服用褪黑激素是否能降低術後老年人譫妄發生率？

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112.02.21

大綱

- 前言
- 譫妄的簡介、評估及現行措施
- 文獻評讀(FAITH)
- 問題與討論

前言

老年人本身就是譫妄好發的族群，特別手術後要面對陌生環境、疼痛、睡眠、噪音、心理等問題，譫妄的發生除了會影響病人的生命徵象、病情恢復，另外，也會增加家屬的擔憂及護理師負擔。

台灣人口結構老化問題一直存在，今後面臨手術的老年人勢必只會增加不會減少，除了譫妄發生後給予相關藥物或是約束，發生前，常規監測及使用非藥物方式預防以外，也想知道是否有其他預防的方法。

譫妄的簡介、評估及現行措施

譫妄的簡介

- 國內病人譫妄好發於加護病房及內科病房，成人加護病房譫妄發生率為40-76%，甚至高達80%。
- 譫妄為急性發作的認知混亂症候群，症狀可持續幾小時到數天，通常不超過5天。
- 急性認知障礙可能原因為神經傳遞物質失衡、炎症介質反應增加或氧化代謝受損，導致網狀激活統遭破壞，目前病理生理文獻顯示沒有明確的單一病因，皆為多層因素交互影響的結果。
- 譫妄病人的注意力明顯降低，思考過程混亂，大多為可逆性。

表 4、ICU 譫妄評估表 The Confusion Assessment method for the ICU (CAM-ICU)

[不適用於RASS -4～-5的病人]

請記得協助病人戴上眼鏡或助聽器 (如果平常常規使用的話)

特徵 1: 精神狀態改變的急性發作或變動的進程

有無任何從基本精神狀態的急性改變?

或

在過去 24 小時中病患變動的精神狀態是否有鎮靜指數 (RASS)、昏迷指數 (GCS)、或CAM-ICU變化為變動的依據?

NO → CAM-ICU Negative 沒有譫妄

YES ↓

特徵 2: 注意力不集中

用注意力篩檢測驗評估注意力---數字 (聽力) 或圖片 (視覺)

注意力篩檢測驗數字: 隨機數字 "1"測試

若病患可以握手: 對病患說, "我要對你讀一個十個數字的序列, 無論何時你聽到數字"1", 就握住我的手"。用正常的音調且每個數字間隔3 秒鐘, 從以下的數字序列中讀出數字。

8 1 7 5 4 1 1 3 6

當病患沒有在 "1" 時握住手或當病患在不是 "1"握住手時, 都算是錯誤。

注意力篩檢測驗圖片: 視覺/ 圖片認知

適用於病患無法握手的情況; 指引與分數置於圖片盒內。

0-2 錯誤 → CAM-ICU Negative 沒有譫妄

>2 錯誤 ↓

特徵 3: 意識程度改變

評估病人的RASS

RASS不為"0" → CAM-ICU Positive 有譫妄

RASS 為0 ↓

特徵 4: 沒有組織的思考

1. 是/否問題: 一次只用一組問題, 可用 A或 B組, 若需要連續天數時可交替使用. 若病患無法言語, 則請它們點頭/搖頭表示意見.

A組	B組
1. 石頭會浮在水面上嗎?	1.葉子會浮在水面上嗎?
2. 海裡會有魚嗎?	2.海裡會有大象嗎?
3. 一公斤是否比兩公斤重?	3.兩公斤是否比一公斤重?
4. 你可以用鐵錘釘釘子嗎?	4.你可以用鐵錘砍木頭嗎?

計分:每當病人回答錯了一個問題, 則計為錯誤一次。

如果綜合 (問題 + 命令) 錯誤數>1 → CAM-ICU Positive 有譫妄

2. 對病人下指令: 對病患說:

第一步: "舉出這麼多隻手指" (檢查者在病患面前舉出兩隻手指)

第二步: "現在用另一隻手做一樣的事" (不要用手示範, 也不要說出手指數目)。如果病患只能移動一側的手, 則在第二步時請病人 "再加上一隻手指"

