SYSTEMATIC REVIEW

Melatonin and Melatonin Agonists for Prevention of Delirium in the Cardiac Surgical ICU: A Meta-analysis

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Abstract

Aim and Background: Delirium is highly prevalent in the immediate postoperative period following cardiac surgery and adversely impacts outcomes. Melatonin has been increasingly used in pharmacological prevention of delirium. We aimed to synthesize the available evidence concerning the role of melatonin and melatonin agonists in preventing delirium in patients after cardiac surgery.

Materials and methods: PubMed, Google Scholar, and Web of Science databases were searched for relevant randomized and non-randomized trials in adults undergoing cardiac surgery investigating melatonin agonists to prevent delirium. Studies incorporating transplants, preoperative organ support, prophylactic antipsychotics, or children were excluded. Risk-of-bias was assessed using Cochrane ROB 2.0 and ROBINS-I tools. A systematic review and meta-analysis were conducted, calculating pooled odds ratio (OR) for the incidence of postoperative delirium using a random effects model with the Mantel–Haenszel method with restricted maximum-likelihood estimator. Trial sequential analysis was also carried out for the primary outcome.

Results: Six randomized trials and one non-randomized trial involving 1,179 patients were included. Incidence of delirium was 16.7 and 29.6% in the intervention and comparator groups respectively, indicating a pooled OR of 0.44 [95% confidence interval (CI) 0.27 – 0.71, $p = 0.04$] favoring melatonin. Two studies had a high risk of bias, and I^2 statistics indicated significant heterogeneity. However, publication bias was insignificant, and trial sequential analysis indicated the significance of the attained effect size.

Conclusion: Based on available studies, perioperative melatonin use significantly decreases postoperative incidence of delirium after adult cardiac surgery. However, the available quality of evidence is low, and larger trials with standardization of nonpharmacological delirium prevention interventions, in high-risk cohorts, and exploring various dosages and regimens should be carried out.

Keywords: Cardiac critical care, Melatonin, Postoperative delirium.

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Highlights

- The neurohormone melatonin, an important modulator of the circadian rhythm, has shown a promising role in the prevention and treatment of delirium in various groups of patients, including the elderly, the critically ill, and those undergoing major surgery.
- This meta-analysis showed significant evidence for melatonin in preventing delirium in the postcardiac surgical intensive care unit (ICU), but also identified knowledge gaps such as optimum dosing and efficacy in high-risk cases.

Introduction

Delirium is a dreaded complication after cardiac surgery. A varying incidence of delirium, ranging from 4–55% has been reported after cardiac surgery and has been linked to increased mortality, morbidity, and long-term neurocognitive dysfunctions.[1,2] Hence, effective prevention and management of postoperative delirium is important to avoid postoperative complications and prolonged intensive care stays, resulting in better outcomes.[3,4] Since most curative options for delirium have significant side effects, preventive strategies are an important focus of research.[5]

Melatonin is an endogenous hormone involved in managing the circadian rhythm and regulating sleep physiology, along with the strong antioxidant, anti-inflammatory, analgesic, and anti-apoptotic activity.[6] Circadian dysregulation is important in the pathogenesis of delirium, leading to interest in melatonin in the prevention of delirium.

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Although single studies like these provide useful information, they are limited by their sample size, local variation, etc., and may not be representative of the global effect of the intervention. In situations such as these, meta-analyses provide a broader picture by pooling the results from multiple similar studies, to try and provide a more robust estimate of the effect of the intervention: the effect size. A few recent meta-analyses have concluded that melatonin and its congeners may be useful in the prevention and management of intensive care unit (ICU) or postoperative delirium.[7–11] However, none of these meta-analyses have exclusively focused on postoperative delirium after cardiac surgeries or used validated psychiatric tools for the evaluation of delirium. Hence, this

meta-analysis attempted to evaluate the efficacy of prophylactic use of melatonin and its congeners in the prevention of delirium exclusively in adults undergoing cardiac surgery.

Materials and Methods

This meta-analysis was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and registered in the International Prospective Register of Systematic Reviews with the ID CRD42021185990.

