

Melatonin in Surgery and Critical Care Medicine

Lars P. H. Andersen^{1*}, Mads U. Werner², Jacob Rosenberg¹ and Ismail Gögenur¹

¹Department of Surgery D, Herlev Hospital, University of Copenhagen, DK-2730 Herlev, Denmark

²Multidisciplinary Pain Center 7612, Neuroscience Center, Rigshospitalet, DK-2100 Copenhagen, Denmark

*Corresponding author: Lars Peter Holst Andersen, Department of Surgery D, Herlev Hospital, University of Copenhagen, DK-2730 Herlev, Denmark, Tel: +45 31518908; Fax: +45 38683602; E-mail: lphandersen@gmail.com

Rec date: Apr 11, 2014, Acc date: May 20, 2014, Pub date: May 22, 2014

Copyright: © 2014 Holst Andersen LP. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Administration of exogenous melatonin in surgical and critical care patients has been investigated for various clinical purposes. Studies have demonstrated that melatonin can be used for treatment of preoperative anxiety. The analgesic effect of melatonin is well documented in experimental studies, but still needs to be established further in human clinical studies. The sleep-regulating effects of melatonin in surgical and critical care patients remain unclear. Melatonin has been shown to reduce emergence delirium in the early postoperative period, but no evidence exists in relation to postoperative and intensive care delirium. Limited evidence exists with respect to reduction of oxidative stress in surgical patients. Melatonin has been shown to improve outcome in experimental sepsis models, but still needs to be documented further in human clinical studies. Mechanisms of actions need to be clarified and most importantly dose-response relationships should to be established within the specific procedures and indications. Finally, paramount issues remain in relation to administration form, dosage, timing of administration, and pharmacokinetics of melatonin in surgical and critical care patients.

Keywords: Melatonin; Critical care medicine; Pharmacokinetics

Introduction

Melatonin is a neurohormone secreted from the pineal gland. The main physiological function of melatonin is the regulation of sleep and circadian rhythm [1]. Experimental studies have demonstrated anti-nociceptive [2-4], anxiolytic [5] and anti-oxidative/inflammatory effects [6,7]. Moreover, melatonin has been administered in the treatment of experimentally induced sepsis [8,9]. Recent clinical studies have investigated similar effects of melatonin in surgical and critical care patients [10-18]. These possible clinical effects and the general safety [19] of melatonin make melatonin a potential future supplement to other analgesics, hypnotics, sedatives, and anti-inflammatory drugs used in the treatment of these patient categories.

The aim of this review was to describe the main findings in studies investigating the clinical effects of melatonin in surgical and critical care patients. Moreover, this review discusses the possible role of melatonin in future clinical practice.

Anxiety

Benzodiazepines have traditionally been used to treat preoperative anxiety, but the risk of adverse effects such as heavy sedation, hypoventilation and negative impact on patient mobilization has limited the use in modern fast-track surgery [20]. The preoperative anxiolytic effect of melatonin in surgical patients has been assessed in a recent meta-analysis [21]. Andersen and colleagues demonstrated that melatonin significantly reduced preoperative anxiety, equivalent of 19 mm on a visual analogue scale (VAS) [21]. Final conclusions could, however, not be drawn due to considerable heterogeneity of the included studies. Fifteen singular studies have investigated pre-, intra- and postoperative anxiety [22-36], documenting significant anxiolytic effect in thirteen studies [22-34]. The studies investigated a wide range

of surgical procedures using local, regional or general anesthesia in doses ranging from 3 to 10 mg [21]. The anxiolytic properties of melatonin have not been investigated in an intensive care setting.

Sedation

One study has documented sedation as a desired clinical effect of melatonin administration [37]. This randomized controlled study including 60 patients, investigated melatonin in dental surgery in paediatric patients. The authors could not demonstrate any sedative effects of melatonin administration compared to placebo [37]. Other studies registered sedation as an adverse effect have demonstrated contradictory results [24,26,29,32,33,38-40]. No studies have investigated the administration of melatonin as a sedative in patients in the intensive care unit (ICU), but a study is currently being performed applying melatonin as part of an enteral sedation management protocol [41].