計分: 若病人無法完成整個指令, 則計為錯誤一次。

如果綜合 (問題 + 命令) 錯誤數 0-1 → CAM-ICU Negative 沒有譫妄

現行護理措施

- 譫妄預防措施：
  - 常規監測CAM-ICU、適時給予定向感、調節燈光、鼓勵使用眼罩或耳塞、給予適當的止痛、家人陪伴(疫情前)。

- 譫妄護理措施：
  - 使用鎮靜藥物、物理性約束、家人陪伴(疫情前)。

文獻評讀(FAITH)

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RESEARCH ARTICLE Open Access

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

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Appraisal sheets(FAITH)

- Appraisal Tool

[統合分析 Meta-analysis]

- **步驟 1：研究探討的問題為何 (PICO)**
- 步驟 2：研究的品質如何 (內在效度)
- 步驟 3：研究結果之意義為何 (效益)

步驟 1:系統性文獻回顧探討的問題為何？

Abstract

Background: Older surgical patients are at high risk of developing postoperative delirium. Non-pharmacological strategies are recommended for delirium prevention, but no pharmacological agents have compelling evidence to decrease the incidence of delirium. The purpose of this study was to assess whether perioperative melatonin decreases the incidence of delirium in older adults undergoing surgical procedures.

Methods: A systematic search using PubMed/Medline, Embase, PsycINFO, CINAHL, and references of identified articles published in English between January 1990 and October 2017 was performed. Two independent reviewers screened titles and abstracts, and then extracted data following a full-text review of included articles with consensus generation and bias assessment. Studies reporting outcomes for melatonin or ramelteon use to prevent delirium in postoperative hospitalized patients (mean age ≥ 50 years) were eligible for inclusion. Data were pooled using a fixed-effects model to generate a forest plot and obtain a summary odds ratio for the outcome of interest (delirium incidence). Cochran's Q and I^2 values were used to investigate heterogeneity.

Results: Of 335 records screened, 6 studies were selected for the qualitative analysis and 6 were included in the meta-analysis ($n = 1155$). The mean age of patients in included studies ranged from 59 to 84 years. Patients in intervention groups typically received melatonin or ramelteon at daily doses of two to eight milligrams around cardiothoracic, orthopedic, or hepatic surgeries for one to nine days, starting on the evening before or the day of surgery. The incidence of delirium ranged from 0 to 30% in the intervention groups versus 4–33% in the comparator groups, and was significantly reduced in the melatonin group, with a summary effect of the meta-analysis yielding an odds ratio of 0.63 (95% CI 0.46 to 0.87; 0.006; $I^2 = 72.1\%$). A one study removed analysis reduced overall odds ratio to 0.310 (95% CI 0.19 to 0.50), while reducing heterogeneity (Cochran's $Q = 0.798$, $I^2 = 0.000$).

Conclusion: Perioperative melatonin reduced the incidence of delirium in older adults in the included studies. While optimal dosing remains an unanswered question, the potential benefit of melatonin and melatonin receptor agonists may make them a reasonable option to use for delirium prevention in older adults undergoing surgical procedures.

- Population
- Comparison
- Outcomes
- Intervention

PICO

- **Population**：old surgical patient
- **Intervention**：melatonin administration
- **Comparison**：no melatonin administration
- **Outcome**：incidence of delirium

Appraisal sheets(FAITH)

- Appraisal Tool
  - 步驟 1：研究探討的問題為何 (PICO)
  - **步驟 2：研究的品質如何 (內在效度)**
  - 步驟 3：研究結果之意義為何 (效益)

F - 研究是否找到所有的相關證據？

P2

Methods

Search strategy

An experienced health sciences librarian developed a comprehensive search strategy with clinical input from the lead authors. An electronic search was systematically conducted in four bibliographic databases: PubMed/Medline (NLM); Embase (Elsevier); PsycINFO (Ebsco); and CINAHL (Ebsco) in November 2017. In addition, the reference lists of obtained articles and relevant systematic reviews were screened, and searches in pertinent websites were conducted to identify further studies that reported melatonin use perioperatively in hospitalized adults from January 1990 to October 2017. This timeframe was selected to coincide with the development of the Beers Criteria, which was initially published in 1991 and categorized potentially inappropriate medications for older adults, including agents that may cause or exacerbate delirium [25]. A combination of controlled vocabulary and keywords were used to search the databases. To identify delirium, terms such as emergence delirium, perioperative delirium, postoperative delirium, organic brain syndrome, and acute confusion were used; while synonymous terms for melatonin such as ramelteon, melatonin receptor agonist, etc. were used to make the search as comprehensive as possible. The search strategy for NLM, which was used to develop search strategies for subsequent databases, is summarized in Fig. 1. The protocol for this study has not been previously published.

