BMJ Open

Melatonin for the prevention of postoperative delirium in older adults: a protocol for a systematic review and meta-analysis

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To cite: Sewart E, Barnes J, Armstrong RA, *et al*. Melatonin for the prevention of postoperative delirium in older adults: a protocol for a systematic review and meta-analysis. *BMJ Open* 2022;**12**:e063405. doi:10.1136/bmjopen-2022-063405

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-063405).

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Received 03 April 2022
Accepted 31 August 2022

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ABSTRACT

Introduction Postoperative delirium (POD) is a major cause of morbidity, particularly in elderly patients. Melatonin has been suggested as a low-risk pharmacological intervention to help prevent POD. A previous systematic review found limited high-quality evidence to support the use of melatonin in the prevention of POD. Several further randomised studies have since been published. This systematic review aims to synthesise the evidence from randomised controlled trials (RCTs) examining the effect of melatonin on the prevention of POD in older adults.

Methods and analysis A systematic search of RCTs of melatonin (any dose and formulation) in POD will be run across Embase, Medline, CINAHL and PsychInfo. RCTs published from January 1990 until the end of February 2022 and reporting outcomes for melatonin use to prevent POD in patients will be included. Screening of search results and data extraction from included articles will be performed by two independent reviewers. The primary outcome will be incidence of POD in older adults undergoing surgery. Secondary outcomes are delirium duration and length of hospital stay. The review will also describe the dosage, timing and administration regimes of melatonin therapy and as well as the scales and definitions used to describe POD. A registry review of ongoing trials will be also be performed. For the meta-analysis, data will be pooled using a random effects model to generate a forest plot and obtain an odds ratio (OR) for the incidence of POD. Results will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Ethics and dissemination No ethical approval is required. This review will be disseminated via peer-reviewed manuscript and conferences. The results will be used as the basis of work to optimise this intervention for future trials in surgical populations.

PROSPERO registration number This review is registered with PROSPERO (CRD42021285019).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will be an up-to-date assessment of the effectiveness of melatonin in the prevention of postoperative delirium.
⇒ The study will be based on a comprehensive search strategy, including published and unpublished trials.
⇒ The review will provide additional information to previous systematic reviews including a methodological review (dose, timing and administration regime).
⇒ Language restriction to English may exclude additional studies published in other languages.

INTRODUCTION

Rationale

Postoperative delirium (POD) is an acute and fluctuating disturbance in attention, awareness and cognition not explained by another neurocognitive disorder[1] that occurs in the postoperative period, up to 1 week postprocedure or before discharge, whichever occurs first.[2] It develops most commonly between 1 and 3 days after surgery.[3] Although often multifactorial in aetiology, triggers that may precipitate POD include pain, blood loss, polypharmacy, sedative drugs and major surgery.[4–8] POD is a common postoperative complication, seen in 17%–61% of patients undergoing surgery.[9–11]

POD incurs major health and socioeconomic burdens. It is associated with increased length of hospital stay, higher rates of ongoing cognitive impairment, increased care needs and increased mortality.[12–14] It is thought that around 30%–40% of cases are preventable,[15 16] and strategies to prevent POD have been highlighted as an important priority for healthcare systems.[17] Many interventions examined so far have failed to yield an effect on clinical outcomes.[18–20]

Melatonin is a hormone produced by the pineal gland, known to play an important role in circadian rhythm regulation.[21] It has therapeutic uses including treatment of sleep–wake disorders[22] and jet lag[23] and has been implicated as playing a role in several disorders of the mind including schizophrenia,

depression and POD.[24–26] Melatonin has emerged as an attractive candidate as an agent for the prevention of POD given its low cost and potentially benign side effect profile. A 2017 systematic review of six studies examining the use of melatonin and its agonists in the prevention of POD in older adults found some evidence to suggest a beneficial effect.[27] However, these studies were mostly small, heterogeneous in their methodology and demonstrated conflicting results. Several further randomised controlled trials have since been published.

This protocol outlines an updated systematic review and meta-analysis of the evidence for the use of melatonin in prevention of POD in older adults. It will be reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement.[28]

Aim

The aim of this systematic review is to assess the impact of melatonin on the incidence and duration of POD as well as the length of hospital stay in older adults.

Specific objectives

1. Identify the surgical populations in which randomised controlled trials (RCTs) have been performed comparing the impact of melatonin on the incidence and duration of POD in older adults.
2. Describe the exact dosage regimes, including timing and duration of melatonin therapy used in these RCTs.
3. Describe which scales and definitions were used to assess POD.

METHODS

This protocol was developed using the statement and checklist of PRISMA-P. This review will include a review of methodologies from randomised controlled trials and a meta-analysis of results.

Information sources and search strategy

This review will be an update of the review by Campbell *et al* in 2019.[27] The search strategy (online supplemental appendix 1) has therefore been developed based on a repeat of the previous search, with support from an experienced academic librarian. The search will be run across Embase, Medline, CINAHL and PsychInfo. Studies published between 1 January 1990 and 28 February 2022 and written in English will be included. No limits will be placed on the country of study. A registry review of ongoing trials will also be performed.

