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Melatonin for preventing postoperative delirium in elderly patients

A multicenter randomized placebo-controlled pilot study

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Abstract

Background: Postoperative delirium (POD) in older adults is associated with high risk of morbidity and mortality. With limited treatment options, prevention is essential. Melatonin has been suggested to prevent delirium through regulating the sleep-wake cycle and serotonin metabolism, which has been shown to be disrupted in patients with POD. However, the evidence regarding the use of melatonin for POD prevention is limited and inconclusive.

Methods: Our multicenter, 2-arm, parallel-group, feasibility randomized controlled trial evaluated the effect of melatonin on POD incidence after noncardiac surgery in patients >65 years (n = 120). Patients were randomized to 3 mg oral melatonin or placebo once preoperatively and for 7 days postoperatively. Patients were assessed twice daily for delirium and followed at 3 months postoperatively. Feasibility outcomes were recruitment rate, medication adherence, and proportion completing 3-month follow-up. Clinical outcomes were delirium incidence, sleep quality, institutional discharge, and cognitive status at 3 months.

Results: Between September 2021 and June 2023, 85 patients were randomized (~1 patient/wk); of these, 92.9% adhered to study medications and 87.1% completed the 3-month follow-up. POD occurred in 9 patients with no statistical difference between the groups (melatonin group, n = 7; placebo group, n = 2; adjusted odds ratio: 1.12; 95% confidence interval: 0.006–150.1). There were no differences in any other clinical outcomes. Pandemic-related challenges, including interruption of surgeries and restrictions on research procedures impacted feasibility and the study was terminated early due to futility.

Conclusions: Based on our observations, a sample size of >1000 patients is required for a definitive trial to evaluate the role of melatonin in reducing the incidence of POD. Design changes need to be considered to address feasibility challenges and ongoing post-pandemic modifications to patient care.

Abbreviations: 3D-CAM = short-form confusion assessment method, ASA = American Society of Anesthesiologists, BMI = body mass index, CI = confidence interval, ICU = intensive care unit, JH = Juravinski Hospital, Hamilton, Ontario, Canada, LHSC = London Health Sciences Centre, London, Ontario, Canada, MMSE = mini mental state examination, PACU = post-anesthesia care unit, POD = postoperative delirium, POSS = Pasero Opioid-induced sedation scale, RCSQ = Richards–Campbell sleep questionnaire, RCT = randomized controlled trial, REDCap = research electronic data CAPture, SJHH = St. Joseph's Healthcare Hamilton, Hamilton, Ontario, Canada.

Keywords: feasibility, melatonin, postoperative delirium, randomized controlled trial

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Informed consent was obtained from all individual participants included in the study.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

The study protocol has been approved by the Hamilton Integrated Research Ethics Board in September 2019 (project #5506).

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This trial was conducted in accordance with the principles laid down in the Declaration of Helsinki, Good Clinical Practice, as defined by the International Conference on Harmonisation. Appropriate approval and notice of authorization were obtained from Health Canada for the use of melatonin as an investigation drug for the indication of postoperative delirium prevention.http://dx.doi.org/10.1097/MD.0000000000041615

1. Introduction

Delirium is an acute and fluctuating disturbance in cognition characterized by alterations in the level of attention and awareness from subject's baseline, developing over a relatively short period of time.[1,2] Its incidence increases with age, occurring in nearly 50% of elderly inpatients.[2] The reported incidence of postoperative delirium (POD) is 15% to 74%, varying with type of surgery and population.[1,3–5] POD increases risk of patient morbidity and mortality and thus costs to the health care system.[6] Increased risk of mortality can persist even 3 years after hospitalization[7,8] and is an independent risk factor even after controlling for possible confounders.[8] Other complications associated with POD include prolonged hospital stay, needing institutional stay, long-term cognitive impairment, urinary incontinence, falls, and decubitus ulcers.[8–10] Costs due to POD may be increased 2 to 3 times.[11]

Multiple pathways are proposed to cause POD,[1,12] with factors including age, alcoholism, depression, loss of executive control, prior history of delirium, sleep deprivation, changes to circadian rhythm and electrolyte imbalances.[3,13–15] Although general anesthesia was considered to increase the risk of POD over regional or neuraxial anesthesia, newer studies indicate no such risk.[16]

