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Efficacy and Safety of Melatonin as an Anxiolytic and Analgesic in the Perioperative Period

A Qualitative Systematic Review of Randomized Trials

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ABSTRACT

Melatonin possesses sedative, hypnotic, analgesic, antiinflammatory, antioxidative, and chronobiotic properties that distinguish it as an attractive alternative premedicant. A qualitative systematic review of the literature concerning the perioperative use of melatonin as an anxiolytic or analgesic in adult patients was carried out using the recommended guidelines provided by the Cochrane Handbook for Systematic Reviews of Interventions. Nine of the 10 studies showed statistically significant reduction of preoperative anxiety with melatonin premedication compared with placebo. An opioid-sparing effect or reduced pain scores were evident in five studies whereas three studies were contradictory. Thus, melatonin premedication is effective in ameliorating preoperative anxiety in adults, but its analgesic effects remain controversial in the perioperative period. Additional well designed randomized controlled trials are necessary to compare melatonin premedication with other pharmacological interventions, investigate its effect on more varied surgical populations, and to delineate its optimal dosing regimen.

THE existing literature suggests that many surgical patients experience some anxiety and pain during the perioperative period.[1–3] Preoperative anxiety is described as an unpleasant state of uneasiness or tension that is secondary to a patient being concerned about a disease, hospitalization, anesthesia and surgery, or the unknown.[4] Preoperative anxiety may also serve a critical role in the chain of events that control the postoperative pain response.[5,6] The relationship between perioperative anxiety and pain is particularly important to the perioperative physician because preoperative anxiety can be reduced with certain pharmacological interventions.[5] Benzodiazepines are commonly used to alleviate anxiety but may impair psychomotor performance and suppress the duration of rapid eye movement sleep.[7–9]

The incidence of moderate pain after day surgery remains as high as 25%, whereas 25–50% of surgical inpatients experience moderate to severe pain, indicating that the standards of care for postoperative pain by the Audit Commission (1997) are not being met.[10–13] Opioids are potent analgesics widely utilized to provide perioperative analgesia, but their use is sometimes limited because of adverse effects such as sedation and respiratory depression. Moreover, postoperative opioid use can lead to an increase in hospital morbidity and cost.[14,15] Therefore, the search for a substance that may reduce the severity of postoperative pain is desirable.

Recently accumulated experimental evidence supports an important role of melatonin (*N*-acetyl-5-methoxytryptamine) in anxiolysis and analgesia.[16–18] Melatonin is a naturally occurring hormone in the human body that is secreted by the pineal gland in the dark and inhibited by exposure to light. The manufacturing and general use of exogenous melatonin remain unregulated because melatonin is not a Food and Drug Administration-approved drug. Oral administration of 1–5 mg of melatonin results in plasma levels of 10–100 times more than the observed endogenous nighttime levels.[19] It has an excellent safety profile, and the minor adverse effects that may be associated with its use are drowsiness, headache, gastrointestinal disturbances, rash, and insomnia.[20] In contrast to benzodiazepines, melatonin produces no residual effects or suppression of rapid eye movement sleep.[21]

The anxiolytic and analgesic properties of melatonin distinguish it as a compelling alternative as a premedicant. However, the clinical evidence regarding the anxiolytic and analgesic effects of melatonin in the perioperative period has

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not been reviewed previously. The objective of our systematic review is to evaluate the efficacy and safety of melatonin as a preoperative anxiolytic and analgesic in randomized controlled trials.

Materials and Methods

A systematic review of the literature concerning the perioperative use of melatonin as an anxiolytic or analgesic in adult patients was carried out using the recommended guidelines provided by the Cochrane Handbook for Systematic Reviews of Interventions.#

Search Methods for Identification of Studies

We performed a literature search during November 2009 using MEDLINE (1950–week 2 November 2009), EMBASE (1980–2009 week 47), International Pharmaceutical Abstracts (1970–November 2009), and Cochrane Databases of Systematic Reviews (Issue 4, 2009). Keywords including "anxiety," "pain," "analgesic," "surgery," "perioperative," "antianxiety agents," and "premedication" were combined with "melatonin." The search was restricted to the English language and an adult study population. We sought additional literature through the scanning of the bibliographies of relevant articles. In addition, we contacted the author of the included trials for information not reported sufficiently in the identified publications. We specifically inquired about the criteria of methodological quality and whether tabular data could be provided where such information was missing or unclear.