Search Strategy

A thorough literature review was performed in PubMed, Google Scholar, and Web of Science databases with the following keywords: "melatonin" or "ramelteon"; "delirium" or "delirium" (MeSH) or "CAM" or "CAM-ICU"; "cardiac surgery" or "heart surgery" or "valve" or "CPB" or "coronary" or "cardiopulmonary bypass" or "OPCAB" or "off-pump" or "coronary artery bypass"; "trial" (All Fields) or "RCT" (All Fields) or "cohort" (All Fields) or "non-randomized" (All Fields) or "randomized" (All Fields) or "propensity" (All Fields, by a single investigator (SGN), on 30th August 2022. Abstracts and then full texts were independently screened by two mutually blinded investigators (CN and AS) to determine eligibility. Additional "snowballing" bibliography searches were conducted from the shortlisted studies. Disagreements, if any were settled by discussion among all investigators.

Treatment Definitions and Inclusion/Exclusion Criteria

We included studies involving adults more than or equal to 18 years of age, undergoing on-pump or off-pump cardiac surgery, with the use of melatonin or melatonin agonists such as ramelteon to prevent the occurrence of delirium. An intervention was defined as administration of at least one dose within 2 preoperative days to 3 postoperative days. The comparator was the usual institutional practice of sedation, anxiolysis, and analgesia (including opioids, benzodiazepines, and α-agonists). Studies involving transplants, preoperative extracorporeal or mechanical support, prophylactic antipsychotics, or children and adolescents aged less than 18 years were excluded.

We included randomized clinical trials comparing the above interventions and comparators, and reporting the incidence of delirium using a standardized and validated instrument. Non-randomized studies with a low risk of bias and fulfilling the above criteria were also included in the quantitative synthesis as advised by the Cochrane Handbook.[12] Case series, case reports, and review articles were excluded.

Outcomes

Incidence of delirium, assessed by a standardized and validated instrument was decided as the primary outcome. Influences of dose and time point of melatonin administration (on delirium) were the secondary outcomes. Subgroup analyses were planned for preoperative vs only postoperative use of melatonin and for on-pump vs off-pump surgeries.

Data Extraction and Quality Assessment

Each selected study was examined and the relevant parameters (study design and population, sample size, incidence of delirium, melatonin dosage and time points, etc.) were extracted. If incidence was reported at multiple time points, the largest incidence on any postoperative day in any group was considered.

Cochrane risk-of-bias tool for randomized trials (Cochrane ROB 2.0) and Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tools were used to assess for risk of bias, and results were expressed in a traffic light plot. All suitable studies were included, but a subgroup analysis of only low-risk-of-bias studies was planned as a sensitivity analysis.

Statistical Analysis

Data was analyzed in R 4.1.2, using *meta* and *robvis* packages. The primary outcome was assessed as odds ratio (OR) with 95% CIs. The Mantel–Haenszel method with a restricted maximum-likelihood estimator was used. The Q-profile method was used to calculate the CI of τ^2 and τ.

Synthesis of data in meta-analysis is not without its pitfalls—there may be heterogeneity or variation in outcomes between included studies. This may be addressed by mixed model synthesis, and also by leave-one-out analysis. As the name suggests, leave-one-out analysis checks if the exclusion of any one of the candidate studies alters the net direction, that is, positive or negative, of the pooled effect size. Here, between-study heterogeneity was estimated by I^2 statistic, with a value less than 0.25 (25%) denoting low and I^2 >0.5 (50%) denoting high heterogeneity. A random effects model was used in the presence of high heterogeneity. Heterogeneity was further explored by "leave-one-out" analysis.

There might also be publication bias because studies with positive results have a higher likelihood of getting published. This can be checked by the creation of a funnel plot, where asymmetry indicates an absence of negative studies from the literature.

In this study, publication bias was evaluated with a funnel plot. If it revealed significant asymmetry, the "Trim-and-Fill" method was used to test for the robustness of the pooled effect size as a sensitivity analysis.

Finally, a combination of false positive results of many small-sized studies in a meta-analysis may cause an overestimation of the effect size, since we only look at the pooled effect size and not whether the total sample size was adequate to report that effect size. Trial sequential analysis is a recently described method of cumulative meta-analysis, which weighs types I and II errors and can estimate when the effect size is large enough so that it is unlikely to be affected by any further studies on the topic. Thus, trial sequential analysis is a powerful tool to assess the conclusiveness of meta-analyses. In this study, trial sequential analysis was used to check if an adequate cumulative sample size was reached to obtain the pooled effect size. Two-sided O'Brien–Fleming alpha spending boundaries were created using a maximum type-I error risk of 5%. Requisite information size for a power of 95% was calculated based on relative risk (RR) reduction in the included studies, using model-variance-based heterogeneity correction. A cumulative *Z*-score crossing the alpha spending boundary indicated a significant result independent of multiple testing, whereas a cumulative sample size crossing the requisite information size indicated adequate power to report the requisite effect size.