With no effective treatment, focus is on prevention, both pharmacological and non-pharmacological.[12] Non-pharmacological strategies are multifaceted and involve different interventions.[17] Non-pharmacological interventions with potential for POD prevention include patient education, shared decision making, preoperative risk assessment/ comprehensive geriatric assessment, optimizing modifiable risk factors, promoting early mobilization, hydration and nutrition support, optimizing vision and hearing, engaging the surgical team and enhancing sleep quality.[17,18] The interventions can be implemented as a single intervention or as multicomponent interventions such as the Hospital Elder Life Program, or delirium units and joint care wards.[18,19] However, there are significant challenges to implementation, *as many of them* involve major changes to clinical practice.[12] For example, a recent survey of anesthesiologists in Canada identified several barriers to performing preoperative risk assessment for POD and discussing such risks with patients in preoperative visits, including lack of time and avoiding additional anxiety for the patients.[20] Attempted pharmacological options include dexmedetomidine, haloperidol, olanzapine, gabapentin, and others.[21,22] However, none have shown much promise, and have associated adverse effects.

Melatonin, a pineal gland hormone, regulates the sleep-wake rhythm. Disruption of the sleep-wake cycle is observed in delirium.[23] Abnormal tryptophan metabolism is hypothesized as a cause for delirium and melatonin supplementation is observed to decrease the breakdown of tryptophan and serotonin through positive feedback[24]; low tryptophan and serum melatonin levels were observed in patients with POD.[25,26] Other advantages of melatonin include improved sleep, sparing of sedatives, minimal potential for abuse, and no hangover effects.[27] Few randomized controlled trials have evaluated melatonin for delirium prevention. A recent systematic review of 11 studies (1224 patients) suggest that melatonin or a melatonin agonist may reduce the incidence and duration of POD,[28] where 4 studies (one unpublished) found lower incidence of POD in the melatonin group compared with placebo or no treatment,[29–32] while 7 showed no significant difference in the incidence of POD between the melatonin and control groups.[33–37] However, the review highlighted several limitations due to large heterogeneity, inconsistency and variations in the methodology of the included studies particularly regarding the dose and duration of treatment and outcome assessment (timing and consistency of delirium assessment). A large, well-designed study is clearly needed to establish definitive evidence.

The MIND after Surgery study assessed the feasibility of a large multicenter RCT to compare the effect of melatonin supplementation, vs placebo, on the incidence of POD in elderly patients undergoing elective noncardiac surgery. Our secondary objectives were to compare the incidence of POD during the hospital stay; quality of sleep; incidence of intensive care unit (ICU) care; length of hospital stay; cognitive status at 3 months after surgery; adverse outcomes of melatonin; and mortality up to 3 months.

2. Material and methods

2.1. Design, registration and ethics

This placebo-controlled, 2-arm parallel-design pilot RCT was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. It was approved by the Hamilton Integrated Research Ethics Board (project no. 5506; File 1, Supplemental Digital Content, http://links.lww.com/MD/O412) and registered on clinicaltrials.gov (#NCT03785158) (File 2, Supplemental Digital Content, http://links.lww.com/MD/O413). The use of melatonin as an investigative drug for the indication of POD prevention was approved by Health Canada. The study was conducted at St. Joseph's Healthcare Hamilton (SJHH), Hamilton, Ontario, Canada; Juravinski Hospital (JH), Hamilton, Ontario, Canada; and London Health Sciences Centre (LHSC), London, Ontario, Canada. This manuscript follows the consolidated standards of reporting trials checklist for reporting randomized pilot and feasibility trials.

2.2. Patients

Men and women > 65 years of age, undergoing major elective noncardiac surgery (vascular, thoracic, gynecological, otolaryngeal, general and gastrointestinal) with an expected hospital stay of ≥2 days and able to provide informed consent, were included. Exclusion criteria were as follows: refusing to participate; active delirium or dementia; planned postoperative ventilation; previous study participation; allergy to melatonin; hepatic impairment defined as alanine aminotransferase >500 IU/L; previous liver transplant or liver cirrhosis of Child-Pugh classes B and C; language barrier; or pregnant or breastfeeding women (as required by Health Canada).