Study Selection Criteria

Two reviewers (FY and ES) independently assessed titles, abstracts, and/or the full text paper of the records retrieved from the electronic database and the hand searches for possible inclusion according to the predefined selection criteria, *i.e.*, any randomized controlled trial evaluating the efficacy and safety of melatonin as an anxiolytic and/or analgesic in the perioperative setting and in adult patients (age older than 18 yr) in which validated measurement tools were used for evaluation. Studies published in the non-English language or studies without preoperative assessment of anxiety were excluded. Disagreements between the authors were resolved by the senior author (FC).

Assessment of Methodology Quality

Two authors (FY and ES) assessed the methodological quality of each trial using individual aspects of methodological quality proposed by Schulz *et al.*[22] These criteria specify four items of assessment: double-blinding, allocation concealment, follow-up completeness, and methods used to achieve randomization. In each study, the above-mentioned components were graded as "adequate," "unclear," or "inadequate." We resolved any conflicts in the assessment of methodological quality of eligible studies through discussion, and if necessary, through evaluation by the senior author (FC).

Data Extraction and Analysis

The data were extracted by FY and ES individually and validated by FC, by double data entry. Details of study population, interventions, and outcomes were extracted using a standardized data extraction form, which included general information, trial characteristics, study population characteristic, interventions, and outcomes. The primary outcomes of the review included: *perioperative anxiety*, assessed with the Visual Analog Scale (VAS) or State-Trait Anxiety Inventory or any other validated assessment tool; *perioperative pain*, assessed with the VAS or Verbal Numerical Scale or any other validated assessment tool; *intraoperative opioid use*; and *postoperative analgesic consumption*. We also listed melatonin-related adverse effects reported in terms of psychomotor impairment, sedation, and orientation in time or place among the studies. Comparisons were made between melatonin and placebo, melatonin and another anxiolytic or analgesic, and different dose(s) of melatonin.

This study is a "qualitative systematic review" without meta-analysis. We summarize and present the results in several tables. To identify the significant findings in each paper, we considered a P value < 0.05 as a level of statistical significance. There were several reasons that made us decide not to carry out meta-analysis in this review. First, there were obvious clinical inconsistencies among the papers in terms of the study population, time of assessment of outcomes, and the dosing of melatonin. Second, the data were presented in a format of median and range in the papers; however, only mean and SD could be used for meta-analysis. Also, presenting the results in median and range by the papers could indicate that the respective data were not normally distributed, and therefore the normality assumption could not be achieved to do a valid meta-analysis. Finally, in many papers the data were only presented in a figure or graph, and tabular data were not available. We contacted the authors to get the tabular data; however, the authors of only two papers provided us with the required information.[23,24] We did not carry out meta-analysis on these two papers because they were only a portion of the literature on the topic, and the final results could not represent the current available evidence.

Results

Description of Selected Studies

Our search strategy for the topic of melatonin and anxiety yielded 249 results and for the topic of melatonin and pain yielded 534 results (fig. 1). Ten and eight studies met our inclusion criteria for the role of melatonin in anxiety and pain, respectively. There were eight studies in which both outcomes have been reported, so a total number of 10 studies (n = 788 patients) were included in this review (table 1).[23–32] The average sample size was 75 patients with a range

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 (updated September 2009). The Cochrane Collaboration, 2009. Available at: www.cochrane-handbook.org.