Reporting of Quality of Evidence

Grading of recommendations, assessment, development, and evaluation (GRADE) system was used to assess the quality of the included studies and the parameters considered were risk-of-bias, between-study heterogeneity, indirectness, imprecision, and publication bias. The strength of recommendation was rated as high, moderate, low, or very low.

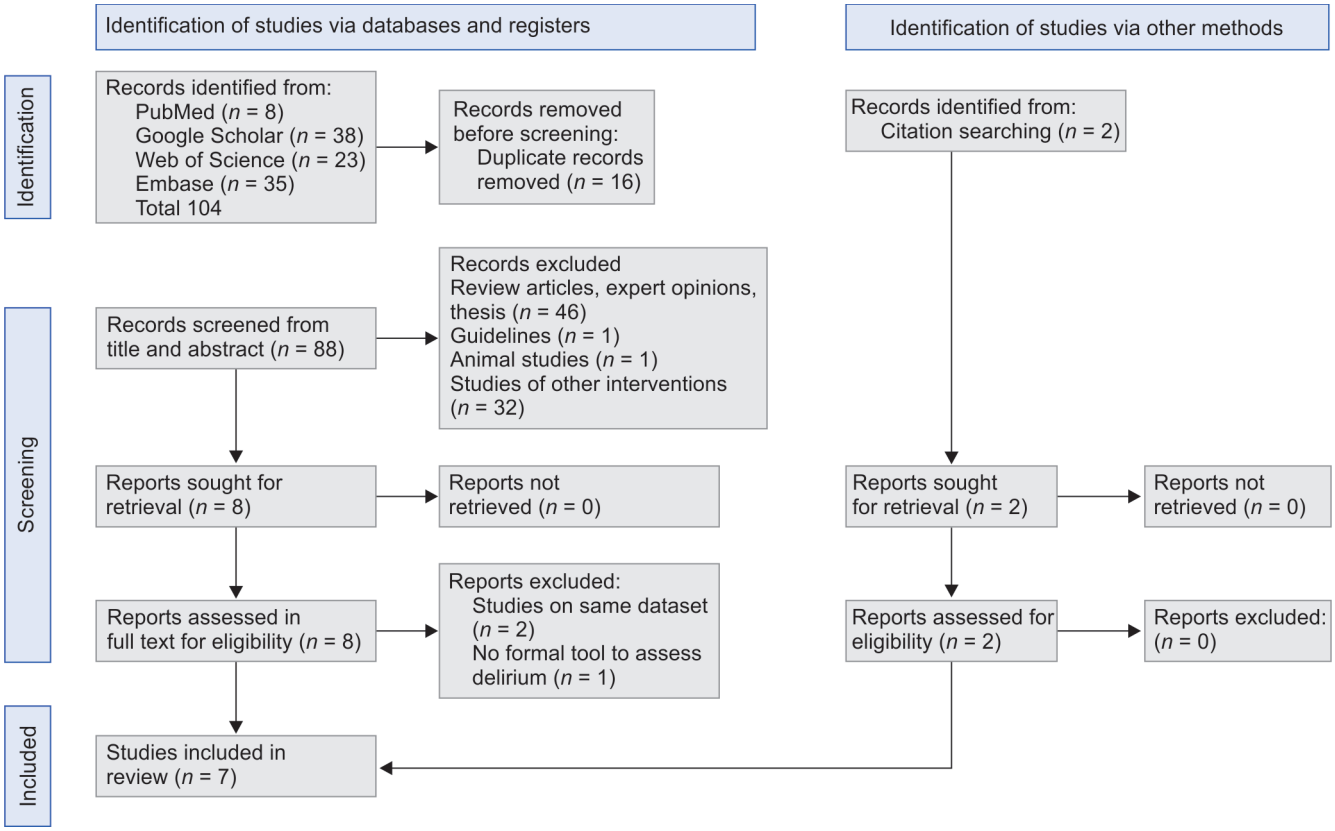

Fig. 1: The flow diagram for the included studies

Results

Search Results

Literature searches according to the decided strategy returned 104 articles, and after the exclusion of 16 duplicates 88 unique articles were taken for screening. After abstract and full text-based screening as outlined in Figure 1, five articles were selected. Another two articles were included based on bibliography searches from the selected articles (Fig. 1). The seven selected studies are described in Table 1.[13–19]