- ✅使用兩個主要資料庫。
- ✅文獻搜尋同時使用MeSH字串及一般檢索詞彙。

(melatonin[MH] OR Ramelteon[TW] OR Rozerem[TW] OR "melatonin agonist*"[TW] OR "N-Acetyl-5-methoxytryptamine"[TW] OR Melatoniin*[TW] OR Melatonin*[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[TW] 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: January 1, 1990 – October 31, 2017 Other limits on search: None
The search method for PubMed/MEDLINE was used to develop search strategies for all of the subsequent databases.

Study selection

All identified studies were title screened to identify studies that appeared to address our study aim. Then, two independent reviewers screened each abstract to determine their eligibility for inclusion using an abstract screening tool developed specifically for this study. Abstracts that were conducted before 1990 were excluded from full-text review. Abstracts that were unclear if they met the inclusion criteria were included for full text review to determine eligibility. A data extraction tool was used to identify the final studies for inclusion in the systematic review and meta-analysis. To be included in the systematic review and meta-analysis, studies had to be written in English, report outcomes for melatonin use to prevent delirium in postoperative hospitalized patients with a mean age of 50 or older, and be published in peer-reviewed journals between January 1990 and October 2017. Additionally, the studies also had to be randomized controlled trials, cohort studies, or case control studies with both a melatonin (or equivalent) group and a comparison group. Inclusion and exclusion criteria are summarized in Fig. 2.

