SLEEP IN THE ICU
AN OVERVIEW
Morning Conference

Polysomnography

- Polysomnography measures:
  - Patient’s airflow though the nose and mouth
  - Movements of respiratory muscles and limbs
  - Eye movements
  - Arterial blood pressure
  - EKG
  - Pulse oximetry
  - EEG

Stage of Sleep

- Polysomnography findings:
  - EEG readings are divided into 30 second periods
  - Sleep is divided into different stages
  - REM Sleep
  - Non-REM Sleep
    - Stage one
    - Stage two
    - Stage three
    - Stage four

Sleep in the ICU

Magnitude of the Problem

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- 76 patients were interviewed by an intensivist
- Intensivist hadn’t seen them before.
- ICU Staff were unaware that patients would be interviewed.
- 76 patients were interviewed by an intensivist
  - Sleep (patient’s perceptions)
    - 46 (61%) reported sleep deprivation
    - Top 3 major source of anxiety behind pain and intubation
    - Pain was reported by 33 (43%) patients.
      - 31 (94%) said that analgesics requested did not yield the expected pain relief
      - 49 (63%) recalled being thirsty.
      - 30 (52%) had been hungry.
      - 28 (37%) and 21 (28%) had been uncomfortably hot and cold respectively.
      - 47 (63%) patients had been afraid or anxious.
      - 35 (46%) had felt lonely or isolated.
      - 25 (33%) lacked information about their condition and procedures.
Sleep in the ICU

• ICU Polysomnography studies have shown:
  – ICU sleep is predominantly Stage 1 and Stage 2 sleep
  – Absent or decreased stage 3 and 4 and REM sleep
  – 40%-50% of ICU total sleep occurs during the day
  – Patient’s have 41 +/- 28 sleep periods a day
    – Each cycle last 6-24 minutes at a time.
  – Altered sleep cycles often do not improve over the course of the ICU stay
  – Sleep cycles may not return to normal until several days after being discharged from the ICU.

Sleep in the ICU

• Mechanisms of altered wake sleep cycles
  – They are poorly understood
• Noise:
  – Most often cited reason for disrupted sleep
  – Increases in noise intensity are known to cause arousals from sleep
  – 18-24 PSG recordings in ICU patients have attributed 11-18% of arousals and 17 to 24% of awakenings to environmental noise.
• Environmental Protection Agency recommends:
  – Hospital noise levels not exceed 45 dB during the day and 35 dB at night.
  – Studies have shown that noise levels in the ICU are substantially higher than the EPA recommendations.
  – Noise levels in the ICU range from 60 dB to 84 dB throughout a 24-h period.
    – A busy office has average noise levels of 70 dB.
    – A pneumatic drill heard from 50 ft away has a noise level measured at 80 dB.
    – Noise levels below 40 dB are generally required for a normal individual to fall asleep.

Nocturnal Care Interaction

• Examined frequency, pattern and types of nocturnal care interactions in 4 ICUs
• Reviewed 50 patients randomly selected
• Data from over 147 nights (7pm to 7AM)

Nocturnal Care Interaction

• Interactions were most common at midnight and least common at 3 am
• Only 9 uninterrupted periods of 2-3 hours were available for sleep (6% of the 147 nights studied)
• Frequency in interactions correlated with patient’s acuity
• 62% of daily baths were performed between 9pm and 6am
• A sleep promoting intervention was documented for only 1 of the 147 nights
Patient Perceptions of Poor Sleep

Why we can’t sleep

- Questionnaire at UPENN:
  - Given to patients day of discharge to assess sleepiness compared to home:
- The environmental stimuli that were evaluated included:
  - noise
  - light
  - nursing interventions (bathing, etc.)
  - diagnostic tests (i.e., chest radiographs)
  - evaluation of vital signs
  - blood sampling
  - administration of medications
- Patients were also asked to assess the effects of different ICU noises on sleep disruption

Disruption from human interventions and diagnostic testing were perceived to be as disruptive to sleep as environmental noise.

Poor sleep quality and daytime sleepiness are problems common to all types of ICUs, and affect a broad spectrum of patients.

The environmental etiologies of sleep disruption in the ICU are multi-factorial.