Analgesia

Opioids have a well-known risk of inducing serious adverse effects including hypoventilation, postoperative nausea and vomiting (PONV), and bowel dysfunction [42]. Recent observational studies demonstrated that non-steroidal anti-inflammatory drugs (NSAIDs) may also induce serious adverse effect, such as cerebrovascular and cardiovascular events, and postoperative complications such as anastomotic leakage after colorectal surgery [43-45]. Experimental animal studies have demonstrated dose-dependent anti-nociceptive effects of melatonin [3], whereas results of human studies have been conflicting [10]. A meta-analysis demonstrated that melatonin reduced postoperative pain scores compared to placebo, corresponding to 20 mm on a VAS [21]. Profound heterogeneity, however, also limited the conclusions of this meta-analysis. A total of 13 singular randomized controlled studies have investigated the

analgesic effects of melatonin, documenting pain scores and/or analgesic requirements in the intra- and/or post-operative period [22-24,26-30,32,33,35,38,46]. Six of the 13 studies demonstrated significant analgesic effects [22-24,27,30,38], whereas seven studies were unable to document any analgesic effects of melatonin compared to placebo [26,28,29,32,33,35,46].

In critical care, Gitto and colleagues administered melatonin as part of the analgesic regimen before intubation of infants [14]. The study was a randomized controlled trial including 60 patients. The authors demonstrated that 10 mg/kg body weight of intravenously administered melatonin reduced pain scores significantly for 72 hours measured by the premature infant pain profile (PIPP). Nociceptive reflexes in relation to the intubation procedure did not differ between the groups, measured by the neonatal infant pain scale (NIPS). The authors also demonstrated significant reduction in pro-inflammatory cytokine levels (interleukin (IL) 6, 8, and 12) in patients receiving melatonin [14].

Sleep quality

Sleep architecture is altered during the perioperative period. Rapid eye movement (REM) and slow-wave sleep (SWS) are reduced the first night after surgery [47]. Moreover, the sleep-wake cycle is changed for several weeks after surgery depending on the type of surgical procedure [48]. Similarly, endogenous melatonin plasma levels are decreased following surgery with a subsequent rebound release on the 2. postoperative day [49]. Exogenously administered melatonin has been shown to improve sleep in the treatment of various sleep and circadian rhythm disorders [50].

Four studies have demonstrated significant subjective and objective sleep regulating effects of melatonin administration in the perioperative period [23,25,38,46]. These effects included minor improvements in sleep quality measured by self-reported questionnaires [25,38,46] or increased circadian rhythmicity within the first postoperative week demonstrated by accelerometric movement-related measurements [23]. The randomized double-blind study by Gögenur and colleagues investigated the effect of 5 mg of oral melatonin on postoperative sleep quality [46]. The study demonstrated that the administration of melatonin significantly reduced self-reported sleep latency the first postoperative day. The study did not document other changes in sleep-related outcomes with the administration of melatonin compared to placebo.

Patients in the ICU are similarly known to suffer from impaired sleep and altered circadian rhythms [51]. Sleep changes include sleep loss, sleep fragmentation and sleep-wake cycle disorganization. Furthermore, melatonin secretion is altered with an abolished nocturnal peak [52]. Three studies have investigated the administration of oral melatonin in patients in the ICU using bispectral index (BIS) [53], nurse observation scoring [54] and accelerometric movement-related measures [55]. One study demonstrated that the 'area-under-the-curve of the bispectral index' (AUC-BIS) was significantly reduced in patients treated with melatonin, indicating improved sleep quality [53]. The two other studies did not document any significant differences compared to placebo/controls [54,55]. All studies lacked pre-study power calculation, and only two of the studies were randomized [53,54].

Postoperative-, Intensive Care Unit- and Emergence Delirium

Despite medical advances, the risk of delirium remains high in both surgical and critical care patients, with reported incidences up to 18% and 32%, respectively [56, 57]. The development of delirium is multifactorial, and studies have documented that non-pharmacological multimodal interventions may reduce the duration of symptoms as well as the mortality in these patients [58], whereas limited evidence exists with respect to specific medical interventions [59].

No randomized studies investigating the effect of melatonin as treatment or prophylaxis of delirium in postoperative patients or in the ICU have been published. However, delirium prophylaxis and the administration of melatonin have been investigated in patients in an internal medicine ward [60]. This double-blinded randomized study included 122 patients, and demonstrated that daily low dose melatonin (0.5 mg) significantly reduced the incidence of delirium (12% vs. 31%) in patients treated with melatonin compared to placebo.

Emergence delirium describes a state of confusion in the period following general anesthesia, and occurs with an incidence up to 20% depending on the patient population [61,62]. The effect of melatonin as emergence delirium prophylaxis has been investigated in three randomized controlled paediatric studies [25,36,63]. Melatonin administration was compared to inactive and/or active placebo (midazolam/placebo [25], midazolam [36], dexmedetomidine/midazolam/placebo [63]). All three studies demonstrated that melatonin reduced the incidence of emergence delirium, however, the diagnosis was based on various non-validated diagnostic scales.