P2

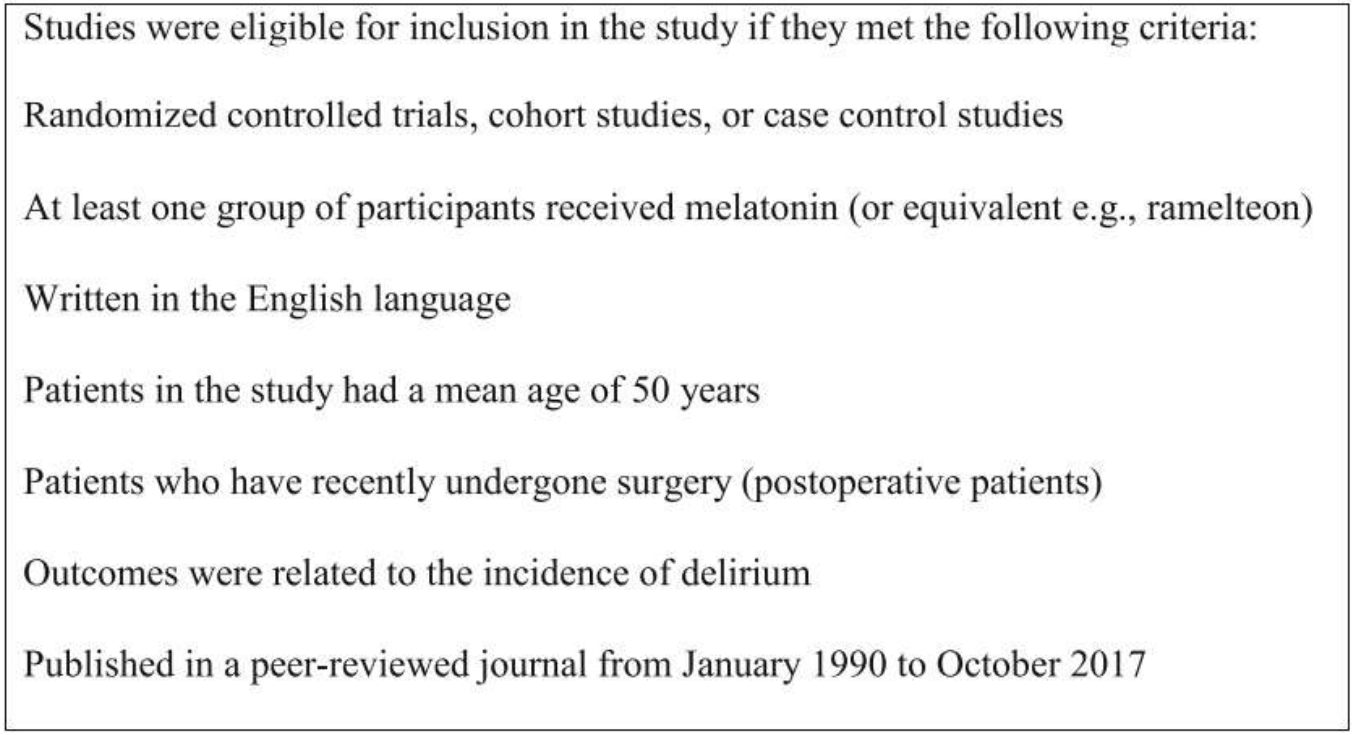


Fig. 2 Study inclusion criteria

- 文獻有列出納入與排除的原因。

P3

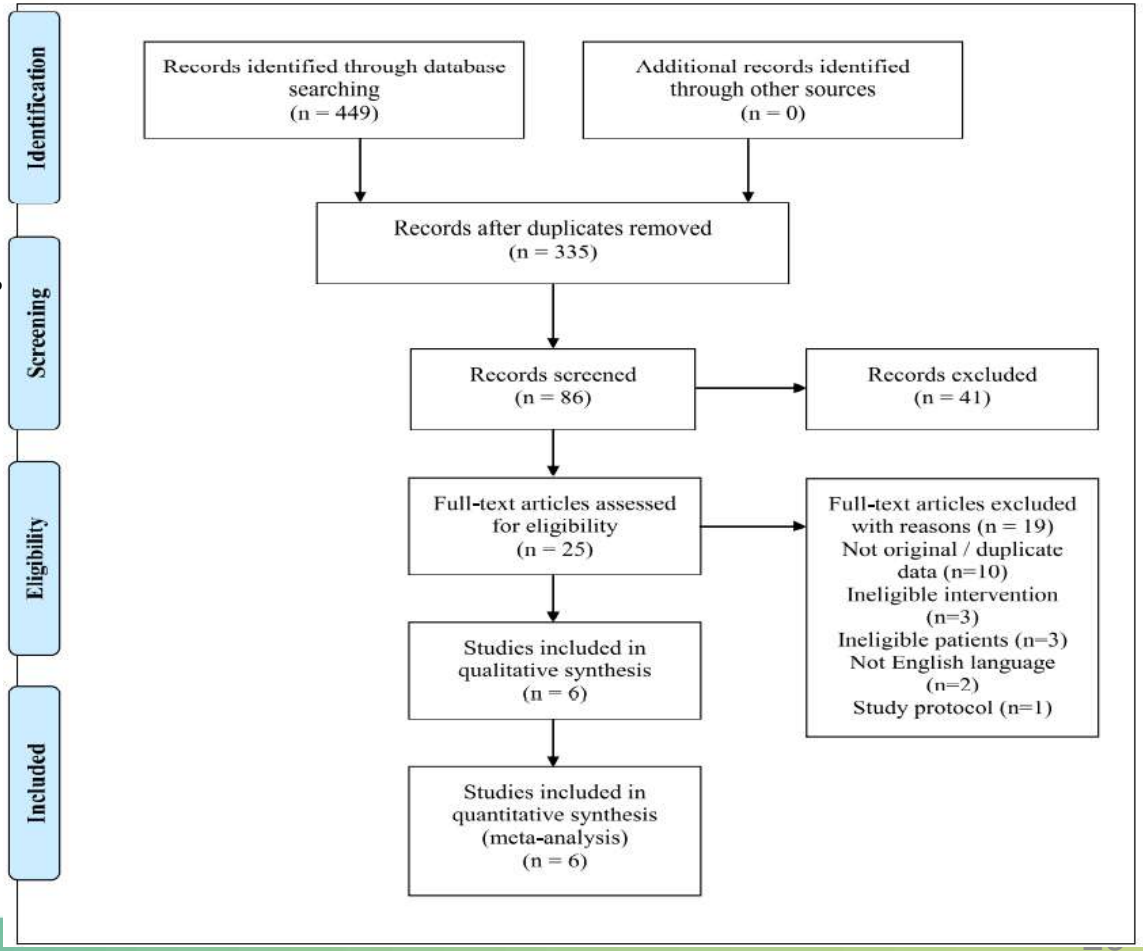
Results

Study selection

The search yielded a total of 335 unique records after the removal of duplicates. Of these, 86 abstracts were screened, 25 articles underwent full-text review, and six were included in the systematic review and meta-analysis [29–34]. The study selection process is described in Fig. 3 [34].

P5

- 有詳細搜索策略的說明包含搜索年限以及文獻納入與排除的數量。
- 呈現PRISMA的流程圖。



P6

Table 1 Characteristics of the studies and study patients

Author (year); Country	Drug (dose)		Duration of Therapy (days)	Study design / (blinding)	Reason for surgery	Patients N		Age Mean (SD) unless otherwise indicated		Male gender N (%)		Scale used to assess delirium	Mean (SD) duration of surgery (minutes)	
	I	C				I	C	I	C	I	C		I	C
Artemiou (2015); Slovakia [30]	Melatonin (5 mg)	No treatment	5	Prospective observational (none)	Cardiac	250	250	64.3 (±10.1)	65.2 (±10.3)	179 (71.6)	171 (68.4)	CAM-ICU	NR	NR
de Jonghe (2014); The Netherlands [29]	Melatonin (3 mg)	Placebo	5	RCT (double)	Hip fracture	186	192	Mean (SD) 84.1 (±8)	Mean (SD) 83.4 (±7.5)	53 (28.5)	62 (32.3)	DSM-IV	NR	NR
Miyata (2017); Japan [31]	Ramelteon (8 mg)	Placebo	7	Retrospective chart review (none)	Pulmonary resection	24	58	79 (70–89)[a]	Median (Range) 76.5 (70–87)	21 (88)	43 (74)	ICDSC	293 (±108)	280 (±91.4)