Severity of Illness and Sleep


Gravity of Illness
- Parthasarathy and Tobin
  - Measured acuity of illness by APACHE 2
  - Discovered that severity of illness correlated with sleep fragmentation
  - In another study however, the same authors did not find the correlation
  - Possible mechanism could be due to alterations in IL-1 and TNF which play a role in maintaining sleep.
    - They are altered in illness

Environmental Factors

- Pharmacologic issues: Opioids
  - They exert their sedative/hypnotic effect on the ponto-thalamic arousal pathway most active in REM generation rather than the hypothalamic pathway more affected by the GABA agonists
  - As a result, they have a potent, dose-dependent REM-suppressive effect mediated by the mu receptor.
  - In addition, they also decrease SWS and increase stage II NREM sleep by EEG criteria.
  - A single low dose of an opioid was associated with a 30% to 50% reduction in SWS in healthy adult volunteers
Environmental Factors: Medications

• Pharmacologic issues: Opioids
  - Sleep disturbances for individuals with pain occur in 50-70% of chronic pain patients.
  - Poor sleep may increase patients’ perception of pain
  - Despite opioids negative effect on sleep architecture by decreasing pain opioids may:
    - Improve subjects’ perception of sleep quality
    - Improve other subjective measures of sleep quality

GABA agonists

• GABA agonists:
  - Include benzodiazepines and propofol
  - Are the medications recommended as first-line sedation in the ICU
  - Trend toward improved patient perception of sleep

GABA agonists: Benzodiazepines:

• Benzodiazepines:
  - Activate the alpha subunit of the GABA receptor.
  - Enhance the most potent CNS inhibitory system and leading to the psychomotor depression seen clinically
• Benzodiazepines: Effect on the EEG is to induce a
  - Dose-dependent increase in EEG characteristics of NREM sleep.
  - A mild reduction of REM sleep, a potent suppression of SWS.
  - An increase in spindle activity (an EEG hallmark of stage II NREM sleep).

Environmental Factors

• Pharmacologic treatment: Benzodiazepine
  - Can improve behavioral aspects of sleep by:
    - Decreasing time necessary to fall asleep
    - By decreasing awakenings
    - By increasing sleep efficiency
    » Sleep efficiency is the ratio of time spent asleep (total sleep time) to the amount of time spent in bed
  - Can also:
    - Increase stage 2 sleep
    - Suppress restorative sleep
    - Decrease EEG amplitude and frequency
    - Insomnia, hallucinations & nightmares have also been described
GABA agonists: Propofol

- **Propofol:**
  - Is believed to bind to the GABA receptor at a site distinct from the benzodiazepines’ binding site where it enhances activity of the receptor.
  - Similar to the benzodiazepines it suppresses SWS
  - Propofol has no definite effect on REM sleep.
  - Propofol given to healthy volunteers was associated with a delay in sleep onset latency.

- **Propofol and animal studies**
  - Rats sedated with propofol during normal sleep time did not demonstrate clinical sings of sleep deprivation
  - Concluded that sedation with propofol is compatible with restorative process similar to that during natural sleep
  - Rats deprived of sleep for 24 hours
  - Could propofol allow for recovery from sleep deprivation?
  - Recovery sleep was no different under the influence of 6 hours of propofol compared with normal recovery

Ventrolateral preoptic nucleus (VLPO)

- Group of neurons in the hypothalamus.
- Active during Non-rapid eye movement sleep
  - Inhibit neurons involved in wakefulness.
- Release inhibitory neurotransmitters galanin and GABA to inhibit the monaminergic cell groups in the locus ceruleus, the raphe nucleus, and the tuberomammillary nucleus.

α-2-Agonist

- Pharmacologic treatment: dexmedetomidine α-2-Agonist
  - In the United States, dexmedetomidine is the only parenteral agent in this class of sedatives available for use.
  - It binds to receptors in locus ceruleus, which reduces norepinephrine release and thereby disinhibits the VLPO neurons that inhibit the arousal
  - Its effects on the EEG are to induce a
    - Dose-dependent slowing
    - A decrease in percentage of REM sleep
    - An increase in percentage of SWS
    - An increase in percentage of stage II based on an increase in spindle activity.
  - The spindles observed under sedation with dexmedetomidine are similar qualitatively to those during natural sleep but have a longer duration.
Pharmacologic treatment: dexmedetomidine α-2-Agonist

- Sedation with dexmedetomidine more closely resembles natural sleep than sedation under the GABA agonists.
- Patients sedated with α-agonists are more easily aroused and more cognitively intact when aroused.
- Dex interacts with the natural sleep pathway at a site farther upstream than the GABA agonists and leads to a state with clinical features similar to natural sleep.
- These theoretical advantages have not been demonstrated to improve patients' perception of their sleep in the ICU.
- Role of dexmedetomidine in improving sleep in the critically ill remains to be defined.