2.3. Screening and recruitment

Patients were screened from the preoperative list and consented on the day of preoperative anesthesia meeting. Baseline variables collected included age, sex, medical comorbidities, active medications, history of delirium, surgical diagnosis, cognitive status by mini mental state examination (MMSE), sleep quality, and presence and severity of depression by screening questions and if positive, followed by patient health questionnaire-9.

2.4. Randomization and allocation

Patients were randomized centrally to treatment or control group in a 1:1 ratio, using a computer-generated, permuted, variable block randomization, stratified by site using Research Electronic Data capture (REDCap) software. At each site, on the working day prior to surgery, the research assistant informed the pharmacy and confirmed the patient details, study sequence number, and the surgical details (time, date and procedure). Trained pharmacy research personnel logged on to the REDCap randomization system to allocate the patient and note the study sequence number; no other research personnel were aware of the allocation. Study medications were dispensed in preprepared syringes with no identifiers, with the

first dose sent to the day surgery unit and subsequent doses to the postsurgical ward. The pharmacy at each site maintained a dispensing log kept in the study operations binder. Any emergency unblinding or accidental unblinding was noted, recorded and reported to the ethics board and regulatory authorities as per procedures.

2.5. Blinding

Patients, research assistants involved in patient recruitment and follow-up, health care providers, nurses caring for the patient, and data analysts were blinded.

2.6. Study interventions

Patients in the intervention group received 3 mg of melatonin syrup by oral route for up to 8 days. The first dose was given 1 to 2 hours before surgery, followed by bedtime doses (between 7 and 9 PM) starting postoperative day 1 until discharge or for the first 7 days. Control patients received similar-looking and -smelling placebo syrup administered on the same schedule. Patients took all their regular medications as necessitated clinically. Patients already taking melatonin and willing to participate in the study were asked to abstain from taking any melatonin 2 days prior to surgery and up to 7 days after surgery (duration of intervention). There were no restrictions on anesthetic management or usual clinical care. Patients with delirium received care as per the hospital policy or guidelines. Prophylactic benzodiazepines (other than 1 dose for preoperative sedation), haloperidol or other antipsychotics, or any other sleep-inducing medications were avoided, other than for treating active delirium.

2.7. Data collection and follow-up

Patients were assessed twice daily (morning and evening) during hospitalization by research personnel to check for delirium. The protocol was subsequently amended to allow observations during other periods if the research personnel were notified of possible delirium by hospital personnel looking after study patients. After discharge, patients were followed at 3 months after surgery, either in-person or by telephone, as convenient. All study data and outcomes were captured in REDCap forms.

2.8. Outcomes

The following criteria were used to assess our feasibility outcomes. Recruitment rate: number of patients recruited per week (per site and overall) with a goal of 2 to 3 patients/site/week; adherence to study medication: percentage of patients who had at least 2 doses of study medications with a goal of >85% of study patients; and proportion of patients completing 3-month follow-up with an expectation of >90% patients.

Incidence of POD was assessed after post-anesthesia care unit (PACU) discharge until time of hospital discharge, using the short-form confusion assessment method (3D-CAM) based on the CAM-S criteria,[38] or the CAM-ICU tool,[39] if the patient is mechanically ventilated. We did not consider confusion in PACU as POD as patients can be momentarily confused during the initial recovery period. Incidence was recorded as a binary variable (yes/no), without considering either the duration or number of POD episodes.

Sleep quality was assessed each morning using Richards–Campbell sleep questionnaire (5 questions with visual analogue responses).[40] Need for ICU or critical care during hospitalization was noted as binary outcome along with duration of stay. Length of hospital stay was noted in days. Institutional discharge was recorded as a binary outcome.

At 3-month follow-up, cognitive status was assessed using the MMSE (in-person follow-up),[41] or the telephone version of MMSE. Mortality (up to 3 months post-discharge) and sedation during hospital stay (Pasero Opioid-induced sedation scale score of 3 or 4) were noted as binary outcomes.