Oxidative stress

Free radicals are highly reactive oxygen- or nitrogen-derived molecules [64]. An increased production of free radicals exceeding natural anti-oxidative mechanisms is termed oxidative stress, and can result from surgery, various diseases, or infection [65, 66]. Increased oxidative stress has been correlated to poor clinical outcome in surgical patients- and ICU patients [67,68]. Specific anti-oxidative treatment against oxidative stress has been shown to improve outcome in patients in the ICU [69]. Melatonin is a powerful antioxidant, working both as a free radical scavenger and inducing the natural anti-oxidant defence system [70].

Gitto and colleagues investigated the administration of melatonin in infants undergoing surgery in a cohort study including 40 patients [17]. New-borns are believed to be especially susceptible to oxidative damage due to lower levels of natural anti-oxidant defence, exposure to high oxygen concentrations, and high concentrations of free iron in plasma and erythrocytes. The authors demonstrated that melatonin reduced oxidative stress and inflammatory parameters compared to controls [17]. In adult patients, Küçükakin and colleagues demonstrated that surgery induced oxidative stress, but the authors could not detect any differences between the melatonin-treated patients and patients receiving placebo [39,40]. A recent study demonstrated that long-term preoperative melatonin treatment increased a specific transcription factor (Nrf2) involved in activation of the natural anti-oxidative defence [71]. Clinical outcomes were not investigated in the study.

In the ICU, Gitto and colleagues investigated oxidative stress and the administration of melatonin in infants during medical illnesses,

such as respiratory distress and asphyxia [13,15,16,18]. The administration of melatonin improved cytokine- and anti-inflammatory parameters, and improved clinical outcomes. Two other studies by Gitto, also investigating oxidative stress, are described in the relevant sections of this review (see analgesia and sepsis) [12,14]. In general, the studies by Gitto et al. did not include pre-study power calculations and investigated only few patients with narrow inclusion criteria.

Sepsis

Sepsis is defined as systemic inflammation and the presence of concomitant infection [72]. The mortality rate in severe sepsis still remains approximately 30% [73]. Melatonin has been shown to reduce both inflammatory/oxidative response and improve outcome in lipopolysaccharide (LPS) models and in experimentally induced sepsis [8,74].

A randomized controlled study investigated the effect of administration of 10 + 10 mg of oral melatonin in infants with sepsis [12]. The study demonstrated a significant reduction in oxidative and inflammatory parameters within the first 48 hours after melatonin administration compared to controls. Moreover, the authors described that 3 of 10 untreated patients died, whereas none of the 10 patients in the melatonin-treated group died. The clinical effect of melatonin in adult patients with sepsis has not yet been investigated. However, a recent randomized controlled study by Alamili and colleagues demonstrated that melatonin infusion (100 mg) during LPS-induced endotoxemia significantly reduced levels of the inflammatory markers IL-1beta and YKL-40 (human cartilage glycoprotein) compared to placebo in 12 healthy volunteers [9].

Discussion

Melatonin has been investigated for several clinical effects in the treatment of surgical and critical care patients (Table 1 and 2).

Indication	Number of studies	Total number of patients	Number of studies showing significant effects
Anxiety	15 [22-36]	1266	13 [22-34]
Sedation	1 [37]	60	0
Analgesia (pain scores and/or analgesic requirements)	13 [22-24,26-30,32,33,35,38,46]	941	6 [22,24,27,30,38]
Sleep	4 [23,25,38,46]	311	4 [23,25,38,46]
Delirium	3 [25,36,63]	353	3 [25,36,63]
Oxidative stress	3 [39,40,71]	121	1 [71]
Sepsis	-	-	-

Table 1: The table documents all randomized studies investigating the effect of exogenous melatonin administration in patients undergoing surgery

Indication	Number of studies	Total number of patients	Number of studies showing significant effects
Anxiety	-	-	-
Sedation	-	-	-
Analgesia (pain scores and/or analgesic requirements)	1 [14]	60	1 [14]
Sleep	2 [53,54]	56	1 [53]
Delirium	-	-	-
Oxidative stress	4 [13,15,16,18]	334	4 [13,15,16,18]
Sepsis	1 [12]	30	1 [12]

Table 2: The table documents all randomized studies investigating the effect of exogenous melatonin administration in patients in the intensive care unit.

Dashes indicate that this indication has not been investigated in this patient category.