Pharmacologic treatment: Antipsychotics

- The most commonly used typical antipsychotic, haloperidol, has been associated with (in healthy volunteers):
  - Increased sleep efficiency
  - Increased stage II sleep
  - Little effect on SWS
- The atypical antipsychotics, such as olanzapine and risperidone:
  - Increase total sleep time.
  - Increase sleep efficiency.
  - Increase SWS.

Medication Withdrawal on Sleep

- Those deprived of sleep begin to build up pressure to recover the lost sleep
- EEG of recovery sleep depend what was lost
  - If the patient is deprived of REM sleep, the recovery sleep period could be expected to have disproportionately high % of REM sleep (REM rebound)
  - Similar affects maybe seen with REM suppressive medications such as opiates and benzodiazepines
    - Critically ill patients maybe at increased risk during recovery

Environmental Factors

- Mechanical ventilation
  - The influence of mechanical ventilation is just starting to become known
  - One confounding factor is sedation
    - Ventilatory mode and setting and patient ventilator interaction could influence sleep quality in the ICU.
  - Previous studies that 2/3 of patient on MV complained of sleep alterations due to ventilator adaptation difficulties
Environmental Factors

- Mechanical ventilation PSV vs. ACV
  - Parathasarathy and Tobin
    - Compared PSV vs. Assist Control Ventilation
    - PSV level set to achieve the same TV as ACV
    - TV ACV was 8ml/kg
    - Mean PSV was 17 cm H2O
    - Authors found *increase in the number of arousals and awakenings* when the patient was ventilated with PSV as compared to ACV

Mechanical Ventilation

- MECHANICAL VENTILATION
  - Pressure support vs. proportional assist ventilation
    - To understand the role of patient ventilator asynchrony in the etiology of sleep disruption.
    - Understand if optimizing patient ventilator interactions by using proportional assist ventilation improves sleep.
    - Randomized crossover trial at university medical center.
    - Measures polysomnography & light, noise, esophageal pressure, airway pressure and air flow.

- Concluded
  - Quantity of sleep was unchanged
  - Data showed the:
    - Occurrence of asynchrony significantly correlated to the proportion between ventilator applied and patient generated pressures.
    - Patient ventilator asynchronies per hour correlated significantly with the number of arousals per hour.
  - Better quality of sleep on PAV
    - Decreased VE at night with increased CO2
    - PAV compensates for this PSV did not
    - Overall improvement in sleep architecture
    - Reduced sleep fragmentation

- In the overall series the mean TST was 446 ± 50 min.
- Of the 20 patients 19 showed sleep periods during the night.
- However, regardless of the mode of mechanical ventilation used sleep architecture was altered
  - With up to 40% of the night spent in wakefulness.
  - A predominance of stages 1 and 2 NREM sleep (51 ± 28% of TST).
  - Stages 3 and 4 NREM sleep were rare (4 ± 5% of TST).
  - REM sleep was also reduced (2 ± 2% of TST).
In the second 4-h period stages 3 and 4 NREM sleep were observed only with ACV
  — Stage 3 NREM, 6.3 ± 7.7% with ACV vs. 0.3 ± 1.0% with PVS, p < 0.01;
  — Stage 4 NREM, 5.4 ± 13.2% with ACV vs. 0.0 ± 0.0% with low PSV, p < 0.05;
  — But no significant differences were observed in wakefulness, stages 1 and 2 NREM sleep, REM sleep

In near-to-wean ICU patients with acute on chronic respiratory failure ACV is associated with better sleep quality than is low levels of PSV.
  — Significant increases in stages 1 and 2 NREM sleep and a reduction in wakefulness during the first part of the night
    • (10 p.m.–2 a.m.)
  — Significant increases in stage 3 and 4 NREM sleep during the second part of the night with ACV compared to low PSV
    • (10 p.m.–2 a.m.)

Compared the influence of three ventilatory modes on sleep via comparative, crossover study.
  — Fifteen conscious, nonsedated, mechanically ventilated with
    • assist-control ventilation
    • clinically adjusted pressure support ventilation (cPSV)
    • automatically adjusted pressure support ventilation (aPSV).