2.9. Sample size

Based on chart review, we estimated that at least 2 patients/week could be recruited at each center (8–10 patients per month/site). To establish feasibility, we aimed to recruit 120 patients, approximately 10% of the full sample for the definitive trial. Assuming an incidence of 15% at baseline and with a relative risk reduction between 25% and 33%, we estimated that approximately 1000 to 1200 patients would be needed for the definitive trial, with a 2-sided alpha (α) = 0.05 and 80% power.

2.10. Data analysis

We used descriptive statistics to summarize patient demographics and baseline characteristics. Continuous variables are summarized as number of subjects (N), mean (standard deviation), or median (25th and 75th percentiles). Categorical variables are described as frequency distributions (N and %). Patients were analyzed in the groups they were randomized to (intention-to-treat). Analyses were performed using R software (R version 4.3.2).[42] Feasibility outcomes are reported as proportions and rate with corresponding 95% confidence intervals. Analysis of clinical outcomes was exploratory. Binary and categorical variables were analyzed by χ^2 test and mixed-effects logistic regression for repeated measures (adjusting for baseline variables including age, sex, duration of surgery, previous history of delirium, study site and POD diagnosis approach [prespecified timepoints using 3D-CAM or POD episode observed by nursing or research team]) to estimate the relative risk and associated 95% CI. Continuous variables were analyzed based on an independent *t*-test. For all tests involving comparisons, statistical significance is inferred with a *P*-value of <.05.

3. Results

3.1. Recruitment and baseline

Between September 17, 2021, and June 12, 2023, we screened 186 patients for eligibility at 3 sites: SJHH, JH, and LHSC. The consolidated standards of reporting trials flow chart is presented in Figure 1. Due to the COVID-19 pandemic, there were significant interruptions to the study and specific challenges to patient recruitment after implementation of virtual care. Major interruptions happened between December 2021 and February 2022, and between April and November 2022. Due to continued challenges in recruitment at 2 of the sites, and need for important changes to the main study protocol to establish feasibility (including the need to involve other sites and funding), the study was terminated in June 2023 after recruiting 76% of our target sample size.

Baseline and perioperative characteristics were similar between the melatonin and the placebo groups (Table 1). Most had either thoracic or abdominal surgeries under general anesthesia with 1 patient in each group having epidural analgesia for postoperative pain relief. Preoperative MMSE scores were comparable between groups.

3.2. Feasibility outcomes

Over the 95-week period, we recruited 88 patients (approximately 1 patient/wk). Of these, 85 were randomized (3 patients withdrew consent before randomization). Most patients were recruited from SJHH (74/88), at a rate of 1.1/wk. Among the study sites, the recruitment rates were highest at SJHH, followed by LHSC then JH. Seventy-nine patients (92.9%) adhered to study medications, receiving at least 2 doses. Retention rate was

