Efficacy of melatonin in decreasing the incidence of delirium in end of life patients: A randomized double blinded placebo controlled pilot study

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Delirium: disturbance in consciousness with reduced ability to focus, sustain, or shift attention (DSM-V)

- One of the most common and serious cognitive disorders in patients with terminal illness
- Attention/level of consciousness fluctuates over time
- Sudden and abrupt onset
- Compared to dementia, delirium is usually reversible

Incidence of delirium:

- In palliative care patients with advanced cancer = 42% on admission
- In final weeks of life = 85%
Background

- Delirium can lead to...
  - Significant morbidity and mortality
  - Impaired physical and cognitive recovery
  - Lengthy hospital stays and frequent visits to ER or clinics, institutionalization, etc. → increased health care cost ($100 billion - 2005 US dollars)
  - Loss of independence → social isolation
Background

- Delirium at end of life...
  - Inability to interact with family in the final days
  - Increased fall risk
  - Worsening of quality of dying

- Mortality
  - Patients with persistent delirium were 2.9 times more likely to die during one year follow up
  - When delirium was resolved, the risk of death decreased

Current Treatment of Delirium

- Antipsychotics: haloperidol and methotrimeprazine, quetiapine, risperidone, and olanzapine
  - Use of an anti-psychotic for this purpose is not Health Canada approved
  - Many adverse effects: alteration in mental alertness, QT interval prolongation, increased fall risks

- Use of benzodiazepines associated with worsening of cognition

- Can we look for an alternative?
Role of Melatonin in the body

- Hormone secreted by pineal gland
- Released in response to evening darkness and promotes the onset of sleep
- Possibly synchronizes the circadian rhythm
  - Diurnal rhythm
    - Peak levels of melatonin are found between 12am and 8am
    - Levels gradually decrease with exposure to light during the day
Changes in melatonin

- Melatonin levels decrease as we age
- Abnormal levels of melatonin are also found in patients with critical illness
- Correlations have been found between disrupted circadian release of melatonin and ICU delirium
Melatonin is currently used as a natural health food supplement for sleep disorders.

- Potentially corrects the sleep-wake cycle and circadian rhythm.
1) Al-Aama et al:
- P: patients 65 years or over admitted to an acute internal medicine unit in a tertiary care center (N=145)
- I: 0.5mg melatonin every night for 14 days
- C: placebo
- O: incidence of delirium

Results:
- Melatonin was associated with a lower risk of delirium (12% vs. 31%, p=0.014)
- Odds ratio (adjusted for dementia and co-morbidities) = 0.19 (95% CI 0.06-0.62)
- Exogenous low dose melatonin administered nightly to elderly patients may potentially be protective against delirium

2) Sultan S. et al
- P: patients > 65 years old undergoing hip arthroplasty (N=222)
- I: 5mg melatonin, 7.5mg midazolam, or 100mcg clonidine
- C: placebo
- O: incidence of postoperative delirium

Results:
- Patients treated with melatonin pre-operatively had a statistically significant decrease in incidence of post-operative delirium (9.42% vs. 32.65%, p=0.003)
- Other interventions showed a higher incidence of delirium vs. placebo (but statistically insignificant)

Current Research

- No studies conducted to test the efficacy of melatonin or other medications to manage delirium in the terminally ill population
- Few studies done on how to prevent or treat delirium
- No medication that have been approved by Health Canada or FDA for treatment or prevention of delirium
Research Objectives

- Determine if we can prevent delirium in end-of-life populations with administration of melatonin
- Provide information for the planning and justification for a full scale RCT
- Collect data on the safety and efficacy of melatonin used to prevent delirium
Research Question

Is melatonin effective in decreasing the incidence of delirium?
Study Design and Methods

- Randomized double-blinded placebo controlled pilot study
- Study will take place in a 10 bed tertiary hospice palliative care unit (N52) and a 20 bed community-based hospice (Laurel Place) within SMH campus
- All patients admitted to the units will be assessed for eligibility using the **Palliative Performance Scale (PPS)**
- Patients are followed for 2 weeks from time of recruitment or development of delirium
Patient Recruitment

- All patients over 19 years old admitted to the tertiary palliative care unit
- Attending physician or patient care coordinator will ask within 48 hours of admission (+/- 60 mins) for patient participation
- Research nurse performs initial assessment for eligibility
Informed Consent

- Patient will be approached by a research nurse that is not directly involved in patient’s care.
- Patient is given 24 hours for consideration.
- If patient is too fatigued to have in-depth informed consent discussion, the substitute decision maker may be approached.
- Punjabi translation will be present if needed.
- Consent is valid for both sites.
Randomization

- Eligible patients are randomized 1:1 to 0.5mg melatonin or placebo
- Each patient will be assigned unique study number to ensure confidentiality
- In emergencies, attending physician may request unmasking
Intervention

- Two arms:
  - 1) Melatonin 0.5mg (tablet/capsule) orally
  - 2) Placebo (identical in appearance, contains lactose powder)

- Patients monitored for 14 days or until the development of delirium

- Patients assessed twice a day for delirium at the end of each nursing shift (e.g. 12 hours 03:30 & 18:30)

- Diagnostic tool: CAM = Confusion Assessment Method
Confusion Assessment Method (CAM)

- To be conducted by a trained nurse rater
- Diagnostic instrument for identification of delirium for use in alert, non-intubated patients
- Four key delirium criteria:
  - 1) acute mental status change
  - 2) inattention
  - 3) disorganized thinking
  - 4) altered level of consciousness
- Diagnosis = 1 and 2 plus EITHER 3 or 4
Potential benefits of the study

- Currently, no highly effective intervention to prevent delirium development in any patient population
- Prevention and treatment in a timely manner can positively benefit the patient’s quality of life (e.g. physical and cognitive recovery, decreased hospitalization)
- Contribute to the understanding of the pathophysiologic mechanisms that cause delirium
- **Determine if melatonin is effective for delirium prevention and/or treatment**
Potential risks of the study

- Low potential for any side effects:
  - Low incidence of side effects: physiologic doses (0.5-6mg daily) was found to have a good safety profile
  - Safe in vulnerable populations, such as the elderly and the cognitively impaired

- Minor adverse events reported as a change in sleep pattern, headaches, nausea, dizziness, fatigue, transient depression
Questions?

- Thank you!