

General Anesthesia and Sleep

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Editorial

Are patients really 'asleep' during surgery? Anesthesiologists ensure the patient is immobilized, has no pain response, and has no waking memory of the procedure. Resembling sleep, general anesthesia is by no means a restful experience, with the potential of disrupting a patient's photo-entrained circadian rhythm [1].

EEG patterns of deep anesthesia can appear more like coma or brain stem death [2], while sleep EEGs can cycle from an active (spindles and K-complexes) to a slow-wave pattern that is found in NREM stage 3. Sleep is not a passive state and the brain cycles (roughly 90-min intervals) through characteristic periods of low-amplitude, high-frequency bursts during REM, converting into the ever-slowng waves of NREM. At the slowest (SWS, or slow-wave sleep), NREM stage 3 resembles the intermediate phase of general anesthesia. At this shared state, natural sleep switches to active REM, while anesthesia can be guided deeper. It can be said, then, that the sleeping brain is more active than the anesthetized brain. Regarding the nature of unconsciousness at surgical level, different agents (i.e. propofol, sevoflurane, ketamine and dexmedetomidine), curiously, elicit unique EEG signatures, presumably attributed to pharmacological interruption of select neuronal circuits [3]. The circuits that are associated with sleep/arousal, which are photo-entrained, reveal rhythmicity and may continue to clock-on independently of the anesthesia-interrupted circuits. Conversely, there may be several linkage-points between anesthesia-labile neuronal wiring and those of sleep, and these have yet to be fully understood. Can circuitry disruptions during anesthesia adversely affect future sleep? Or, is emergence from anesthesia a form of re-booting that only requires minor reinforcement of photo-entrainment?

Post-operative sleep disturbance is common in the first six nights (Rosenberg-Adamsen et al. offer a comprehensive starting point in this field of medical research) [4]. For the first couple of nights in the hospital, most patients exhibited sleep deprivation in the form of total sleep decline with noticeable REM and SWS impairment. Others presented with fragmented sleep, referring to a disruption of sleep rhythmicity. Following the first couple of nights, then, REM and SWS normally rebound with patients spending more time in these specific stages of sleep. Most sleep disturbances then resolve themselves. Still, 25% of post-surgery patients exhibited sleep quality changes lasting more than two weeks after discharge. Furthermore, the duration of post-operative sleep disturbance correlated with the duration of the surgery. It stands to reason that anesthesia may, at the very least, be considered complicit in bringing about sleep disturbance. But, there are many other factors that could contribute to sleep disturbance, including the invasiveness of the surgery (pain, cytokine release etc.), environmental factors (noise, lighting, noxious odors, unfamiliarity etc.), psychological factors (anxiety, psychosis, stress etc.), and a myriad of care-related issues (vitals, medications, diagnostic

procedures etc.) particularly as the implementation of EMR protocols are now taking priority. Not surprising, the number one factor that patients noted in questionnaire-type studies as contributing to sleep disturbance was 'pain'. What if these other factors were left out, like, for example, in a study of non-surgery volunteers that have undergone 3-hour general anesthesia? In this study, isoflurane caused a modest reduction in SWS and an increase in NREM stage 2 for only one post-operative night, and there were no REM changes noted [5]. While the restorative benefits of NREM stage 2 are readily not apparent, the restorative importance of SWS is described throughout the literature; so, one can speculate that anesthesia with isoflurane may either act as a minor surrogate for SWS, or alternately, transiently impair the SWS stage. In light of all the data, it may be fair to surmise that the role of anesthesia in sleep disturbance following surgery is rather small (compared to the other factors described above), but that this role may be highly variable depending on the health status and age of the individual. Continued surveillance of this medical issue is desired, particularly in the elderly.

More research is needed, for example, in defining the molecular correlates to the restorative properties of sleep, in order to assess the role of anesthesia in affecting these restorative mechanisms. Sleep-wake cycles have been modeled to include non-transcriptional mechanisms involving redox processes, such as antioxidant peroxiredoxin proteins [6]. The synchronization of redox repair and the sleep stages may indeed provide the explanation of the restorative nature of sleep. Further investigation using animal models, including zebrafish which have strict requirements for periods of light-dark, may yield translatable results. It would be wise to focus on archetypal ancestral proteins, like the highly-conserved and abundant housekeeping enzyme, GAPDH (MIM: 138400). GAPDH is pivotal in regulating light events in plants. In humans, it is known to regulate GABAergic signals, a logical starting point for investigating the cyclical modulation of sleep-circuits. GAPDH's rather long half-life may represent a neuronal sensor of redox degeneration of all cellular proteins, signaling a cycle of repair and regeneration.

So, are patients really 'asleep' during surgery? Yes and no. Portions of brain waves do show some resemblance. Yet, the differences may suggest that the restorative events that occur in sleep may be disturbed with deep anesthesia. Discovering proactive measures to prevent restorative sleep loss, thereby increasing positive outcomes, should be a research goal for the future.

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