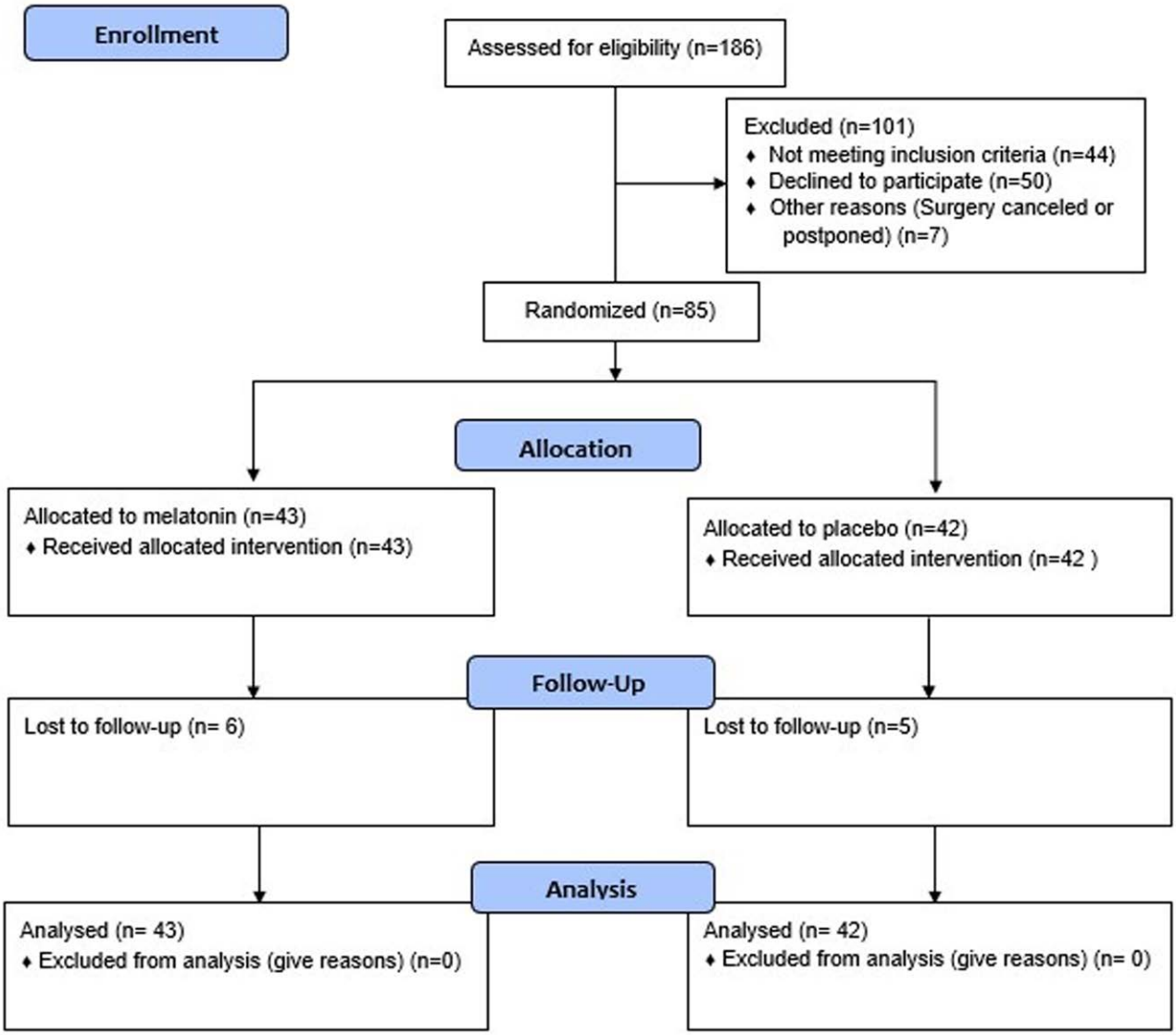

Figure 1. CONSORT flow diagram. CONSORT = consolidated standards of reporting trials.

87.1%, with 74 patients completing the 3-month follow-up. Table 2 presents the overall and site-specific feasibility outcomes.

3.3. Clinical outcomes

In total, 9 patients (10.6%) were observed to have POD (no statistical difference between the 2 groups: adjusted odds ratio = 1.12; 95% CI = 0.006–150.1; $P = .95$) (Table 3). There were no differences in the overall sleep quality or within individual measures of sleep depth, latency, awakening, return to sleep and quality, or in the need for ICU admission, length of hospital stay, incidence of institutional discharge, postoperative MMSE scores, or the incidence of mortality between the 2 groups. Significant sedation was not observed (Table 4). Notably, postoperative MMSE scores (mean of 24, mild cognitive impairment)[43] showed deterioration compared with preoperative scores (mean of 29, normal range), in both groups.

4. Discussion

In this study, we assessed the feasibility of conducting a large RCT to evaluate the effect of perioperative melatonin administration on the incidence of POD after noncardiac surgery and explored the effects of intervention on clinical outcomes. Our feasibility outcomes showed lower recruitment and retention rates than the rates we prespecified as acceptable for advancing to the main trial. Patients' adherence to the study interventions met our prespecified target rate. We did not observe important differences in the incidence of POD or other clinical outcomes.

