al. 1990). Patients may report decreased sleep time, increased arousals or awakening, lowered sleep quality and increased nightmares (Rosenberg-Adamsen et al. 1996). During the subsequent postoperative phase, sleep structure gradually returns to normal with a REM sleep rebound within one week (Knill et al. 1990).

Causes of Sleep Disturbance in ICU Patients

Many factors are responsible for sleep disturbance in ICU patients. These include the ICU environment, the severity of illness, mechanical ventilation, pain, sedatives and analgesics, and various other therapies (Hofhuis et al. 2012; Friese 2008). For postoperative patients, pain, needing to use toilet facilities, disturbances from healthcare staff and other patients, environmental noise as well as many other discomforts constitute the major causes (Dolan et al. 2012). In addition, the severities of preoperative comorbidity (Yilmaz et al. 2016) and surgery (Knill et al. 1990; Rosenberg-Adamsen et al. 1996) may also contribute to sleep abnormalities. A study by Yilmaz et al. (2016) showed that the severity of preoperative angina pectoris is independently associated with worse sleep quality after coronary artery bypass graft surgery. And sleep disturbance is more severe after major surgery (Rosenberg-Adamsen et al. 1996).

Sleep Disturbances and Delirium

Sleep disturbances are considered important causes of delirium. In a pilot study of adults over 40 years of age, sleep disruption was more severe before surgery in the patients who experienced postoperative delirium (Leung et al. 2015). Poor sleep quality was also proved to be associated with an increased risk of developing delirium among patients enrolled in a hospice (Slatore et al. 2012) and patients after elective knee replacement (Flink et al. 2012). In recent systematic reviews, use of earplugs and/or eye masks in ICU patients significantly improved subjective sleep quality and reduced the risk of delirium (Litton et al. 2016; Hu et al. 2015).

Similar to delirium, the occurrence of sleep disturbances also produces significant adverse consequences in ICU patients; these include immune system compromise, delayed weaning from mechanical ventilation, cardiovascular events, and post-ICU physical and mental health decline (Kamdar et al. 2012; BaHammam 2006; Salas and Gemaldo 2008; Weinhouse et al. 2009; Roche Campo et al. 2010; Ackermann et al. 2012). Sleep disturbances after surgery are associated with worse outcomes, including prolonged hospital stay and increased long-term cardiac events (Kjolhede et al. 2012; Fernandes et al. 2014).

Effects of Dexmedetomidine on Sleep

Given the importance of good sleep on patients' recovery from critical illness and major surgery, multiple nonpharmacologic interventions have been implemented to improve patients' sleep quality in the ICU, such as elimination of unnecessary noise and light, consolidation of patient care interactions, use of earplugs and eye masks, relaxation techniques, and addition of white noise (Hu et al. 2015; Xie t al. 2009; Li et al. 2011). Unfortunately, traditionally used sedatives and analgesics (such as propofol, benzodiazepines and opioids) deteriorate, rather than ameliorate, sleep architecture disruption in ICU patients, which potentially contributes to the occurrence of delirium (Delaney et al. 2015).

Dexmedetomidine is a selective α2 adrenoceptor agonist with both sedative and analgesic properties (Reardon et al. 2013). Unlike other sedative agents, dexmedetomidine exerts its sedative effects through an endogenous sleep-promoting pathway, preserves sleep architecture to some degree in preclinical settings and produces a N2 sleep-like state (Nelson et al. 2003). In mechanically ventilated ICU patients, nighttime infusion of a sedative dose of dexmedetomidine preserved the day-night cycle of sleep and improved the sleep architecture by increasing sleep efficiency and stage N2 sleep (Oto et al. 2012; Alexopoulou et al. 2014). In a recent study, 76 elderly patients who were admitted to the ICU after surgery and did not require mechanical ventilation randomly received low-dose dexmedetomidine (0.1 µg/kg/h) or normal saline during the first night after surgery. The results showed that dexmedetomidine infusion prolonged total sleep time, increased sleep efficiency and stage N2 (and decreased stage N1) sleep, and improved subjective sleep quality (Wu et al. 2016).

Dexmedetomidine and Delirium Prevention

Dexmedetomidine is increasingly used for sedation in mechanically ventilated ICU patients (Wunsch et al. 2010), where its use is associated with a decreased prevalence of delirium when compared with other sedatives (Pandharipande et al. 2007; Xia et al. 2013; Riker et al. 2009; Djaiani et al. 2016). Sleep promotion is one of the possible mechanisms of its delirium-sparing effects (Oto et al. 2012; Alexopoulou et al. 2014). However, in these studies, dexmedetomidine was compared with an active sedative drug that modulates the GABA-A receptors, which could aggravate sleep disturbances and increase delirium risk (Fraser et al. 2013).

In a recent large sample size study, 700 elderly patients (≥ 65 yrs), who were admitted to ICU after surgery randomly received either low-dose dexmedetomidine (0.1 µg/kg/h) or normal saline infusion from ICU admission until 8 am the next day after surgery. The results showed that dexmedetomidine infusion significantly decreased the prevalence of delirium on postoperative days 1 to 3 (OR 0.28, 95% CI 0.16 to 0.50, $p < 0.0001$; OR 0.43, 95% CI 0.24 to 0.77, $p = 0.005$; and OR 0.26, 95% CI 0.13 to 0.53, $p < 0.0001$, respectively). This was in accordance with significantly improved subjective sleep quality during the three nights of the same period (all $p<0{\cdot}0001$) (Su et al. 2016). Therefore, low-dose dexmedetomidine infusion reduces delirium in this patient population, possibly by improving postoperative sleep.

Conclusions

Sleep disturbances are common in ICU patients and can produce harmful effects including delirium. Both sedative-dose and low-dose dexmedetomidine can be used to improve sleep quality and decrease delirium occurrence in ICU patients. Future studies are required to verify the casual relationship between sleep promotion and delirium-sparing effects as well as the long-term outcomes of dexmedetomidine administration. ■

Conflict of Interest

Xian Su declares that she has no conflict of interest. Dong-Xin Wang has received lecture fees and/or travel expenses for lectures given at domestic and international academic meetings from Jiangsu Hengrui Medicine Co., Ltd., China, Yichang Humanwell Pharmaceutical Co. Ltd., China, and Baxter Healthcare Trading (Shanghai) Co., Ltd.

Abbreviations

ICU intensive care unit
REM rapid eye movement
SWS slow wave sleep

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