Concluded:
  — Sleep architecture was highly abnormal, with a short REM stage and a high degree of fragmentation.
  — The ventilatory mode did not influence sleep pattern, arousals, awakenings, and ineffective efforts
Consequences of Sleep Alterations in ICU Patients

- Many physiologic parameters that could negatively affect the underlying pathophysiology, treatment and recovery from acute critical illness in the ICU are due to sleep deprivation

Sleep and NIMV

- 27 hypercapnic pts
- 17 hr polysomnography
- Days 2-4 after NIV
- 50% late NIV failures had sleep abnormalities
- Only 8% of those treated successfully with NIV had sleep abnormalities

Consequences of Sleep alterations in ICU patients

- Recent studies in healthy people have shown
  - An increase in:
    - pro-inflammatory cytokines
    - Interleukin(IL-6)
    - Tumor necrosis factor
    - C-reactive protein
    - Natural killer lymphocyte activity
    - These effects can last for more than 24 hours after acute sleep deprivation

SLEEP AND THE IMMUNE SYSTEM

- Animals studies
    - Examined 26 mammalian species.
    - Those with more total sleep time had higher number of WBC.
    - Used red blood cells as controls since they were derived from the same hematopoietic precursors.
    - Increased WBCs thought to be more immunocompetent.
SLEEP AND THE IMMUNE SYSTEM

• 20 Adults
• Kept awake for 64 hours
• Measured WBC and specific cell types
  – Sleep loss was associated with leukocytosis and increased NK cell activity
  – At the maximum sleep deprivation, increases were observed in counts of WBC, granulocytes, monocytes, and NK activity
  – Counts of CD4, CD16, CD56, and CD57 lymphocytes declined after one night without sleep, whereas CD6 and CD57 counts increased after two nights

SLEEP AND THE IMMUNE SYSTEM

• 42 healthy volunteers
• Sleep deprived between 10pm and 3 am
• Looked at NK cell activity
• Lymphokine-activated killer cell activity and number
• Found a reduction in activity in NK and LAK number and activity

Consequences of Sleep Alterations in ICU Patients

• Decreased insulin sensitivity
  • Poor glycemic control
• Diminished strength of respiratory muscles
  • 1 night of sleep loss associated with decreased PFTs
• Delirium link between sleep deprivation and in the ICU is currently unproven

SLEEP AND THE IMMUNE SYSTEM

• Moldofsky and colleagues:
  – Reported in 10 men that 40 h of sleep loss induced a prolonged decline in NK activity and a delayed nocturnal rise in lymphocyte proliferation
• Palmblad and colleagues:
  – Found decreased lymphocyte proliferation after 48 h of wakefulness in 12 men and increased interferon production and decreased phagocytic activity in 8 women deprived of sleep for 77 h
Sleep deprivation and Delirium

- Central components of delirium such as inattention, fluctuating mental status and cognitive dysfunction are also characteristics of sleep deprivation
- Many sleep deprived people show signs similar to hypoactive delirium (less so with hyperactive delirium)
- In sleep deprived people psychotic behavior was noted more at night and less during the day (as in delirium)

Similarities shared by delirium and sleep disruption

- Clinical features
  - Inattention
  - Fluctuating mental status
  - Impaired cognition, specifically those relating to executive function (memory, planning, creative thinking, judgment)
  - Delayed recovery after the insult is removed
- Risk factors
  - ICU admission, Mechanical ventilation
  - Pain, Stress
  - Pre-existing cognitive impairment, head injuries
  - Advanced age, Alcoholism, Depression
  - Sepsis
  - Medications
    - Sedatives, Anticholinergics, Sympathomimetics, Corticosteroids, Anticonvulsants
- Pathophysiology
  - Cholinergic deficiency
  - Dopaminergic excess
  - Altered metabolism at specific regions of the central nervous system
    - Prefrontal cortex
    - Posterior parietal cortex

Melatonin therapy


- Evaluated the effect of exogenous melatonin on nocturnal sleep quality in critically ill mechanically ventilated patients
- Randomized double-blind placebo-controlled trial in 24 patients
- 10 mg melatonin or placebo administered at 9pm for 4 nights
- Measured BIS, actigraphy, nurse and patient assessments.

Result

- Melatonin use was associated with an increase in nocturnal sleep
- Melatonin use was associated with a decrease in BIS indicating better sleep

Conclusion

- Melatonin use was associated with increased nocturnal sleep efficiency
- 10mg dose might have been more than needed. 1-2mg could be all than is needed.
Conclusion

• Based on current available data.
  – Focused approach with attention to the potential cause of sleep disruption should be under taken
    – Is there anxiety, pain, depression, noise, patient-care activities etc
  – Allow sleep to occur naturally
  – Nonpharmacologic efforts to maintain a quiet environment.
    – Ear plugs
    – White noise
  – Eliminate unnecessary patient interruptions.
    – The use of benzodiazepines and narcotics.
    – Need close monitoring.
    – Adjustment to the lowest effective dosages.
  – Cautious monitoring for the onset of delirium with the use of opiates and benzodiazepines is warranted.
  – Determining the best sedative will be important.
  – Ensuring patient ventilator interaction is optimized.
  – Avoid hyperventilation, especially at night.