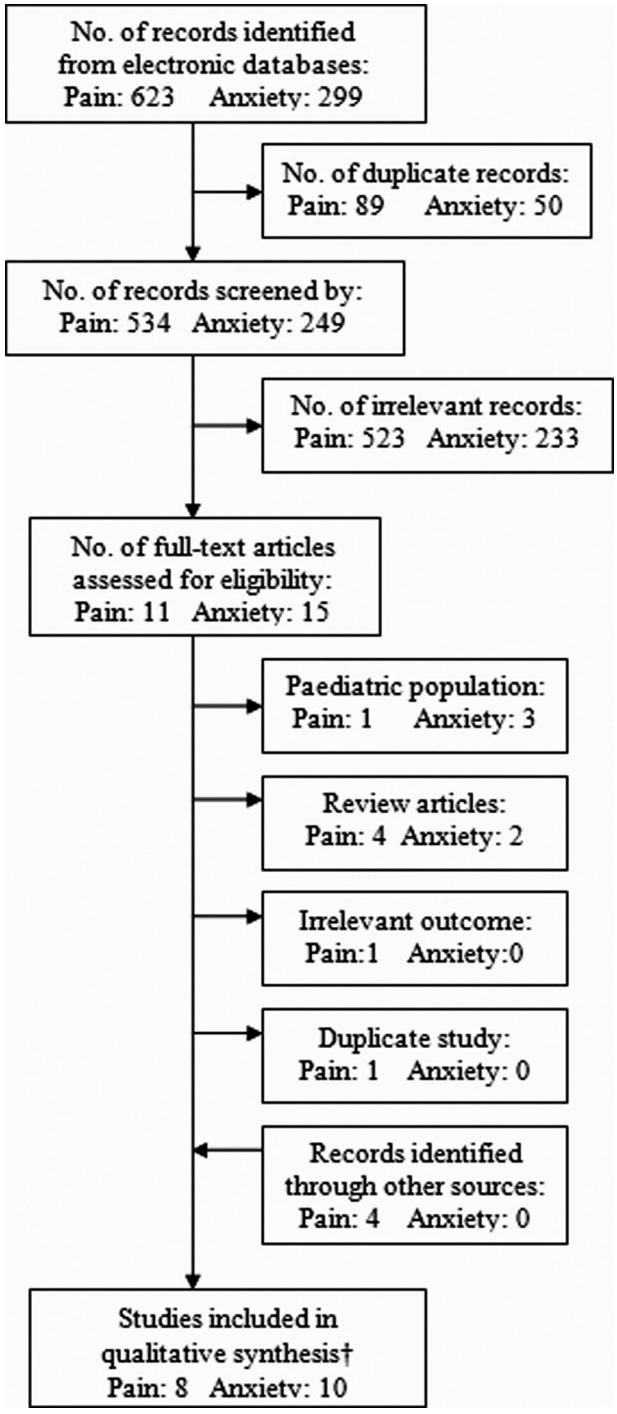

Fig. 1. Flow chart of the literature search, screening, and inclusion of the studies. † Total number of the included studies is 10 because there are 8 papers studying the effect of melatonin on both pain and anxiety.

of 33–200 patients. The main characteristics of the included studies are shown in table 1.

Risk of Bias in Included Studies

Schulz's quality criteria were adequately met for the specific items of methodological quality in two trials.[23,25] The method of randomization in these two trials was either computer-generated or advanced simple randomization without blocking or stratification. In these trials, the allocation concealment was achieved with the use of sealed envelopes. The remaining eight trials were subject to potential moderate risk of bias because one or more elements of methodological quality, that is, randomization, allocation concealment, blinding, or follow up, were considered unclear (table 2).[26–32] In three studies, the randomization lists were kept by the person (for example, a pharmacist) who was responsible for preparing the medication (or placebo).[23,25,32] This person was not involved in administering the medication to the patients, the patient's care, or data collection. The safety assessor(s), responsible for the subjective safety assessments, were blinded to the treatment assignment in all studies. Four studies clearly reported the number and reasons for patient withdrawals.[23,25–27]

Clinical Evidence of Anxiolytic Effects of Melatonin in the Perioperative Period

Ten studies reported preoperative anxiety as outcome measures (table 3). VAS, verbal rating scores, and the original or modified State-Anxiety Trait Inventory were used in the assessment of anxiety. The basic characteristics of these trials are shown in table 1. The sample size ranged from 33 to 200 patients with a mean age of 28–73 yr and average weight of 60–78 kg. The surgical populations included gynecological, laparoscopic cholecystectomy, hand, cataract, and mixed surgeries. The anesthetic technique included general anesthesia, regional anesthesia (epidural, spinal, Bier block), and local anesthesia with or without sedation. The exogenous melatonin dose ranged from 3 to 15 mg and was administered 50–90 min preoperatively *via* an oral[23–25,27–29,32] or sublingual route.[26,30,31] Three studies followed a dual regime of melatonin administration in which an additional dose of melatonin was administered on the night before surgery.[24,25,27]

Nine of the 10 studies showed statistically significant reduction of preoperative anxiety with melatonin premedication compared with placebo. Only one study refuted its anxiolytic effects.[23] The timing of anxiety assessment varied among the trials, but a significant statistical difference in anxiety scores was evident at different points of time in the melatonin group (table 3).

The preoperative anxiety assessment time varied among the studies from 10 to 90 min after administration of melatonin (all P values < 0.05). Two studies at 10 min, three studies at 30 and 60 min, and five studies at 90 min after premedication showed that anxiety was less in the melatonin groups compared with the placebo groups (all P values < 0.05).[26,28–31] In another study by Naguib *et al.*, the anxiety score was statistically lower in the melatonin group *versus* the placebo group at 50 min (P value < 0.05).[32] Ismail *et al.* also demonstrated reduced anxiety scores intraoperatively during cataract surgery in the melatonin group *versus* placebo.[28]

During the postoperative period, melatonin was shown to be associated with less anxiety compared with placebo. The assessment times were 15, 30, 60, and 90 min after surgery in

