Effect of Administration of Ramelteon, a Melatonin Receptor Agonist, on the Duration of Stay in the ICU: A Single-Center Randomized Placebo-Controlled Trial

Background:

- Delirium in the ICU is associated with a longer length of ICU stay, higher rates of mortality, increased ventilator time, and increased cost.
- One theory towards preventing delirium is to increase the length of restful, uninterrupted sleep.
- Ramelteon is a melatonin-like agonist that in theory should produce more restful sleep.

Objective:

- Determine if ramelteon can decrease delirium and reduce the duration of ICU stay.

Methods:

- **Design:** A single center, placebo controlled, triple blind, stratified randomized study.
- **Study duration:** Participants were enrolled in the study from the moment they took their first dose, to the moment they were discharged from the ICU.
- **Inclusion criteria:** Age ≥ 20 years old, admitted to EMICU, can receive medications by mouth or nasogastric tube during first 48 hours of ICU admission.
- **Exclusion criteria:** Patients already receiving ramelteon or fluvoxamine prior to admission, allergy to ramelteon, or if consent was refused.
- **Number of patients enrolled:** 92 total participants
- **Drug regimen:** Ramelteon 8mg or placebo taken by mouth or nasogastric tube each night at 8pm.
- **Primary outcome measure:** median length of stay in the ICU.
- **Secondary outcome measure:** rate, duration, and frequency of delirium episodes, and sleep variables.
- **Power:** The study was unable to achieve the goal power of 80%
- **Data handling:** Intent to treat

Results:

- 88 participants completed the study (45 study group vs. 43 control)
- **Primary outcome:** Median duration of ICU stay, ramelteon vs. placebo, showed a difference of 4.56 (2.10 – 7.07) vs. 5.86 (2.97 – 14.16) ($p = 0.082$).
- **Secondary outcomes:** Occurrence of delirium was 24.4% (11/45) in the study group and 46.5% (20/43) in the placebo group (p-value = 0.044, OR 2.69 [1.09 – 6.65]). Duration of delirium was reported as 0.78 vs. 1.40 days ($p = 0.048$). Mortality rate at discharge was 6.7% (3/45) in the study group, versus 7.5% (3/43) in the control ($p = >0.999$). Sleep variables showed mixed results: significantly fewer nighttime

awakenings [0.80 vs. 1.31 each night (p = 0.045)], and significantly higher proportions of nights without awakenings (51% vs. 30% [p = 0.048]). Yet the difference in average number of sleeping hours each night was not significant (p = 0.252).

- **Author's conclusions:** Use of ramelteon in the ICU demonstrated a trending associated with a decreased duration of ICU stay. Ramelteon use was however showed significant improvements in the occurrence rate and duration of delirium in ICU patients.

Strengths

- Rationale
- Methods were clearly defined and appropriate
- Statistical analysis tests used were appropriate

Limitations

- Sample size was insufficient
- Omission of melatonin
- Use of other delirium medications
- The authors did not mention exactly what the chief complaint was for every patient

Conclusions

- The authors demonstrated a statistical significance in rate and duration of delirium, yet there was no difference in number of average sleeping hours per night. Also the differences that were statistically significant were not clinically significant as the patients were still experiencing more than half a day with delirium.
- Future studies will need to occur in order to gain a more complete picture of the benefits of ramelteon in the ICU setting. These studies will need to focus on attaining a much larger sample size, inclusion of melatonin as an active –control, and randomizing patients based on diagnosis and severity.

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