Preliminary heterogeneous meta-analyses have demonstrated significant anxiolytic and analgesic effects of melatonin in the perioperative period, but further studies need to confirm this. Individual studies investigating sleep-regulating effects of melatonin have shown minor but significant results. Melatonin can be used for emergence delirium prophylaxis, but no evidence exists in relation to prophylaxis or treatment of patients with postoperative- and ICU-related delirium. The anti-oxidative effects of melatonin have been demonstrated in infants, and in a single study in adult surgical patients. One pediatric study has investigated the use of melatonin in the treatment of sepsis, and future studies may document a potential clinical effect in adult patients.

Mechanisms of action

The mechanisms of actions of melatonin have been extensively investigated in several experimental studies, but still remains to be established in humans [2,3,8]. The anxiolytic and sedative effects of melatonin are thought to depend on regulation of central GABA and benzodiazepine-receptors [75,76]. Experimental studies have documented that the analgesic effects of melatonin is regulated through specific melatonin receptors (MT1 and MT2). These receptors are located throughout the lumbar and thoracic spinal cord, and in various regions of the brain. These G protein-coupled receptors regulate several intracellular second messengers, generally leading to decreased levels of cyclic AMP [3]. Furthermore, widespread interaction with various receptor-systems such as the opioid, benzodiazepine, GABA, and NMDA receptors has been documented in several experimental animal studies [2]. Finally, potassium and calcium ion-channels seem to be involved in the analgesic action of melatonin [2,3]. Similarly, the sleep inducing properties of melatonin are thought to be due to these specific melatonin receptors located in the suprachiasmatic nucleus of the hypothalamus [77]. As seen above, the mechanisms behind anxiety, analgesia and sleep seem closely related. It is possible that these clinical phenomena are individually as well as interdependently regulated by the administration of exogenous melatonin. This intimate interaction is also indicated clinically by

studies documenting concomitant anxiolytic, analgesic, and sleep regulating effects in surgical patients [22,23,38].

Another element of the clinical effects of melatonin resides from potent peripheral anti-oxidative and anti-inflammatory effects [70]. Melatonin acts as a direct and indirect free radical scavenger. Furthermore, several anti-oxidative enzymes, such as superoxide dismutase, catalase, GPx enzymes, gammaglutamylcysteine synthase and glutathione reductase are stimulated by the administration of melatonin [64]. Finally, melatonin also regulates well-known inflammatory markers such as lipooxygenase (LOX), cyclo-oxygenase (COX), and phospholipase A2 (PLA2), [78-80]. These anti-oxidative/inflammatory effects are also thought to account for the effect on sepsis [8]. Experimental sepsis studies have documented that melatonin significantly reduced markers of oxidative stress [81], increased levels of anti-oxidant enzymes [82], and reduced pro-inflammatory cytokines [83] in LPS-models and experimentally induced sepsis [8]. Collectively, these mechanisms are thought to restore redox-levels in the cells and improve mitochondrial respiratory chain function in sepsis [74].

Limitations

The correct choice of a clinically effective dose of melatonin still remains uncertain in almost every area of indication. Only a few clinical studies have investigated a proper dose-response relationship for melatonin. The effective dosage as anxiolytic premedication is well documented and is approximately 5 mg of oral melatonin. Within other indications, the clinical effective dosage has been empirically chosen, and still needs to be established further. Gitto and colleagues showed that the repeated administrations of high-dose melatonin (10 x 10 mg/kg BW) improved anti-inflammatory/oxidative parameters and clinical outcomes in infants [17], whereas these outcomes remained unchanged in another study in adult surgical patients receiving 50 mg of melatonin intravenously [40]. Similarly, pain during intubation was reduced using 10 mg/kg BW in infants, while results in pain studies in adults administering 3-10 mg of oral/sublingual melatonin are conflicting [10].

The timing of administration is similarly not well established. As an anxiolytic agent, melatonin possesses clinical effect when administered between 30-100 min before the surgical procedure [21]. With respect to oxidative stress, Kucükakin and colleagues administered melatonin at the time of surgical incision without demonstrating any anti-inflammatory/oxidative effect [39,40], whereas other studies have administered melatonin for extended periods both before and after a surgical insult, demonstrating significantly reduced markers of oxidative stress and improved clinical outcomes [17,71]. In pain research, four of six positive studies administered melatonin the evening before surgery [22-24,38], but as in other indications, the mechanisms behind these observed clinical effects and the specific timing of administration remain uncertain.

Finally, considerations concerning administration route and pharmacokinetics should be addressed. Melatonin can be given by the intravenous, dermal, sublingual and oral administration route in humans. However, studies have shown that only 15% of oral melatonin reaches systemic circulation, and the inter-subject variability is high [84]. Furthermore, clinical studies document alterations of pharmacokinetic properties of melatonin during medical illness, e.g. indicating reduced elimination rates in critically ill patients [85].