Table 1. Basic Characteristics of the Included Clinical Trials

Study ID	Sample Characteristics				Anesthesia	Surgery	Intervention *vs.* Control	Melatonin Dosage
	Sample Size	M:F	Age	Weight (kg)				
Ismail[28] 2009	40	21:19	71 ± 8	69 ± 12	Topical	Cataract	Melatonin, Placebo	PO 10 mg, Single-dose
Caumo[25] 2009	59	0:59	45 ± 5	61 ± 6	Epidural and sedation	Abdominal hysterectomy	Melatonin, Clonidine, Placebo	PO 5 mg, Dual-dose
Ionescu[24] 2008	53	?	41 ± 11	75 ± 13	GA	Lap. chole.	Melatonin, Midazolam, Placebo	PO 3 mg Dual-dose
Mowafi[29] 2008	40	18:22	44 ± 11	78 ± 11	Bier block	Hand	Melatonin, Placebo	PO 10 mg, Single-dose
Caumo[27] 2007	33	0:33	44 ± 4	60 ± 5	Epidural and sedation	Abdominal hysterectomy	Melatonin, Placebo	PO 5 mg, Dual-dose
Capuzzo[23] 2006	138	69:69	73 ± 6	?	GA & spinal	Mixed	Melatonin, Placebo	PO 10 mg, Single-dose
Naguib[32] 2006	200	83:117	33 ± 9	74 ± 11	GA	Mixed	Melatonin, Placebo	PO 0.2 mg/kg Single-dose
Acil[26] 2004	66	?	39 ± 7	68 ± 7	GA	Lap. chole.	Melatonin, Midazolam, Placebo	SL 5 mg, Single-dose
Naguib[31] 2000	84	0:84	28 ± 6	68 ± 13	GA	Lap. gynecol.	Melatonin, Midazolam, Placebo	SL 0.05 or 0.1 or 0.2 mg/kg Single-dose
Naguib[30] 1999	75	0:75	30 ± ?	67 ± 11	GA	Lap. gynecol.	Melatonin, Midazolam, Placebo	SL 5 mg, Single-dose

Capuzzo[23] and Naguib[32]: studies with anxiety outcome only; the rest were studies with both anxiety and pain outcomes. Age and weight are expressed as mean ± SD.

GA = general anesthesia; Lap. chole. = laparoscopic cholecystectomy; Lap. gynecol. = laparoscopic gynecological; PO = per oral; SL = sublingual; ? = missing data.

one study and 6, 24, and 48 h after surgery in two studies, all showing a significant decrease in the anxiety scores of the melatonin groups *versus* the placebo groups (all P values < 0.05).[25–27] On the contrary, Capuzzo *et al.* demonstrated a lack of statistically significant anxiolytic effects after melatonin premedication in the elderly surgical patients at 90 min preoperatively, after surgery in the recovery room, and 7 days after hospital discharge.[23]

In four studies, the anxiolytic effects of melatonin were also compared with midazolam, a short-acting benzodiazepine commonly used as a premedication.[24,26,30,31] There was no statistically significant ($P > 0.05$) difference in the anxiety scores between melatonin and midazolam groups during preoperative anxiety assessments, but both groups showed a statistically significant reduction in anxiety levels compared with the placebo group.[24,26,30,31] Postoperatively, a statistical difference between melatonin and midazolam groups in anxiety scores was exhibited at 15, 30, 60, and 90 min in one study, and melatonin was also shown to have a superior anxiolytic effect compared with midazolam at 60 min and 24 h in another study.[24,26] However, Naguib and colleagues reported equivalent anxiety scores in melatonin, midazolam, and placebo groups postoperatively.[30,31] The anxiolytic effect of melatonin was also compared with clonidine, a central α-adrenergic agonist, illustrating equivalent anxiolysis with both interventions that were statistically superior to the placebo.[25]

The tabular data for melatonin premedication was available in only four studies (table 4) and other studies published only graphical data.[23,28,29,32] The baseline anxiety in the control and melatonin groups was similar. However, a statistically significant reduction in anxiety scores was achieved 50–90 min after melatonin administration in four studies. Because the data were reported in different formats among the studies (mean *vs.* median), statistical integration of data (meta-analysis) was not feasible, and overall efficacy of the medication was not calculated. However, a statistically significant anxiolytic effect of melatonin is evident in 9 of 10 studies.