Characteristics of Included Studies

Melatonin in doses ranging from 3 to 5 mg/day was used in 6 of the included studies.[13,15–19] One study used ramelteon, a melatonin receptor agonist, at 8 mg/day.[14] One study was observational and the others were placebo-controlled trials. Most studies involved patients undergoing coronary artery bypass grafts. Two studies also included other adult cardiac surgeries like valve replacements.[13,15] One study included patients undergoing pulmonary thrombo-endarterectomies.[14] Only one study included patients undergoing off-pump surgeries.[13]

A range of benzodiazepines including oxazepam and midazolam was used for premedication in three studies, whereas it was not specified in others.[13,17,19] Postoperative analgesia was achieved with morphine, fentanyl, tramadol, pitofenone, etc., and patients were usually sedated with propofol or dexmedetomidine. However, ICU management protocols, including nonpharmacological interventions were not described in any study.

A total of 1,179 patients were included across the studies, with 587 receiving the intervention and 592 in the comparator group. Geriatric patients predominated, with mean ages in most of the cohorts above 60 years. Most studies used the confusion assessment method (CAM) or confusion assessment method for the intensive care unit (CAM-ICU) to assess delirium. Incidence of delirium was 16.7% (98/587) in the intervention group and 29.6% (175/592) in the comparator group, varying between 8.0 and 35.7% in the intervention group and 20.2 and 68.6% in the comparator group.

Assessment of Risk of Bias

Both Cochrane ROB 2.0 and ROBINS-I tools were used to assess the risk of bias for randomized and non-randomized studies (Supplementary Fig. 1). One of the randomized studies were judged to have a high risk of bias, which was predominantly in the selection of reported result and measurement of outcome.[17] The single non-randomized study included had a low overall risk of bias, and hence was included in the quantitative synthesis.[13]

Quantitative Synthesis

The OR of developing delirium varied from 0.22 to 1.08 across the studies. A random effect meta-analytic method was used to synthesize the evidence. The I^2 statistic of 54% indicated significant heterogeneity among the studies. The synthesized model indicated a pooled OR of 0.44 (95% CI: 0.27–0.71, $p = 0.04$, $I^2 = 54\%$) favoring the intervention group (Fig. 2). Assuming a 34% population incidence of delirium (i.e., the mean incidence in comparator cohorts of included studies), this implies that the number-needed-to-treat (NNT) to prevent one case of delirium with melatonin or ramelteon would be 6.4 (95% CI: 4.6–13.7).

A subgroup analysis of only the low risk-of-bias studies revealed a pooled OR of 0.47 (95% CI: 0.24–0.94, $p = 0.02$, $I^2 = 65\%$),