Nickkholgh (2011); Germany [32]	Melatonin (50 mg/kg)	Placebo	1	RCT (double)	Liver resection	25	23	Mean (SD) 59 (±10)	Mean (SD) 56 (±11)	17 (68)	11 (48)	NR	202 (±80)	212 (±79)
Sultan (2010); Egypt [33]	Melatonin (5 mg)	No treatment	2	RCT (double)	Hip arthroplasty	53	49	Mean (SD) 70.4 (±7.1)	Mean (SD) 72.3 (±6.4)	24 (45.3)	22 (44.9)	AMT	126.8 (±44.9)	119.7 (±36.7)
Yamaguchi (2014); Japan [33][b]	Ramelteon (8 mg)	Placebo	4	RCT (double)	Total knee arthroplasty	22	23	≥70	≥70	NR	NR	ICDSC	NR	NR

- 摘要表格呈現所納入的試驗結果並進行統合分析。

評讀結果：

- ☐是
- ☐否
- ☐不確定

A - 文獻是否經過嚴格評讀？

Data extraction

Data were collected on study characteristics, patient characteristics, and study outcomes using a standardized data extraction tool created specifically for this study. Two independent reviewers extracted data from each study report and brought any discrepancies to the research team for resolution through consensus. Study characteristics included: drugs and dose used in the intervention and comparator groups; study duration; study setting; study design; blinding; reasons for surgery; and concurrent diseases and medications. Patient characteristics included: total number included and analyzed; age; and gender. Study outcomes included the incidence of delirium and duration of delirium (if delirium was experienced by the patient).