The MIND after Surgery pilot study was initiated during the COVID-19 pandemic. Surgical delays and inconsistencies in the surgical schedule during the pandemic resulted in significant recruitment challenges. Additionally, the trend to same-day discharge, which increased during the pandemic, resulted in further limitations to recruitment as we only included patients with an expected hospital stay of ≥2 days. The COVID-19 pandemic led to challenges in several aspects of clinical trial conduct.[44] Although certain modifications overcame some challenges, other aspects still faced important limitations based on the original trial design and the necessity to ensure study validity and integrity.[45] Surgical patients were more hesitant to participate in studies due to the general anxiety and additional requirements that a study may impose on them.[46] Concurrently, we also noted important differences among our study sites regarding recruitment. At JH, it was a result of changes in the operations of the preoperative clinic where patients were primarily recruited. Considering the larger study to assess the impact of

Table 1

Baseline characteristics and relevant covariates.

Characteristics	Melatonin group (n = 43)	Placebo group (n = 42)
Age, yr; mean (SD)	74.0 (5.23)	73.5 (6.13)
Sex, female; n (%)	22 (51.2)	25 (59.5)
BMI, kg/m^2; mean (SD)	28.6 (5.17)	30.7 (5.51)
History of stroke; n (%)	0 (0.0)	0 (0.0)
History of postoperative delirium; n (%)	0 (0.0)	1 (2.4)
Visual or hearing impairment; n (%)	2 (4.7)	3 (7.0)
Ongoing life-threatening cardiac or respiratory illness; n (%)	1 (2.3)	1 (2.4)
Ongoing substance abuse; n (%)	0 (0.0)	1 (2.4)
Ongoing alcohol abuse; n (%)	–	–
Chronic pain needing daily opioid prescription; n (%)	2 (4.7)	0 (0.0)
Current use of medications; n (%)		
Opioids	2 (4.7)	0 (0.0)
Benzodiazepines	2 (4.7)	0 (0.0)
Anticholinergics	0 (0.0)	0 (0.0)
Baseline (preoperative) MMSE score; mean (SD)	29.3 (1.30)	29.0 (4.65)
Type of surgery; n (%)		
General	5 (11.6)	3 (7.1)
Orthopedic	0 (0.0)	0 (0.0)
Gynecological	0 (0.0)	0 (0.0)
Head and neck	1 (2.3)	2 (4.8)
Thoracic	21 (48.8)	17 (40.5)
Abdominal	12 (27.9)	12 (28.6)
Urological	4 (9.3)	7 (16.7)
Missing		1
Surgical procedure; n (%)		
Laparoscopic	26 (60.5)	26 (61.9)
Open	17 (39.5)	15 (35.7)
Missing		1
ASA grade; n (%)		
1	0 (0.0)	0 (0.0)
2	0 (0.0)	2 (4.8)
3	25 (58.1)	20 (47.6)
4	18 (41.9)	19 (45.2)
Type of anesthesia; n (%)		
General	42 (97.7)	40 (95.2)
Spinal or epidural	1 (2.3)	1 (2.4)
Missing		1
Perioperative medications		
Perioperative opioids; n (%)		
Remifentanyl	31 (72.1)	31 (73.8)
Fentanyl	32 (74.4)	28 (66.7)
Sufentanyl	6 (14.0)	3 (7.1)
Morphine	0 (0.0)	0 (0.0)
Hydromorphone	24 (55.8)	30 (71.4)
Missing		2
Perioperative benzodiazepines; n (%)		
Midazolam	27 (62.8)	25 (59.5)
Lorazepam	0 (0.0)	0 (0.0)
Missing		2
Ketamine	25 (58.1)	24 (57.1)
Missing		2
Dexmedetomidine	13 (30.2)	9 (21.4)
Missing		2

ASA = American Society of Anesthesiologists, BMI = body mass index, MMSE = mini mental state examination, SD = standard deviation.