Study selection, inclusion and exclusion criteria

RCTs studying melatonin or melatonin receptor agonists for the prevention of POD will be included. Studies in paediatric patients will be excluded. Cohort, case–control and other non-randomised studies will be excluded.

No restrictions will be placed on the programme of drug administration, including timing, dose and additional treatments used. Studies of melatonin and melatonin receptor agonists, including ramelteon, tasimelteon and agomelatine, will be included. Studies not reporting outcomes related to POD will be excluded. If multiple publications report results from the same study, these will be treated as a single unit for the purpose of analysis.

Study records

Data management

Citation management and data collection will be undertaken in Covidence (Covidence, Melbourne, Australia).[29]

Selection process

Title and then abstracts from all citations identified in the searches will be screened independently for eligibility by two reviewers (JB and RM). Full text screening (JB/RM) will follow, with any disagreements resolved by a third reviewer (BG) if necessary.

Data collection process

Data will be extracted by two reviewers (JB/ES) on to a standard data extraction form. Any discrepancies or disagreements in data extraction will be resolved by a third reviewer (RM) if necessary.

Data items

Data to be extracted will include:

1. Publication details: authors, year of study conduct/publication and country where study was carried out.
2. Participant demographics: sex, age, number, inclusion/exclusions and surgery type.
3. Intervention details: drugs used, dose, timings and details of control interventions.
4. Criteria/scales used for diagnosing and grading POD.

The primary outcome of this systematic review is the incidence of POD in older adults undergoing surgery. The secondary outcomes are: the duration of delirium and length of postoperative hospital stay.

Risk of bias

Risk of bias at the study level will be assessed using the Cochrane risk of bias tool version 2.[30] We will assess bias in the following domains:

1. Risk of bias arising from the randomisation process.
2. Risk of bias due to deviations from the intended interventions (effects of assignment to intervention and effect of adhering to intervention).
3. Risk of bias due to missing outcome data.
4. Risk of bias in measurement of the outcome.
5. Risk of bias in selection of the reported result.

Trial quality and overall risk of bias (low risk, high risk and some concern) will be determined for each study.

Data analysis

A PRISMA flow chart of search and study selection will be reported, and excluded studies will be presented, including reasons for study exclusion. Extracted study data will be presented in tables.

A narrative description of the included studies will be provided. This will include tables summarising study

details, including trial design, participant characteristics and reported outcome measures. This will allow comparison of methodology and outcome reporting between different studies. Secondary outcome measures will be tabulated, and a narrative description will be provided.

Meta-analysis of the primary outcome will be undertaken using Stata (StataCorp LLC, Texas, USA). The incidence of POD will be summarised using ORs (with associated 95% CIs) for individual studies and combined using random effect meta-analysis. If sufficient studies report the secondary outcomes of delirium duration and postoperative length of stay, data will be summarised using mean differences (with associated 95% CIs) for individual studies and by fixed effects meta-analysis. If sufficient data are available, subgroup analysis of studies reporting on cardiac and non-cardiac surgery will be performed. Forest plots will be produced.

Assessment of heterogeneity

Between-study heterogeneity will be assessed using the I^2 statistic, and random-effects estimates will be presented if significant heterogeneity is present. A funnel plot will be used to assess publication bias, and an influence analysis will be performed by the leave-one-out method. Sensitivity analyses will be undertaken where issues are identified during the review process. Potential analyses include participant characteristics (eg, varying the lower age limit) and characteristics of comparators (eg, placebo or usual care).

Patient and public involvement

There was no patient and public involvement in the development of this research question or study design. No patients or public members are required to complete this systematic review.

Contributors JB and ES are joint first authors, and RM and BG are joint final authors. All authors have contributed fully to the concept and design of the review for which this protocol has been written. JB, ES, BG and RM wrote and reviewed the manuscript before submission. RA supervised the meta-analysis. MP, RA and RH reviewed and edited the manuscript before submission. RM is the guarantor of the review.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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Search Strategy

[melatonin(MH) OR ramelteon(TW) OR rozerem(TW) OR "melatonin agonist*"(TW) OR "N-Acetyl-5-methoxytryptamine"(TW) OR melatonin*(TW) OR Melatoniin*(TW) OR circadin(TW) OR "HT 903"(TW) OR melapure(TW) OR armonia(TW) OR melamil(TW) OR benedorm(TW) OR "BP 2013"(TW) OR BP2013 OR JL5DK93RCL(TW)]

AND

[delirium(MH) OR "emergence delirium"(MH), OR delirium(TW) OR "perioperative delirium"(TW) OR "postoperative delirium"(TW) OR "organic brain syndrome"(TW) OR "acute confusion"(TW)]

Dates: 1st January 1990 – 28th February 2022

Other limits: Nil