Table 1: Characteristics of included studies

Article	*Type of study*	*Study population*	*Intervention and control (time of intervention)*	*Premedication and anxiolysis*	*Postoperative sedation and analgesia*	*Incidence of delirium and sample size in each group*	*Mean age in each group*	*Delirium assessment tool*	*ROB 2.0*
Artemiou et al.[13]	Single-center prospective observational (non-randomized) study	Elective cardiac surgeries Included off-pump cases (32/250 in control and 24/250 in intervention groups)	Melatonin, prolonged-release tablet, 5 mg vs no control From preoperative evening, once daily at night, to POD 3	Oxazepam tablet, 10 mg, evening before surgery, intravenous midazolam before surgery	Propofol infusion, Morphine infusion, metamizole, pitofenone, fenpiverinium, tramadol	52/250 in control; 21/250 in intervention	65.2 ± 10.3 years in control; 64.3 ± 10.1 years in intervention	CAM-ICU	Low
Sharaf et al.[16]	Single-center prospective, double-blinded randomized, placebo-controlled trial	Elective on-pump coronary artery bypass graft surgeries	Melatonin tablet, 3 mg vs placebo From preoperative night, 30-minute preoperatively, once daily at night, from extubation to POD 3	–	–	7/25 in control; 2/25 in intervention	67.8 8 ± 4.13 years in control; 66.56 ± 4.79 years in intervention	ICDSC	Low
Kasnavieh et al.[18]	Single-center prospective, double-blinded randomized, placebo-controlled trial	Elective off-pump coronary artery bypass graft surgeries	Melatonin tablet, 3 mg vs placebo Once daily at night from 3 days preoperatively, till POD 3	–	–	48/70 in control; 25/70 in intervention	64.5 years in control; 64.03 years in Intervention	CAM-ICU	Low
Jaiswal et al.[14]	Single-center prospective, double-blinded randomized, placebo-controlled trial	Elective on-pump pulmonary throm-boendarterectomies	Ramelteon tablet, 8 mg vs placebo Once daily at night, from preoperative night till 6 days	–	Propofol infusion Intravenous fentanyl	22 of 58 in control; 19 of 59 in intervention	56.1 ± 15.8 years in control; 58.1 ± 14.1 years in Intervention	CAM-ICU	Low
Ford et al.[15]	Multicentre prospective, double-blinded randomized, placebo-controlled trial	Elective coronary artery bypass grafting or valve replacement surgeries	Melatonin tablet, 3 mg vs placebo Once daily at night, from 2 days preoperatively till 7 days	–	–	21/104, in control; 21/98 in intervention	67.6 ± 8 years in control; 69 ± 8.3 years in intervention	CAM	Low
Mahrose et al.[17]	Single-center prospective, double-blinded randomized, placebo-controlled trial	Elective on-pump coronary artery bypass graft surgeries	Melatonin tablet, 5 mg vs placebo Once daily at night, from preoperative night to POD 3	Intravenous midazolam	Infusion dexmedetomidine at 0.2–0.7 µg/kg/hr following 0.4 µg/kg bolus	15/55 in control; 6/55 in intervention	66.1 ± 6.3 years in control; 67.0 ± 6.7 years in intervention	CAM-ICU, CAM	High
Zadeh et al.[19]	Single-center prospective, double-blinded randomized, placebo-controlled trial	Elective on-pump coronary artery bypass graft surgeries	Melatonin prolonged-release tablet, 3 mg vs placebo Preoperative night, and on morning of surgery. Once daily at night, till POD 2	Intravenous midazolam at 0.1–0.2 mg/kg Intravenous sufentanil at 0.5–1 µg/kg	Infusion propofol at 0.5 mg/kg/hr and infusion dexmedetomidine at 0.3 µg/kg/hr Infusion morphine 2 mg/hr	14/30in control; 4/30 in intervention	62.9 ± 8.08 years in control; 60.26 ± 9.50 years in intervention	CAM-ICU	Low

CAM, confusion assessment method; CAM-ICU, confusion assessment method for intensive care unit; ICDSC, intensive care delirium screening checklist; POD, postoperative day; ROB, risk of bias

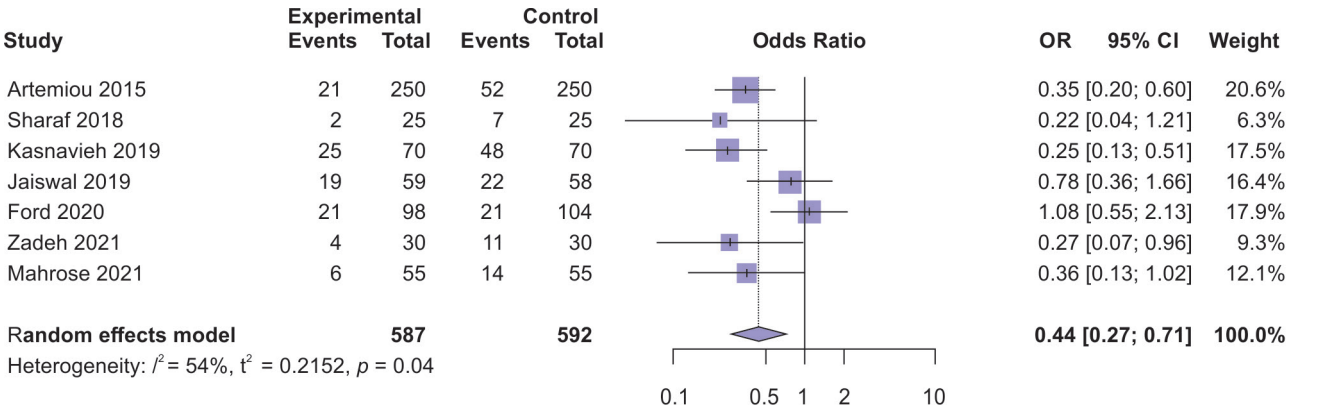

Fig. 2: Forest plot of pooled delirium incidence

similarly favoring the intervention group, but with a wider CI (Supplementary Fig. 2).