Safety

Melatonin does not have any serious immediate or long-term adverse effects in animals or in humans [86,87]. Melatonin has been tested in humans in doses ranging between 1 mg and 3,500 mg without any adverse effects [10,19]. Moreover, long-term treatment is without any apparent adverse effects [88]. Finally, none of the studies referred in this review documented any adverse effects with the administration of melatonin.

Conclusion

Melatonin has been applied for several indications, and might have beneficial clinical effects in surgical and critical care patients. The current literature supports that melatonin can be used in the treatment of preoperative anxiety in doses of approximately 5 mg. The analgesic effect of melatonin still remains to be established in humans before routine clinical use is recommended. The sleep-regulating effect of melatonin has been documented in sleep disorders, but a clinical effect in surgical and critical care patient needs to be established. A possible clinical effect of melatonin has been shown in emergence delirium, but no evidence exists in relation to postoperative- and ICU delirium. Melatonin has been shown to reduce levels of oxidative stress in infants, and in a single study in adults undergoing surgery. Only one study in infants has investigated the effect of melatonin in sepsis, but findings still remain to be confirmed in future human clinical studies. In general, mechanisms of action and documentation of clinically significant effects need to be established in future studies investigating the administration of melatonin in surgical and critically ill patients. Moreover, dose-response relationship needs to be clarified. Finally, central questions remain to be answered in relation to administration route, dosage, timing of administration and pharmacokinetics of melatonin in the surgical and critical care setting.

References

1. Claustrat B, Brun J, Chazot G (2005) The basic physiology and pathophysiology of melatonin. *Sleep Med Rev* 9: 11-24.
2. Ambriz-Tututi M, Rocha-González HI, Cruz SL, Granados-Soto V (2009) Melatonin: a hormone that modulates pain. *Life Sci* 84: 489-498.
3. Srinivasan V, Pandi-Perumal SR, Spence DW, Moscovitch A, Trakht I, et al. (2010) Potential use of melatonergic drugs in analgesia: mechanisms of action. *Brain Res Bull* 81: 362-371.
4. Wilhelmsen M, Amirian I, Reiter RJ, Rosenberg J, Gögenur I (2011) Analgesic effects of melatonin: a review of current evidence from experimental and clinical studies. *J Pineal Res* 51: 270-277.
5. Ochoa-Sanchez R, Rainer Q, Comai S, Spadoni G, Bedini A, et al. (2012) Anxiolytic effects of the melatonin MT(2) receptor partial agonist UCM765: comparison with melatonin and diazepam. *Prog Neuropsychopharmacol Biol Psychiatry* 39: 318-325.
6. Esposito EI, Paterniti I, Mazzon E, Bramanti P, Cuzzocrea S (2010) Melatonin reduces hyperalgesia associated with inflammation. *J Pineal Res* 49: 321-331.
7. Alamili M, Klein M, Lykkesfeldt J, Rosenberg J, Gögenur I (2013) Circadian variation in the response to experimental endotoxemia and modulatory effects of exogenous melatonin. *Chronobiol Int* 30: 1174-1180.
8. Srinivasan V, Pandi-Perumal SR, Spence DW, Kato H, Cardinali DP (2010) Melatonin in septic shock: some recent concepts. *J Crit Care* 25: 656.
9. Alamili M, Bendtzen K2, Lykkesfeldt J3, Rosenberg J4, Gögenur I4 (2014) Melatonin suppresses markers of inflammation and oxidative damage in a human daytime endotoxemia model. *J Crit Care* 29: 184.