P3

✅資料由兩位人員分別審查，並將差異提交給研究團隊協商一致的解決方式。

Risk of Bias assessment

Risk of bias was assessed using one of two tools depending on the study design. Randomized controlled trials (RCTs) were assessed using the Cochrane risk of bias tool [26]. This tool assessed six bias domains: 1) selection; 2) performance; 3) detection; 4) attrition; 5) reporting; and 6) other bias, which could be reported as having a low, unclear, or high risk of bias [26]. Risk of bias in observational studies was assessed using the Risk of Bias in Non-Randomized Studies – of Interventions (ROBINS-I) assessment tool [27]. This tool assessed seven bias domains: 1) confounding; 2) selection of participants into the study; 3) classification of interventions; 4) deviations from intended interventions; 5) missing data; 6) measurement of outcomes; and 7) selection of the reported result, which could be reported as having a low, moderate, serious, or critical risk of bias [27]. Two investigators independently assessed the risk of bias for each study and scored each domain then met to resolve differences by consensus.

P3

評讀結果：

☐是

☐否

☐不確定

✅根據不同的文章類型，選擇適合的評讀工具。

I - 是否只納入具良好效度的文章？

Table 3 Risk of bias assessment for included studies

Author (year); Country							
Randomized controlled trials	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	
de Jonghe (2014); The Netherlands [29]	Low	Low	Low	High	Low	Low	
Nickkholgh (2011); Germany [32]	Low	Low	High	Low	Unclear	Unclear	
Sultan (2010); Egypt [33]	Unclear	Low	Unclear	Unclear	Low	Low	
Yamaguchi (2014); Japan [34]	Unclear	Unclear	Unclear	Unclear	Low	Unclear	
Observational studies	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results
Artemiou (2015); Slovakia [30]	Moderate	Low	Low	Low	Low	Moderate	Low
Miyata (2017); Japan [31]	Moderate	No information	Low	Low	Low	Low	Low