Table 2. Methodological Quality of the Included Studies

Study ID/Year	Criteria Adequately Met
Ismail[28] 2009	R, B
Caumo[25] 2009	R, C, B, F
Ionescu[24] 2008	C, B, F
Mowafi[29] 2008	R, B
Caumo[27] 2007	R, B, F
Capuzzo[23] 2006	R, C, B, F
Naguib[32] 2006	C, B
Acil[26] 2004	B, F
Naguib[31] 2000	B
Naguib[30] 1999	B

B = blinding; C = concealment; F = follow-up; R = randomization.

Clinical Evidence of Analgesic Effects of Melatonin in the Perioperative Period

Eight studies that reported pain as the outcome measures were included in our review (table 1). VAS and verbal rating scores were used to assess pain at different time points. Intraoperative opioid use or postoperative analgesic consumption was recorded in seven studies.[24,25,27–31] The sample size ranged from 33 to 84 patients with a mean age of 28–71 yr and average weight of 60–78 kg. The surgical populations studied in these trials included gynecological, laparoscopic cholecystectomy, cataract, and hand surgeries under general anesthesia, epidural with sedation, Bier block, or topical an-

Table 3. Anxiety Scores in the Melatonin *vs.* Placebo groups in Perioperative Period

			Preoperative					Postoperative							
Study ID	Tool	Before Premed	10 min Post-dose	30 min Post-dose	50 min Post-dose	60 min Post-dose	90 min Post-dose	15 min	30 min	60 min	90 min	6 h	24 h	36 h	48 h
Ismail[28] 2009	VAS	—					↓								
Caumo[25] 2009	STAI	—										↓	↓		↓
Ionescu[24] 2008	STAI (mod.)	—						↓		↓		↓	↓		
Mowafi[29] 2008	VAS	—					↓								
Caumo[27] 2007	STAI	—										↓	↓	↓	↓
Capuzzo[23] 2006	VNS	—					—								
Naguib[32] 2006	VAS	—			↓										
Acil[26] 2004	VAS	—	↓	↓		↓	↓	↓	↓	↓	↓				
Naguib[31] 2000	VAS	—	—	↓		↓	↓								
Naguib[30] 1999	VAS	—	↓	↓		↓	↓								

(↓) statistically significant decrease in the melatonin *vs.* placebo group ($P < 0.05$); (—) no statistically significant difference between the melatonin and the placebo groups.

STAI = State-Trait Anxiety Inventory; VAS = Verbal Analogue Scale; VNS = Verbal Numerical Scale.

esthesia. The exogenous melatonin dose ranged from 3 to 15 mg and was administered 90–100 min preoperatively *via* an oral[24,25,27–29] or sublingual route.[26,30,31] In three studies with dual-dosing regimen, melatonin was administered the night before and 60–90 min before surgery.[24,25,27]

Five studies demonstrated an opioid-sparing effect or reduced pain scores[24,25,27–29] whereas three studies were contradictory.[26,30,31] Pain scores were assessed perioperatively in seven of eight studies in which four studies[25,27–29] showed statistically significant ($P < 0.05$) improvement in the pain scores in the melatonin group compared with placebo (table 5). Intraoperative pain assessment was performed in only two studies where either topical or regional anesthesia was administered.[28,29] In patients undergoing cataract surgery, pain scores were significantly reduced at 10, 20, and 30 min intraoperatively as well as during the postanesthesia care unit stay in the melatonin *versus* the placebo group.[28] Hand surgery patients in the melatonin group *versus* placebo also reported reduced pain scores at 30, 40, and 50 min after tourniquet inflation.[29]

Postoperative pain scores were assessed in five studies. In the two studies conducted by Naguib *et al.*, there was no significant difference in pain scores in the melatonin group at 15, 30, 60, and 90 min postoperatively.[30,31] Furthermore, Acil *et al.* did not observe any significant difference in pain scores in melatonin *versus* placebo groups during the stay in the postanesthesia care unit.[26] In contrast, the two studies by Caumo *et al.* showed a statistically significant reduction in pain scores in the melatonin group at 6, 12, 18, 24, 36, and 48 h postoperatively.[25,27] It is important to note that melatonin was administered as a single dose in the two studies by Naguib *et al.* and one by Acil *et al.* that showed a lack of

Table 4. Effect of Melatonin as a Premedication for Preoperative Anxiety

	Before Premedication		After Premedication		
Study ID/Year	Melatonin	Placebo	Melatonin	Placebo	Assessment Time (min)
Ismail[28] 2009	5.0 (3.5–6.0)	4 (3.0–6.0)	**3.0 (2.0–3.0)**	**4.0 (2.0–5.0)**	90
Mowafi[29] 2008	5.0 (4.0–6.0)	5 (3.5–6.0)	**4.0 (3.5–4.5)**	**5.0 (3.5–6.0)**	90
Capuzzo[23] 2006	5.0 (3.0–6.0)*	5.0 (2.0–8.0)*	3.0 (1.0–5.0)*	3.0 (1.0–7.0)*	90
Naguib[32] 2006	2.9 (1.0–4.8)	3.0 (0.5–4.7)	**1.0 (0.6–2.7)**	**2.7 (0.3–4.6)**	50

Four out of the 10 included studies presented tabular data results for anxiety scores in the melatonin *vs.* placebo groups. Values are all Visual Analogue Scale of anxiety. N = sample size. Values with statistically significant difference ($P < 0.05$) are in bold font. Data are expressed in median and range.