10. Yousaf F, Seet E, Venkatraghavan L, Abrishami A, Chung F (2010) Efficacy and safety of melatonin as an anxiolytic and analgesic in the perioperative period: a qualitative systematic review of randomized trials. *Anesthesiology* 113: 968-976.
11. Bellapart J, Boots R (2012) Potential use of melatonin in sleep and delirium in the critically ill. *Br J Anaesth* 108: 572-580.
12. Gitto E, Karbownik M, Reiter RJ, Tan DX, Cuzzocrea S, et al. (2001) Effects of melatonin treatment in septic newborns. *Pediatr Res* 50: 756-760.
13. Gitto E, Reiter RJ, Cordaro SP, La Rosa M, Chiurazzi P, et al. (2004) Oxidative and inflammatory parameters in respiratory distress syndrome of preterm newborns: beneficial effects of melatonin. *Am J Perinatol* 21: 209-216.
14. Gitto E, Aversa S, Salpietro CD, Barberi I, Arrigo T, et al. (2012) Pain in neonatal intensive care: role of melatonin as an analgesic antioxidant. *J Pineal Res* 52: 291-295.
15. Gitto E, Reiter RJ, Sabatino G, Buonocore G, Romeo C, et al. (2005) Correlation among cytokines, bronchopulmonary dysplasia and modality of ventilation in preterm newborns: improvement with melatonin treatment. *J Pineal Res* 39: 287-293.
16. Gitto E, Reiter RJ, Amodio A, Romeo C, Cuzzocrea E, et al. (2004) Early indicators of chronic lung disease in preterm infants with respiratory distress syndrome and their inhibition by melatonin. *J Pineal Res* 36: 250-255.
17. Gitto E, Romeo C, Reiter RJ, Impellizzeri P, Pesce S, et al. (2004) Melatonin reduces oxidative stress in surgical neonates. *J Pediatr Surg* 39: 184-189.
18. Fulia F, Gitto E, Cuzzocrea S, Reiter RJ, Dugo L, et al. (2001) Increased levels of malondialdehyde and nitrite/nitrate in the blood of asphyxiated newborns: reduction by melatonin. *J Pineal Res* 31: 343-349.
19. Nickkhogh A, Schneider H, Sobirey M, Venetz WP, Hinz U, et al. (2011) The use of high-dose melatonin in liver resection is safe: first clinical experience. *J Pineal Res* 50: 381-388.
20. Fredman B, Lahav M, Zohar E, Golod M, Paruta I, et al. (1999) The effect of midazolam premedication on mental and psychomotor recovery in geriatric patients undergoing brief surgical procedures. *Anesth Analg* 89: 1161-1166.
21. Andersen LP, Werner MU, Rosenberg J, Gögenur I (2014) A systematic review of peri-operative melatonin. *Anaesthesia*.
22. Caumo W, Levandovski R, Hidalgo MPL (2009) Preoperative anxiolytic effect of melatonin and clonidine on postoperative pain and morphine consumption in patients undergoing abdominal hysterectomy: a double-blind, randomized, placebo-controlled study. *J Pain* 10: 100-108.
23. Caumo W, Torres F, Moreira NL Jr, Auzani JA, Monteiro CA, et al. (2007) The clinical impact of preoperative melatonin on postoperative outcomes in patients undergoing abdominal hysterectomy. *Anesth Analg* 105: 1263-1271, table of contents.
24. Ionescu D, Bădescu C, Ilie A, Miclutia I, Iancu C et al. (2008) Melatonin as a premedication for laparoscopic cholecystectomy: a double-blind placebo-controlled study. *South African J Anaesth Analg* 14: 8-11.
25. Samarkandi A, Naguib M, Riad W, Thalaj A, Alotibi W, et al. (2005) Melatonin vs. midazolam premedication in children: a double-blind, placebo-controlled study. *Eur J Anaesthesiol* 22: 189-196.
26. Acil M, Basgul E, Celiker V, Karagöz AH, Demir B, et al. (2004) Perioperative effects of melatonin and midazolam premedication on sedation, orientation, anxiety scores and psychomotor performance. *Eur J Anaesthesiol* 21: 553-557.
27. Ismail SA, Mowafi HA (2009) Melatonin provides anxiolysis, enhances analgesia, decreases intraocular pressure, and promotes better operating conditions during cataract surgery under topical anesthesia. *Anesth Analg* 108: 1146-1151.
28. Khezri MB, Merate H (2013) The effects of melatonin on anxiety and pain scores of patients, intraocular pressure, and operating conditions during cataract surgery under topical anesthesia. *Indian J Ophthalmol* 61: 319-324.