"Leave-one-out" analysis and Baujat's plot (Supplementary Figs 3 and 4) indicated that the studies by Ford et al., Kasnavieh et al., and Jaiswal et al. contributed the most to heterogeneity.

The funnel plot revealed some asymmetry (Supplementary Fig. 5A), but sensitivity analysis by trim-and-fill method (Supplementary Fig. 5B) showed a corrected OR of 0.46 (95% CI: 0.29–0.72, $p = 0.0007$, $I^2 = 50\%$), indicating insignificant publication bias (Supplementary Fig. 5C).

Trial Sequential Analysis

The required information size was calculated to be a sample size of 1,465 for a power of 95% based on the observed RR reduction (43.54%) across the included studies. Hence only 80.4% (1179/1465) of the required information size has been achieved by the included studies. The cumulative *Z*-score, however, crossed the alpha-spending boundary and did not dip below the inner wedge of futility, indicating a significant attained effect size (Fig. 3).

Influence of Dose of Melatonin

Subgroup analysis based on the administered dose of the drugs indicated a pooled OR of 0.40 (95% CI: 0.16–0.98) based on 4 studies for a dose of 3 mg of melatonin (Supplementary Fig. 6). Pooled OR was 0.35 (95% CI: 0.22–0.57) for 5 mg of melatonin based on 2 studies. Only one study administered ramelteon at 8 mg, giving an OR of 0.78 (95% CI: 0.36–1.66) for the incidence of delirium. Between-group differences, however, were not statistically significant ($p = 0.22$), likely due to the small number of studies included.

Other Subgroup Analyses

All studies administered melatonin or ramelteon from the preoperative period, and only one study incorporated patients undergoing off-pump surgeries. Hence subgroup analyses for this weren't done as planned.

Quality of Evidence

The overall level of evidence was graded as low due to the observed risk of bias and heterogeneity.

Discussion

This meta-analysis examined the effect of perioperative administration of melatonin on the incidence of delirium following adult cardiac surgery. The meta-analysis included 7 studies that enrolled 1,179 patients. Incidence of delirium ranged 20.2–68.6% across the control population. This is similar to the reported incidence of 4.1–54.9% in a recent metaanalysis.[2]

Delirium in the postcardiac surgery cohort is multifactorial. This includes pre-operative frailty, depression, poor neurocognitive reserve, alcohol abuse, poor glycemic control, intraoperative and postoperative hemodynamic alterations, volatile anesthetics, opioids and sedative medications, and postoperative pain as in other cohorts. Additional unique exposures in this cohort include extracorporeal circulation and the resulting hyperinflammatory state, embolic insults, and possible malperfusion.[20] The postcardiac surgery ICU combines all this with stress, sensory deprivation, and constant light or noise. The resultant dysregulation of sleep architecture and circadian rhythm is thought to be an important link in the pathophysiology of delirium.[21,22]

The addition of melatonin to the usual care in the studies included in this meta-analysis led to a reduction in the incidence of delirium (Fig. 3). Melatonin is a neurotransmitter secreted from the pineal gland. It acts on the suprachiasmatic nucleus to regulate and synchronize the circadian sleep–wake cycle. It is a potent hypnotic for sleep onset and a potent free radical scavenger and antioxidant with anti-inflammatory and immunosuppressive actions.[23] These are hypothesized to be behind the cardioprotective action of melatonin found in various studies. Melatonin also attenuates ischemia-reperfusion injury and age-related pathology.[24] Hence, possible action at multiple links in the pathophysiology of intensive-care-associated delirium, combined with a favorable side-effect profile makes melatonin an attractive agent for the prevention of delirium in intensive-care patients.[25]

