Perioperative melatonin: not ready for prime time

L. P. H. Andersen*, J. Rosenberg and I. Gögenur
Department of Surgery, Herlev Hospital, University of Copenhagen, DK-2730 Herlev, Denmark
* Corresponding author. E-mail: lphandersen@gmail.com

Melatonin is an endogenous sleep hormone produced in the pineal gland. The primary physiological role of melatonin is the regulation of circadian rhythms in mammals. Pharmacological doses of melatonin have been shown to be effective in treatment of sleep disorders and circadian rhythm disorders. In recent years, melatonin has been tested in various clinical conditions such as hypertension, diabetes, metastasizing cancer, fibromyalgia, irritable bowel syndrome, and chronic obstructive pulmonary disease. Moreover, a total of 21 randomized trials have investigated the use of melatonin in the perioperative period.1–21

A perioperative course incorporating principles for fast-track recovery requires optimal pain relief and rapid mobilization, and a multimodal focus on the reduction in fatigue, postoperative nausea and vomiting (PONV), cognitive impairment, and sleep disturbances. A possible clinical effect and an appealing safety profile makes melatonin an interesting new drug for the perioperative setting. Moreover, widely used analgesics, anxiolytics, and sedatives are associated with risk of side-effects such as respiratory depression, postoperative delirium, and PONV and might increase the risk of serious complications in the perioperative period. The development of effective anxiolytics, anxiolytics, and sedatives is therefore still relevant to ensure safety for the patient. Melatonin has shown promising results, but one essential question still remains: what is the evidence for the use of melatonin in the perioperative setting and should it be applied in our daily clinical practice?

Thirteen studies have explored the anxiolytic effects of melatonin in the perioperative period.1–3 5 6 8–15 These studies have documented that melatonin is effective in treating perioperative anxiety, showing significant anxiolytic effects in 11 of the 13 studies.1–3 5 6 8–10 13–15 The anxiolytic effects have been documented before operation, intraoperatively, and after operation, on multiple widely accepted anxiety scales (state trait anxiety inventory, Yale preoperative anxiety scale, visual analogue scale, and numerical rating scale), and in comparison with inactive placebo and other anxiolytics/sedatives.1 6 8–10 13

The analgesic effects of melatonin have been investigated in 11 randomized studies.1–11 Six studies have documented significantly improved analgesia, reduced analgesic requirements in the perioperative period, or both,1–6 whereas five studies could not document an analgesic effect of melatonin administration.7–11

Four studies have investigated the effects of melatonin on sleep in relation to surgery, but only documented minor, although significant, effects on subjective and objective sleep parameters.2 4 7 13 Moreover, a positive effect of melatonin on objectively measured sleep parameters was found in a small randomized clinical trial in mechanically ventilated patients in the intensive care unit.22 The sleep-regulating effect of melatonin in surgical patients still remains to be established.

The previously described studies investigating anxiety, analgesia, and sleep quality were all randomized double-blinded placebo-controlled trials. However, the quality of the described studies is heterogeneous and often with a lack of documentation of primary outcomes,5 6 8–11 13–15 19 22 or missing pre-study power calculations.8 14 15 Furthermore, none of the studies has adhered to ‘CONSORT’ guidelines concerning randomized clinical trials. The numbers of patients in the studies were generally low, and the inclusion criteria restrictive, reducing the external validity of the results.

A general issue concerning the studies investigating melatonin has been the time of administration in relation to the wanted effect. Four of the studies investigating anxiety and pain administered melatonin the night before surgery and documented significant positive effects.1 2 4 6 The exact mechanisms of melatonin for these indications are still being investigated, but animal studies have shown specific receptor-mediated effects and interaction with multiple other receptor systems such as the GABA, benzodiazepine, and opioid system.23 Furthermore, in humans, the anxiolytic, analgesic, and hypnotic effects may be inter-related. More detailed knowledge concerning mechanisms of action and correct timing of administration are therefore needed to target maximal effects of melatonin in humans.

Another matter is the choice of effective dosage. In clinical studies investigating anxiety and pain, 3–10 mg of melatonin has shown significant results. Animal studies have used doses ranging from 0.3 µg administered intrathecally, up to 300 mg kg–1 bodyweight administered orally across several animal models documenting dose-dependent anxiolytic and anti-nociceptive effects.23 24 The correct dosage of melatonin in humans seems largely unknown and should be investigated further, documenting dose–response curves for the individual indications.
Melatonin has an extensive first-pass metabolism of ~85%, and a limited half-life of 1 h. The inter-subject differences in bioavailability are however low.\(^\text{25}\) It should however be mentioned that earlier studies have reported very variable bio-availability after melatonin administration and findings of DeMuro and colleagues should be confirmed in future studies. The previously mentioned studies have investigated oral or sublingual administration. Future studies should take proper consideration to the pharmacokinetics of melatonin and examine the potential efficacy differences in the various administration forms.

The lack of studies documenting a strong dose–effect relation in humans, and the absence of preclinical studies (such as human experimental models) raise several questions before melatonin can be used routinely in the clinical setting. Furthermore, an investigation of the link between mechanisms of action and clinical effects should be elaborated in humans. Moreover, a limited number of clinical studies have investigated the perioperative use of melatonin in relation to analgesia and sleep quality, and their findings have been contradictory. Thus, the currently available studies do not support routine perioperative clinical use of melatonin.

The anxiolytic effect of melatonin before surgery is the best-documented effect, and, when used as an anxiolytic agent, melatonin has negligible side-effects. Based on previously documented effect, and, when used as an anxiolytic agent, melatonin has negligible side-effects. Based on previously described studies investigating anxiety and the pharmacokinetics of melatonin, it would appear that 5–10 mg of oral melatonin 30–60 min before operation may have useful effect, but there have been limited data on the dosage.

Declaration of interest

None declared.

References

5. Ismail SA, Mowafi HA. Melatonin provides anxiolysis, enhances analgesia, decreases intraocular pressure, and promotes better operating conditions during cataract surgery under topical anesthesia. Anesth Analg 2009; 108: 1146–51