29. Khezri MB, Oladi MR2, Atlasbaf A3 (2013) Effect of melatonin and gabapentin on anxiety and pain associated with retrobulbar eye block for cataract surgery: a randomized double-blind study. *Indian J Pharmacol* 45: 581-586.
30. Mowafi HA, Ismail SA (2008) Melatonin improves tourniquet tolerance and enhances postoperative analgesia in patients receiving intravenous regional anesthesia. *Anesth Analg* 107: 1422-1426.
31. Naguib M, Samarkandi AH, Moniem MA, Mansour Eel-D, Alshaer AA, et al. (2006) The effects of melatonin premedication on propofol and thiopental induction dose-response curves: a prospective, randomized, double-blind study. *Anesth Analg* 103: 1448-1452.
32. Naguib M, Samarkandi AH (1999) Premedication with melatonin: a double-blind, placebo-controlled comparison with midazolam. *Br J Anaesth* 82: 875-880.
33. Naguib M, Samarkandi AH (2000) The comparative dose-response effects of melatonin and midazolam for premedication of adult patients: a double-blinded, placebo-controlled study. *Anesth Analg* 91: 473-479.
34. Turkistani A, Abdullah KM, Al-Shaer AA, Mazen KF, Alkatheri K (2007) Melatonin premedication and the induction dose of propofol. *Eur J Anaesthesiol* 24: 399-402.
35. Capuzzo M, Zanardi B, Schifffino E, Buccoliero C, Gragnaniello D, et al. (2006) Melatonin does not reduce anxiety more than placebo in the elderly undergoing surgery. *Anesth Analg* 103: 121-123, table of contents.
36. Kain ZN, MacLaren JE, Herrmann L, Mayes L, Rosenbaum A, et al. (2009) Preoperative melatonin and its effects on induction and emergence in children undergoing anesthesia and surgery. *Anesthesiology* 111: 44-49.
37. Isik B, Baygin O, Bodur H (2008) Premedication with melatonin vs midazolam in anxious children. *Paediatr Anaesth* 18: 635-641.
38. Borazan H, Tuncer S, Yalcin N, Erol A, Otelcioglu S (2010) Effects of preoperative oral melatonin medication on postoperative analgesia, sleep quality, and sedation in patients undergoing elective prostatectomy: a randomized clinical trial. *J Anesth* 24: 155-160.
39. Küçükakin B, Klein M, Lykkesfeldt J, Reiter RJ, Rosenberg J, et al. (2010) No effect of melatonin on oxidative stress after laparoscopic cholecystectomy: a randomized placebo-controlled trial. *Acta Anaesthesiol Scand* 54: 1121-1127.
40. Küçükakin B, Wilhelmsen M, Lykkesfeldt J, Reiter RJ, Rosenberg J, et al. (2010) No effect of melatonin to modify surgical-stress response after major vascular surgery: a randomised placebo-controlled trial. *Eur J Vasc Endovasc Surg* 40: 461-467.
41. Mistraletti G, Mantovani ES, Cadringer P, Cerri B, Corbella D, et al. (2013) Enteral vs. intravenous ICU sedation management: study protocol for a randomized controlled trial. *Trials* 14: 92.
42. Kehlet H, Wilmore DW (2008) Evidence-based surgical care and the evolution of fast-track surgery. *Ann Surg* 248: 189-198.
43. Schjerning Olsen AM, Fosbøl EL, Lindhardsen J, Folke F, Charlott M, et al. (2011) Duration of treatment with nonsteroidal anti-inflammatory drugs and impact on risk of death and recurrent myocardial infarction in patients with prior myocardial infarction: a nationwide cohort study. *Circulation* 123: 2226-2235.
44. Barthélémy O, Limbourg T, Collet JP, Beygui F, Silvain J, et al. (2013) Impact of non-steroidal anti-inflammatory drugs (NSAIDs) on cardiovascular outcomes in patients with stable atherosclerosis or multiple risk factors. *Int J Cardiol* 163: 266-271.
45. Klein M, Gögenur I, Rosenberg J (2012) Postoperative use of non-steroidal anti-inflammatory drugs in patients with anastomotic leakage requiring reoperation after colorectal resection: cohort study based on prospective data. *BMJ* 345: e6166.
46. Gögenur I, Küçükakin B, Bisgaard T, Kristiansen V, Hjortso NC, et al. (2009) The effect of melatonin on sleep quality after laparoscopic cholecystectomy: a randomized, placebo-controlled trial. *Anesth Analg* 108: 1152-1156.
47. Knill RL, Moote CA, Skinner MI, Rose EA (1990) Anesthesia with abdominal surgery leads to intense REM sleep during the first postoperative week. *Anesthesiology* 73: 52-61.