melatonin requires > 1000 patients, it becomes important to select centers with high patient volume and consider targeting other surgical populations for better recruitment. However, even with a small sample size, this study is 1 of few evaluating the effect of melatonin on the incidence of delirium in noncardiac surgical population,[31,33] and the sample size is larger than *several* published studies evaluating the effect of melatonin in surgical patients.[28] This further highlights important deficiencies in the current literature and emphasizing the need for a larger well-designed study, to improve power and precision and increase the certainty of evidence regarding the role of melatonin in this population. Currently, in the post-COVID-19 era, several challenges which were posed by the pandemic, such as cancelation of surgeries and restriction on in-person research staff presence in hospitals, have been resolved. However, some of the post-pandemic modifications to the healthcare system persist and can impact the conduct of future trials particularly focusing on POD. For example, the noticeable paradigm shift toward favoring same-day discharge contradicts with eligibility criteria commonly adopted in POD studies, which typically include surgeries requiring at least 1 overnight stay in hospital. This is mostly because these types of surgery are more major and could be associated with higher risk of POD. Moreover, POD typically occurs up to 7 days postoperatively, and therefore early discharge could impact postoperative follow-up and the rate of POD detection. On the other hand, the pandemic emphasized the need for remote monitoring in perioperative research which can facilitate post-discharge follow-ups and improve retention rates. To adopt to these changes, it is important that eligibility criteria focus more on the surgical procedure rather than expected duration of hospital stay, and to utilize advances in remote follow-ups with adequate training of research personnel to improve POD detection post-discharge.

An important challenge we encounter in studies of POD prevention is the variability in the observed incidence of POD in noncardiac surgeries (5% to 52%),[47] likely related to the inconsistencies in study population, definition, and approach to POD screening, including frequency and duration of observation. The overall incidence of POD in our study was 10.6%, which is smaller than our expected event rate. In a recently published study of hip fracture patients, incidence of POD was 5.1% and 6.2% in the regional and general anesthesia groups, respectively.[48] In another study in the same population assessing the effect of melatonin, POD was observed in 29.6% of intervention patients and 25.5% in control group patients.[33] A large prospective study of 1341 patients having noncardiac surgery with a postoperative stay of at least 48 hours reported an overall incidence of 9% in >50 years and 15% in >70 years.[14] Although our observed POD incidence is on the lower side, it was within a range of published studies,[47] and future studies should consider more frequent monitoring and sensitive tools to assess POD.

Melatonin for the prevention and treatment of delirium has been investigated in surgical and nonsurgical settings.[49] In the surgical setting, the most recent systematic review and meta-analysis considered 11 studies using melatonin (or melatonin agonist ramelteon) with 8 studies in noncardiac surgery.[28] The dose of melatonin ranged from 3 to 50 mg/kg with dosing duration of 1 to 7 days. It has been suggested that a dose >5 mg is no more effective,[50] and a small study observed drowsiness with a 10 mg dose.[40] In our study, we used a dose of 3 mg administered in the evening daily for 7 days, starting the first dose preoperatively. Among noncardiac surgeries, 4 involved joint surgeries, and 1 study each on liver resections, mixed surgeries involving neuraxial anesthesia, and pulmonary thromboendarterectomy. Our population predominantly consisted of thoracic and abdominal surgeries. Although we found no statistically significant difference in our exploratory analysis, the published meta-analysis observed that the odds of POD were decreased by melatonin administration, odds ratio = 0.41, 95% CI = 0.21 to 0.80 (P = .01), moderate certainty of evidence.[28] However, there was substantial heterogeneity and variation in doses and duration of intervention. Given the potential for POD reduction and the simplicity of use and relative safety,[15] it becomes important to establish if melatonin administration reduces the risk of POD in older adults. Potentially, one could consider testing 2 different doses or durations of administration and evaluating intervention effects with a subgroup analysis in a definitive trial.

Table 2

Feasibility outcomes.

Outcome	Outcome measure	Site 1: SJHH	Site 2: JH	Site 3: LHSC	Total
Recruitment rate	Number of patients recruited/ wk	74 pts in 67 wk (1.1/wk)	4 pts in 25 wk (0.16/wk)	10 pts in 31 wk (0.32/wk)	88 pts in 95 wk (0.96/wk)
Adherence to study medication	Proportion of patients who had at least 2 doses of study medications	67 (90.5)	3 (75.0)	9 (90.0)	79 (92.9)
Missing		3		1	4
Retention rate	Proportion of patients who complete 3 mo follow-up	62 (83.8)	4 (100.0)	8 (80.0)	74 (87.1)
Missing		3		1	4

JH = Juravinski Hospital, LHSC = London Health Sciences Centre, pts = patients, SJHH = St Joseph's Healthcare Hamilton.