* Number scale of anxiety.

Table 5. Effect of Melatonin as a Premedication for Perioperative Pain Control

	Intraoperatively						Postoperatively										
Study ID	10 min	20 min	30 min	40 min	50 min	PACU	15 min	30 min	60 min	90 min	6 h	12 h	18 h	24 h	36 h	48 h	72 h
Ismail[28] 2009	↓	↓	↓			↓											
Caumo[25] 2009											↓	↓	↓	↓		↓	—
Mowafi[29] 2008	—	—	↓	↓	↓												
Caumo[27] 2007											↓	↓	↓	↓	↓	—	—
Acil[26] 2004						—											
Naguib[31] 2000							—	—	—	—							
Naguib[30] 1999							—	—	—	—							

(↓) statistically significant ($P < 0.05$) decrease in pain score in the melatonin *vs.* placebo group. (—) no statistically significant ($P < 0.05$) difference in pain scores in the melatonin *vs.* placebo group.
PACU = postanesthesia care unit.

analgesic effects of melatonin. However, the two studies by Caumo *et al.* in which the analgesic properties of melatonin were evident utilized a dual-dosing regime of melatonin administration. It is possible that the difference in the dosing regime of melatonin administration among these trials may have contributed to the inconsistency observed regarding the analgesic effects of melatonin.

Intraoperative opioid use was recorded in five studies[24,28–31] in which three studies reported a significantly reduced intraoperative opioid requirement in the melatonin group ($P < 0.05$).[24,28,29] Ionescu *et al.* reported comparable intraoperative fentanyl use in the melatonin and midazolam groups which was statistically lower than the placebo group.[24] The two studies by Ismail and Mowafi *et al.* also demonstrated reduced intraoperative opioid requirement.[28,29] In addition, postoperative analgesic consumption was calculated in five studies[25,27,29–31] in which three studies reported positive results ($P < 0.05$).[25,27,29] The analgesic consumption was reduced in the melatonin group compared with placebo at 6, 12, 18, 24, 42, 48, and 54 h postoperatively in two studies by Caumo and colleagues.[25,27] The total analgesic consumption during the postoperative 24 h was also reduced in a study by Mowafi *et al.*[29] In contrast, there was no significant difference in the intraoperative opioid use or total doses of analgesics consumed in the melatonin, midazolam, or placebo groups during the 90-min postanesthesia care unit stay in the two studies by Naguib *et al.*[30,31]

Tabular data regarding intraoperative opioid (fentanyl) usage and postoperative analgesic consumption in the control and melatonin groups was available in five studies for comparison (table 6).[24,29–31] Statistical significance between control and melatonin groups was reached in three studies regarding a reduced intraoperative opioid requirement and postoperative analgesic consumption. Statistical integration

Table 6. Effect of Melatonin as a Premedication on Perioperative Analgesic Consumption

Study ID/Year	N	Type of Surgery	Dosage		Intraoperative Fentanyl (μg)			Postoperative Analgesic Diclofenac†/ Morphine‡ (mg)		
			Melatonin	Midazolam	Melatonin	Midazolam	Placebo	Melatonin	Midazolam	Placebo
Ismail[28] 2009	40	Cataract	10 mg	—	0 (0–33)	—	48 (30–65)	—	—	—
Ionescu[24] 2009	53	Lap. chole.	3 mg	3.75 mg	**410 ± 134.2**	**420 ± 125.1**	530 ± 89.5	—	—	—
Mowafi[29] 2008	40	Hand	10 mg	—	**15.6 ± 21.9**	—	**45.7 ± 33.4**	**86 ± 27***	—	**116 ± 38***
Naguib[31] 2000	84	Lap. gynecol.	0.05–0.2 mg/kg	0.05–0.2 mg/kg	113 ± 38	104 ± 31	108 ± 36	42 ± ?†	43 ± ?†	36 ± ?†
Naguib[30] 1999	75	Lap. gynecol.	5 mg	15 mg	106 ± 39	105 ± 41	105 ± 30	46±?†	53 ± ?†	42 ± ?†