Past meta-analyses investigating melatonin and its analogs in various cohorts have shown mixed results in the prevention of delirium. A 2019 meta-analysis by Zhang et al., including predominantly medical critically ill patients demonstrated a reduction in delirium incidence (pooled risk ratio = 0.49; 95% CI: 0.2–0.88, $p = 0.017$) and duration of ICU stay (pooled weighted mean difference (WMD) = −0.32; 95% CI: From −0.56 to −0.07, $p = 0.002$) with addition of melatonin.[10] Another review by Han et al., in a mixed cohort of postoperative patients again demonstrated a benefit (pooled OR = 0.45, 95% CI: 0.24–0.84, $p = 0.01$); though the results did not reach significance in the cardiac surgical subgroup (OR = 0.50, 95% CI: 0.24–1.01, $p = 0.05$).[8] Khaing and Nair analyzed the role of melatonin across hospitalized patients and found it to reduce delirium incidence in surgical and critically ill but not in medical patients.[9] However, the most

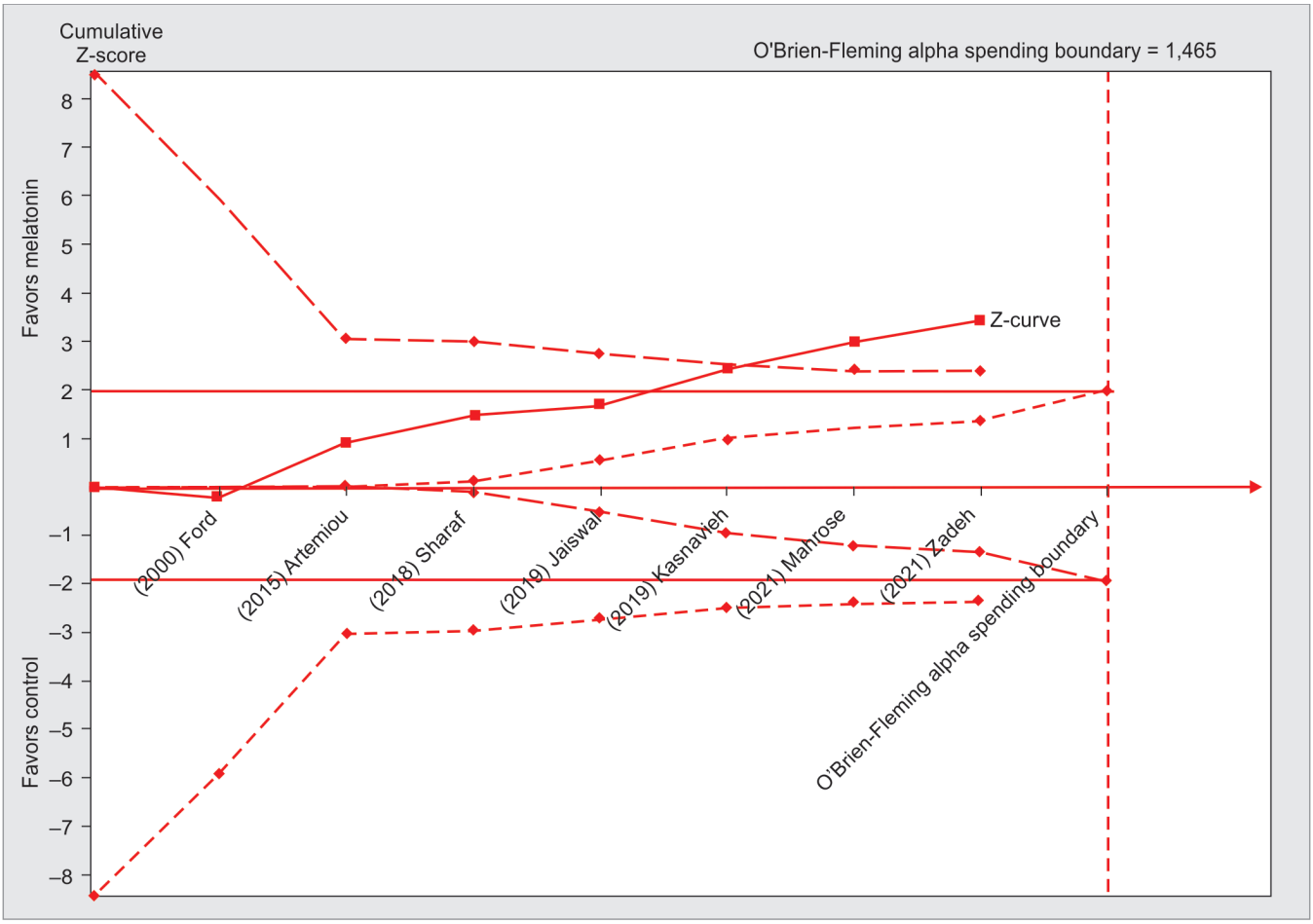

Fig. 3: Trial sequential analysis plot for delirium incidence. The cumulative Z-curve, indicated by the solid line crosses the alpha-spending boundary (large dashed line) and doesn't enter the inner wedge of futility (small dashed line)