Table 3

Incidence of postoperative delirium.

			Chi-square test		Logistic regression*	
	Melatonin Group (n = 43)	Placebo Group (n = 42)	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Incidence of POD, n (%)	7 (16.3)	2 (4.9)	3.74 (0.65–39.16)	.157	1.12 (0.006–150.1)	.951

CI = confidence interval, OR = odds ratio, POD = postoperative delirium.

*Adjusted for *age, sex, duration of surgery, previous history of delirium, study* site and delirium diagnosis approach.

Table 4

Secondary clinical outcomes.

Outcome measure	Melatonin group (n = 43)	Placebo group (n = 42)	Effect estimate		*P*-value
			Mean difference (95% CI)	OR (95% CI)	
RCSQ questionnaire mean scores*; mean (SD)					
Sleep depth	60.4 (30.59)	56.9 (28.92)	3.52 (-2.79–9.83)	–	.273
Sleep latency	66.1 (31.47)	62.0 (31.58)	4.14 (-2.56–10.8)	–	.225
Awakenings†	56.9 (29.73)	55.6 (29.12)	1.29 (-4.97–7.54)	–	.686
Returning to sleep	64.0 (33.02)	63.3 (31.11)	0.76 (-6.05–7.56)	–	.827
Sleep quality	58.2 (32.15)	58.0 (28.96)	0.17 (-6.31–6.65)	–	.959
ICU admission‡; n (%)	0 (0.0)	2 (4.8)	–	-0.05 (-0.14, 0.04)	.453
Length of hospital stay§; median (Q1, Q3)	4.0 (3.0, 7.5)	3.0 (3.0, 6.0)	1.0 (0.0–2.0)	–	250
Institutional discharge incidence‖; n (%)	1 (2.3)	1 (2.4)	–	1.05 (0.01, 84.3)	>0.999
MMSE scores*; mean (SD)	24.0 (1.77)	24.5 (1.68)	-0.50 (-1.38–0.37)	–	.256
Incidence of mortality up to 3 months post-discharge‡; n(%)	1 (2.3)	0 (0.0)	–	0.02 (-0.05–0.09)	>.999
Sedation (indicated by POSS score of ≥3, at least once during in hospital follow-up)‡; n (%)	0 (0.0)	0 (0.0)	–	–	

CI = confidence interval, ICU = intensive care unit, MMSE = mini mental state examination, OR = odds ratio, POSS = Pasero Opioid-induced sedation scale, RCSQ = Richards–Campbell sleep questionnaire, SD = standard deviation.

* Based on *t*-test across time for each outcome.

† There was some small interaction effect for this measure and further post-hoc analysis showed that there was a significant difference in Awakenings between the two groups at observation day 7.

‡ Based on test of proportions due to small/zero counts.

§ Based on Wilcoxon–Mann–Whitney test.

‖ Based on Chi-square test.

Because of the limited treatment options for POD,[51] research is directed toward investigating strategies for its prevention and management. Traditionally, it has been suggested that regional anesthesia is protective; however, newer evidence refutes this observation.[16,52,53] Non-pharmacological interventions include patient and staff education, cognitive training[54] and multicomponent therapies.[55,56] Future studies of POD prevention interventions must ensure equipoise and balance throughout the study as differential use of such strategies might affect the incidence of POD and confound study results.

Our study has some important limitations. The study was terminated early for futility as we realized the need to make important changes to recruitment sites and strategy to achieve our pre-considered objectives and continuing for full recruitment was unlikely to provide additional information. As a feasibility trial, our study was underpowered to detect a difference in the incidence of POD between the melatonin and placebo groups. A relatively lower incidence of POD of 10% indicates the need to ensure the use of sensitive instruments and trained personnel to interview patients to detect episodes of delirium.

5. Conclusion

Perioperative melatonin administration has the potential to reduce the incidence of POD, and important changes to our study design and recruitment are needed to make a larger multisite trial feasible. Based on the overall incidence of POD and possible intervention effects, we would need a large definitive multicenter trial of >1000 patients, involving appropriate sites and susceptible surgical population. We will make suitable changes to our design to address these challenges in our main trial.

Author contributions

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