Values are mean ± SD or median (interquartile range). Values with statistically significant difference *vs.* placebo ($P < 0.05$) are in bold font.
* Postoperative (24 h) diclofenac consumption (mg). † Postoperative (90 min) morphine consumption (mg).
Lap. chole. = laparoscopic cholecystectomy; Lap. gynecol. = laparoscopic gynecology; N = sample size.

of the data (meta-analysis) was not carried out because of significant difference in the dose of fentanyl used in the different studies (*i.e.*, clinical heterogeneity). In view of the opioid-sparing effect or reduced pain scores that were evident in five studies while three studies were contradictory, the analgesic effects of melatonin remain controversial.

Safety of Melatonin Premedication

Melatonin seems to be associated with no significant side effects. No significant adverse events after melatonin administration were reported among the included trials. However, it should be noted that the included trials were not statistically powered to detect the incidence of adverse events of melatonin. Adverse events were evaluated in terms of psychomotor impairment, sedation, disorientation, and amnesia.

Three studies included in this review have evaluated psychomotor performance using the Digit Symbol Substitution Test, Trieger Dot Test, Trail Making A and B test, or Verbal Fluency Test.[26,30,31] In one study, Naguib *et al.* discovered impaired performance on the Digit Symbol Substitution Test at 30 min after premedication and in another study at 10 min after premedication in the midazolam group *versus* melatonin and placebo groups.[30,31] However, Trieger Dot Test scores were not significantly different among the midazolam, melatonin, and placebo groups after premedication in the preoperative period.[30,31] There were also no statistically significant differences in Digit Symbol Substitution Test or Trieger Dot Test performance in the midazolam, melatonin, or placebo groups after surgery up to 90 min. In the study by Acil *et al.*, both melatonin and midazolam groups exhibited statistically significant impaired performance on the Trail Making Tests *versus* placebo at 30, 60, and 90 min after premedication ($P < 0.05$), whereas there were no statistical differences among the groups in the 90-min postoperative period.[26] Verbal Fluency Test performance was only significantly impaired in the midazolam group ($P < 0.001$) compared with placebo at 10, 30, 60, and 90 min after premedication, whereas there was no statistical difference in the melatonin and placebo groups at these time points.[26] At 15, 30, and 60 min postoperatively, verbal fluency scores were significantly poor in the melatonin and midazolam groups *versus* placebo ($P < 0.001$).[26]

Five studies included in this review investigated the effect of melatonin on anterograde memory.[23,24,26,30,31] The lack of amnesic effects of melatonin at 24 h postoperatively were evident in three studies that assessed memory by asking the patients to recall pictures shown before premedication, entering the operating room, or insertion of the intravenous catheter in the operating room.[26,30,31] Memory recall scores remained unaffected at 15 min, 60 min, 6 h, and 24 h postoperatively in the melatonin and placebo groups in the study by Ionescu *et al.* which evaluated memory by asking the patients recall five pictures shown before premedication.[24] Amnesia was statistically significant only in the midazolam group *versus* placebo group in the four studies that compared melatonin, midazolam, and placebo groups.[24,26,30,31] Capuzzo *et al.* assessed immediate and delayed recall memory using Babcock Story Recall Test before premedication, 90 min after premedication, in the recovery room, and 1 week after surgery and found no statistically significant difference between melatonin and placebo groups.[23]

Five studies included in this review compared sedation levels after premedication with melatonin, midazolam, or placebo.[24,26,30–32] The melatonin group exhibited increased levels of sedation only at 90 min after premedication *versus* placebo ($P < 0.05$).[26] However, significantly decreased sedation levels were evident in the melatonin *versus* midazolam group at 10, 30, and 60 min after premedication ($P < 0.001$).[26] There was no statistical difference in the sedation levels among the groups after surgery.[26] Increased levels of sedation in the melatonin and midazolam groups *versus* placebo were also evident at 60 and 90 min after premedication in the two studies by Naguib *et al.*[30,31] The midazolam group showed significantly higher levels of sedation than the melatonin group at 30 and 60 min after premedication.[30]

Postoperatively, a statistically significant increase in sedation levels was observed only at 30 min in both melatonin and midazolam groups in one study and at 90 min only in patients receiving 0.2 mg/kg midazolam compared with 0.05 and 0.1 mg/kg melatonin in the other study.[30,31] Naguib *et al.* also reported increased sedation scores on arrival in the operating room in the melatonin *versus* placebo group.[32] Significantly lower sedation scores in the melatonin *versus* midazolam group were also reported at 15 and 60 min after surgery ($P < 0.05$).[24]