recent meta-analysis in surgical patients found no decrease in the incidence of delirium with melatonin and melatonin analogs (RR 0.93, 95% CI: 0.70—1.24).[7] The postcardiac surgical cohort has a high incidence of delirium, together with unique risk factors that make it susceptible to delirium. A recent meta-analysis has also attempted to evaluate delirium after cardiac interventions but included patients undergoing percutaneous coronary intervention, a cohort with a distinctly different risk profile for delirium.[26] The current meta-analysis is the largest synthesis of evidence exclusively in cardiac surgical patients evaluated using validated instruments for delirium, and the demonstrated benefit, low NNT and significant trial sequential analysis in this analysis strengthens the case for using melatonin for prevention of delirium after cardiac surgery.

The current meta-analysis, found high heterogeneity among the included studies. However, the leave-one-out analysis showed that the removal of none of the major studies altered the net direction of the pooled treatment effect, that is, melatonin reduced the incidence of delirium.[14,15,18] Trim-and-fill analysis showed that correction for publication bias, too did not significantly alter the pooled results.

Both CAM-ICU and intensive care delirium screening checklist (ICDSC), which were used in the included studies, have shown excellent sensitivity and specificity (0.80 and 0.96; 0.74 and 0.82, respectively) in a past meta-analysis.[27] The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) classifies delirium as hyperactive, hypoactive and mixed. The hypoactive phenotype is most prevalent after cardiac surgery and is easily missed.[28] Even CAM-ICU and ICDSC report lower sensitivity for hypoactive delirium.[29] Hence studies depending on non-formal assessment and nursing records were excluded from this meta-analysis, unlike previous analyses. Even so, this is a possible limitation in the assessment of the outcomes that can be a source of heterogeneity.

The following limitations of the literature must be kept in mind while interpreting the results of this meta-analysis. Multiple doses of melatonin or ramelteon have been used across the studies. Very few studies in each subgroup precluded exploration of the optimum dose. This is a possible source of confusion. Similarly, the optimum timing of administration of melatonin could not be explored from the available evidence.

Melatonin is not FDA-regulated in the USA, and marketed as a dietary supplement, unlike its congeners, ramelteon and tasimelteon.[30] More importantly, nonpharmacological strategies such as family visits, reorientation cues, dynamic lighting, or bundled interventions like the ABCDEF or MORE protocols, etc. have often proven as beneficial as pharmacological strategies in the prevention of delirium.[31] However, none of the included articles detailed the intensive care protocols and bundles followed, if any. It is conceivable that the observed heterogeneity in incidence and benefit across included studies may be a result

of the local ICU practices. This represents a serious limitation of this synthesis. We recommend standardization and reporting of the nonpharmacological interventions employed in future trials on delirium.

The included studies predominantly concentrated on coronary artery bypass grafting. Studies in surgeries with longer cardiopulmonary bypass, a greater possibility of hemodynamic compromise, and longer expected ICU stay such as multivalvular interventions, aortic, redo, and congenital surgeries, or in high-risk cohorts such as the elderly, patients with significant atherosclerosis, medical or psychiatric comorbidities merit specific evaluation. It should also be noted that though a significant effect size for efficacy was attained in trial sequential analysis, the required information size was not attained. Moreover, the effect size was also attained with the inclusion of high risk-of-bias study along with a non-randomized one. This underscores the necessity of more high-quality randomized studies in this area.

Conclusion

In conclusion, based on a low level of evidence, the present meta-analysis suggests that perioperative use of melatonin significantly decreases the incidence of delirium in patients following cardiac surgery. Hence, melatonin should be considered as a substitute for the often-used benzodiazepines for sleep during the perioperative period. Future trials in larger cohorts of high-risk patients, with optimum dosing and standardized nonpharmacological interventions are required to further inform and optimize clinical practice.

Supplementary Materials

The supplementary figures are available online on the website of www.ijccm.org

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