P8

評讀結果：

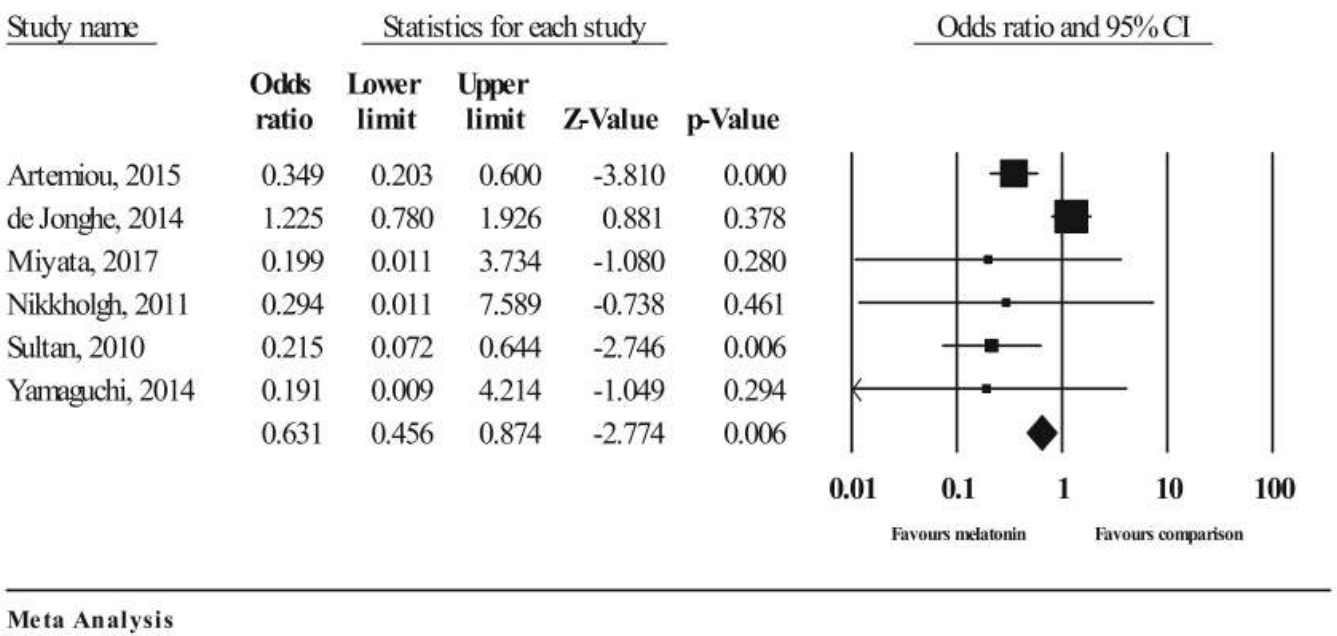
☐是

☐否

☐不確定

- 納入的研究中至少都有一項研究結果是極小偏誤的試驗。

T - 作者是否以表格和圖表「總結」試驗結果？
H - 試驗的結果是否相近 - 異質性？



Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Artemiou, 2015	0.349	0.203	0.600	-3.810	0.000
de Jonghe, 2014	1.225	0.780	1.926	0.881	0.378
Miyata, 2017	0.199	0.011	3.734	-1.080	0.280
Nikkholgh, 2011	0.294	0.011	7.589	-0.738	0.461
Sultan, 2010	0.215	0.072	0.644	-2.746	0.006
Yamaguchi, 2014	0.191	0.009	4.214	-1.049	0.294
	0.631	0.456	0.874	-2.774	0.006

Fig. 4 Forest plot of melatonin studies for the prevention of delirium in postoperative patients

P7

評讀結果：

- ☑ 是
- ☐ 否
- ☐ 不確定

✅ 以森林圖總結研究結果。

odds ratio 0.63 (95% CI 0.46 to 0.87; 0.006; I^2=72.1%)

odds ratio to 0.310 (95% CI 0.19 to 0.50)(Cochran's Q=0.798, I^2=0.000)

H - 試驗的結果是否相近 - 異質性？

Synthesis of results

The summary effect of the six included studies shown in Fig. 4 gives an odds ratio of 0.63 (95% CI = 0.46 to 0.87), indicating that patients taking melatonin had lower odds of experiencing delirium compared to patients taking placebo. There was evidence of publication bias based on visual inspection of the Funnel Plot (Fig. 5); however, Kendall's tau was not significant ($p = 0.775$).

There was evidence of heterogeneity among the data, with a Cochran's Q value of 17.95 (five degrees of freedom; $p = 0.003$) and an I^2 value of 72.14. Visual inspection of the forest plot indicated differences between the de Jonghe study and other studies, so a stratified analysis of the de Jonghe study versus the remaining studies was conducted. The difference in effect for the de Jonghe study versus other studies was significant ($p < 0.001$). A stratified analysis was also conducted by study design (RCTs versus observational studies), but this was not found to have a significant impact on the incidence of delirium ($p = 0.69$).

In the one study removed analysis, exclusion of the de Jonghe study reduced the overall odds ratio to 0.310 (95% CI 0.19 to 0.50), and also reduced the amount of heterogeneity present (Cochran's Q = 0.798, $I^2 = 0.000$).