Four studies included in this review assessed orientation scores with respect to time and place at multiple times during the study period among the intervention and placebo groups.[26,30–32] In two studies, the orientation scores were similar in the melatonin, midazolam, and placebo groups except at 30 min after premedication when the midazolam group exhibited significant disorientation ($P < 0.05$).[26,30] In another study, all patients remained oriented in time and place at all times except at 15 min after surgery when both intervention groups illustrated significant disorientation compared with the placebo group.[31] However, no statistically significant difference was observed in the orientation score between the melatonin and placebo groups in another study by Naguib *et al.*[32]

Discussion

Our review provides, for the first time, an up-to-date qualitative systematic analysis of the existing clinical trials on the anxiolytic and analgesic properties of melatonin in the perioperative setting. The results of our systematic analysis of the eligible clinical trials suggest that melatonin possesses a significant anxiolytic effect and thus may be useful in highly anxious patients undergoing painful surgeries. Compared with midazolam, melatonin has similar anxiolytic efficacy but less psychomotor impairment and fewer side effects.

The evidence regarding its potential analgesic effects in the perioperative setting is inconsistent and limited. There are very few or no adverse effects with short-term melatonin use.[33] On the other hand, midazolam is associated with more excessive sedation, disorientation, impaired psychomotor performance, and amnesia compared with melatonin.[23,24,26,30–32]

It is still unclear whether the anxiolytic effect is applicable to all surgical patients because a possible gender and procedure bias exists in the currently available literature. Most of the included studies consisted of female patients undergoing laparoscopic cholecystectomies or laparoscopic gynecological procedures. The only contradictory study examined an elderly population more than 65 yr old.[23] The elderly population has been shown to be refractory to the hypnotic and anxiolytic effects of melatonin.[34] Furthermore, several confounding variables existed in this study, including different anesthetic techniques and different types of surgical procedures.[23] Although statistical significance was not reached, the absolute level of anxiety scores did decrease by 33% after melatonin premedication *versus* a decrease of 21% in the placebo group.[23]

The clinical impact of melatonin on pain has not been sufficiently explored to justify its use widely. From the current available literature, conflicting evidence exists. Melatonin premedication was associated with an analgesic effect in the studies with pain as a primary outcome, whereas the lack of analgesic effect was observed in studies with pain as a secondary outcome.[25,27–29] This might reflect inadequate power and a type II error (false negative) finding in the latter.

Moreover, the positive studies for analgesia consisted of studies with a narrow and select group of population, mainly females with low body mass indexes, and surgeries with high anticipated postoperative pain (VAS 35–55 mm).[25,27] The analgesic effect of melatonin has been demonstrated in particular for the subgroup of highly anxious patients, with commendable number-needed-to-treat of less than 3.[25,27] A dual-dosing regimen (night before and 60–90 min before surgery) was utilized in the two studies by Caumo *et al.* and in one study by Ionescu *et al.*, which reported reduced pain scores or an opioid-sparing effect in the melatonin group.[24,25,27] In contradistinction, a single preoperative dose was administered in the studies refuting the analgesic effects of melatonin.[26,30,31] Therefore, it appears that a dual-dosing regimen of 3–5 mg melatonin (for female patients) may have a greater impact on pain than a single preoperative dose of melatonin.

There are a few limitations of our systematic review which must be addressed. Our systematic review was confined to the studies published in the English language only. The data retrieved from the reviewed studies was not suitable for meta-analysis because the data were largely expressed in a graphical fashion or in median and range. Conversion of the data presented in median and interquartile range to mean and SD format can potentially compromise its accuracy and therefore was not attempted. In addition, the population studied, time of assessment of outcomes, and the dosing of melatonin varied among the reviewed studies, making it difficult to synthesize the data quantitatively. Baseline pain assessments were not performed, and therefore the validity of pain assessments in the reviewed trials may be questionable. Moreover, our qualitative analysis was limited by the small sample size of the reviewed clinical trials and the deficiencies of methodological quality, thereby exposing the study to a moderate risk of bias.

However, the existing clinical evidence proposes that melatonin with its anxiolytic and possible analgesic effects may serve as the ideal alternative for premedication, potentially leading to better patient care and less opioid-related morbidity.

Conclusion

Review of the literature provides compelling evidence that melatonin premedication is effective in ameliorating perioperative anxiety in adults. The analgesic effects of melatonin in the adult population during the perioperative period remain controversial. Additional well designed randomized controlled trials are necessary to compare melatonin premedication with other pharmacological interventions, investigate its effect on more varied surgical populations, and delineate its optimal dosing regimen.

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