P8

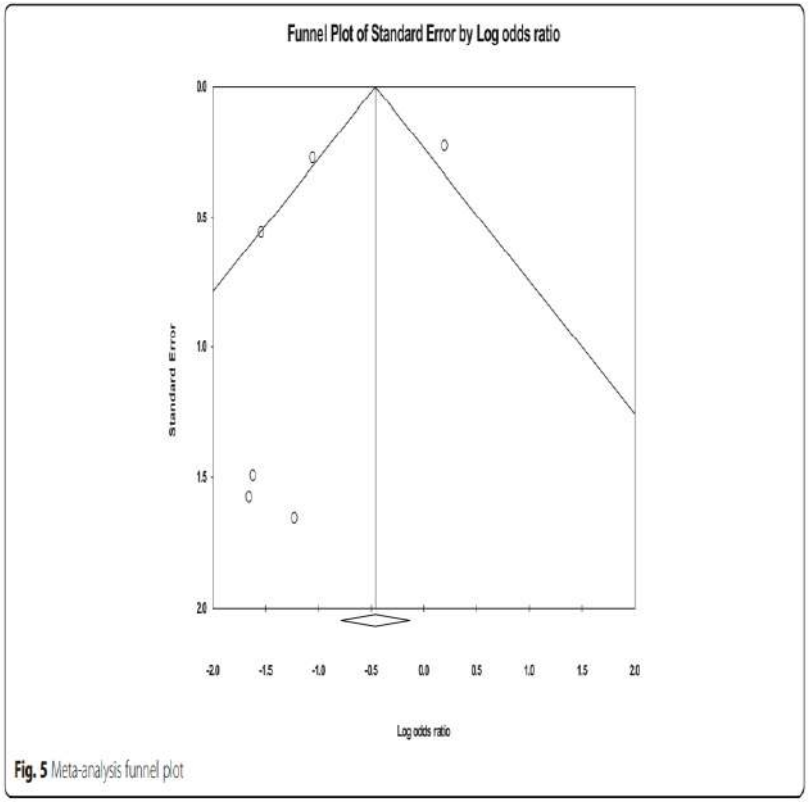


Fig. 5 Meta-analysis funnel plot

Discussion

Currently, there is a very small body of literature examining the use of melatonin for the prevention of postoperative delirium in older adults. In conjunction with clinician input, the exhaustive literature search was driven by a health sciences librarian who is highly experienced in systematic reviews. While the body of literature is small at this time, the findings of this meta-analysis suggest that perioperative melatonin administration may significantly reduce the incidence of delirium in older adults undergoing surgical procedures – a common, yet detrimental complication of surgery in older adults. The odds ratio was highly sensitive to removal of the one study that did not have results in favor of melatonin reducing risk of delirium, resulting in a reduction of the odds ratio from 0.63 to 0.31, and heterogeneity to zero [29]. One possible explanation for the negative results in this particular study may be due discrepancy among the two study groups related to prior delirium. Even though statistics were not reported for the baseline characteristics, the group receiving melatonin appeared to have a greater percentage of patients with a history of delirium (23.7% versus 17.2% in the placebo group), which is a well-established risk factor for developing delirium [6, 36]. Additionally, the authors of the de Jonghe study noted that there was an increased probability of type 2 error, as they had a large number of patients who were excluded post-randomization (withdrawal of consent, delirium at admission, loss to follow-up, etc.). Only 378 patient data were analyzed, while 444 patients were randomized, increasing risk of attrition bias [29].

P5

評讀結果：

☐是

☐否

☐不確定

✔ 有說明異質性高之原因。

總結	評讀結果
F -研究是否找到 (Find) 所有的相關證據？	是
A -文獻是否經過嚴格評讀 (Appraisal)？	是
I -是否只納入 (Included) 具良好效度的文章？	是
T -作者是否以表格和圖表「總結」(Total up) 試驗結果？	是
H -試驗的結果是否相近 - 異質性 (Heterogeneity)？	是

Appraisal sheets(FAITH)

- Appraisal Tool
  - 步驟 1：研究探討的問題為何 (PICO)
  - 步驟 2：研究的品質如何 (內在效度)
  - **步驟 3：研究結果之意義為何 (效益)**

步驟 3：結果為何？
使用何種評估方式，療效有多大（是否來自隨機效果）？

Conclusions

Currently, where there is no supported pharmacological intervention to prevent delirium incidence in older surgical patients, this meta-analysis suggests that melatonin may become that first agent. The odds of developing delirium in patients who received melatonin agonists perioperatively were 37% less ($p = 0.006$) than those who received placebo or no treatment at all. Although optimal dosing remains an unanswered question, the potential benefit, low cost, and benign side effect profile, make melatonin an attractive option to use in older adults undergoing surgical procedures to reduce delirium incidence.

- 研究結果:手術全期服用褪黑激素的老年病人，譫妄發生率比接受鎮靜劑或不治療者低37%。
- 雖然低成本、低副作用，但最佳劑量仍然是一個懸而未解的問題。

limitations

- First, the few studies that met inclusion criteria were small, and not all met their predefined statistical power.
  - 少數符合納入標準的研究規模較小，且並非全部滿足了預期的統計成效
- Another limitation is the heterogeneity of included studies with regards to type of surgical procedure and melatonin dosing.
  - 另一個限制是納入的研究，在手術類型和褪黑激素劑量方面的異質性。
- Additionally, while the requirement for an average age of 50 years and older increased the number of studies meeting inclusion criteria, it also led to a wide age variability.
  - 平均年齡 50 歲以上的要求雖然增加了符合納入標準的研究個案數量，但也導致了廣泛的年齡變異性。

問題與討論

是否贊成服用褪黑激素降低術後老年人譫妄發生率

0票

21票

4票