48. Gögenur I, Rosenberg-Adamsen S, Kiil C, Kjaersgaard M, Kehlet H, et al. (2001) Laparoscopic cholecystectomy causes less sleep disturbance than open abdominal surgery. *Surg Endosc* 15: 1452-1455.
49. Gögenur I, Middleton B, Kristiansen VB, Skene DJ, Rosenberg J (2007) Disturbances in melatonin and core body temperature circadian rhythms after minimal invasive surgery. *Acta Anaesthesiol Scand* 51: 1099-1106.
50. Arendt J, Skene DJ (2005) Melatonin as a chronobiotic. *Sleep Med Rev* 9: 25-39.
51. Freedman NS, Gazendam J, Levan L, Pack AI, Schwab RJ (2001) Abnormal sleep/wake cycles and the effect of environmental noise on sleep disruption in the intensive care unit. *Am J Respir Crit Care Med* 163: 451-457.
52. Shilo L, Dagan Y, Smorjick Y, Weinberg U, Dolev S, et al. (1999) Patients in the intensive care unit suffer from severe lack of sleep associated with loss of normal melatonin secretion pattern. *Am J Med Sci* 317: 278-281.
53. Bourne RS, Mills GH, Minelli C (2008) Melatonin therapy to improve nocturnal sleep in critically ill patients: encouraging results from a small randomised controlled trial. *Crit Care* 12: R52.
54. Ibrahim MG, Bellomo R, Hart GK, Norman TR, Goldsmith D, et al. (2006) A double-blind placebo-controlled randomised pilot study of nocturnal melatonin in tracheostomised patients. *Crit Care Resusc* 8: 187-191.
55. Shilo L, Dagan Y, Smorjick Y, Weinberg U, Dolev S, et al. (2000) Effect of melatonin on sleep quality of COPD intensive care patients: a pilot study. *Chronobiol Int* 17: 71-76.
56. Ansaloni L, Catena F, Chattat R, Fortuna D, Franceschi C, et al. (2010) Risk factors and incidence of postoperative delirium in elderly patients after elective and emergency surgery. *Br J Surg* 97: 273-280.
57. Ouimet S, Kavanagh BP, Gottfried SB, Skrobik Y (2007) Incidence, risk factors and consequences of ICU delirium. *Intensive Care Med* 33: 66-73.
58. Lundström M, Edlund A, Karlsson S, Brännström B, Bucht G, et al. (2005) A multifactorial intervention program reduces the duration of delirium, length of hospitalization, and mortality in delirious patients. *J Am Geriatr Soc* 53: 622-628.
59. Zhang H, Lu Y, Liu M, Zou Z, Wang L, et al. (2013) Strategies for prevention of postoperative delirium: a systematic review and meta-analysis of randomized trials. *Crit Care* 17: R47.
60. Al-Aama T, Brymer C, Gutmanis I, Woolmore-Goodwin SM, Esbaugh J, et al. (2011) Melatonin decreases delirium in elderly patients: a randomized, placebo-controlled trial. *Int J Geriatr Psychiatry* 26: 687-694.
61. Lepoussé C, Lautner CA, Liu L, Gomis P, Leon A (2006) Emergence delirium in adults in the post-anaesthesia care unit. *Br J Anaesth* 96: 747-753.
62. Voepel-Lewis T, Malviya S, Tait AR (2003) A prospective cohort study of emergence agitation in the pediatric postanesthesia care unit. *Anesth Analg* 96: 1625-1630, table of contents.
63. Özcengiz D, Gunes Y, Ozmete O (2011) Oral melatonin, dexmedetomidine, and midazolam for prevention of postoperative agitation in children. *J Anesth* 25: 184-188.
64. Reiter RJ, Tan DX, Osuna C, Gitto E (2000) Actions of melatonin in the reduction of oxidative stress. A review. *J Biomed Sci* 7: 444-458.
65. Kucükakin B (2010) Modification of surgical stress response by perioperative melatonin administration. *Dan Med Bull* 57: B4144.
66. de Matos Cavalcante AG, de Bruin PF, de Bruin VM, Nunes DM, Pereira ED, et al. (2012) Melatonin reduces lung oxidative stress in patients with chronic obstructive pulmonary disease: a randomized, double-blind, placebo-controlled study. *J Pineal Res* 53: 238-244.
67. Cornu-Labat G, Serra M, Smith A, McGregor WE, Kasirajan K, et al. (2000) Systemic consequences of oxidative stress following aortic surgery correlate with the degree of antioxidant defenses. *Ann Vasc Surg* 14: 31-36.
68. Cheng WE, Shih CM, Hang LW, Wu KY, Yang HL et al. (2007) Urinary biomarker of oxidative stress correlating with outcome in critically septic patients. *Intensive Care Med* 33: 1468-1472.
69. Nathens AB, Neff MJ, Jurkovich GJ, Klotz P, Farver K, et al. (2002) Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients. *Ann Surg* 236: 814-822.
70. Korkmaz A, Reiter RJ, Topal T, Manchester LC, Oter S, et al. (2009) Melatonin: an established antioxidant worthy of use in clinical trials. *Mol Med* 15: 43-50.
71. Haghjooy Javanmard S, Ziaei A, Ziaei S, Ziaei E, Mirmohammad-Sadeghi M (2013) The effect of preoperative melatonin on nuclear erythroid 2-related factor 2 activation in patients undergoing coronary artery bypass grafting surgery. *Oxid Med Cell Longev* 2013: 676829.
72. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D et al. (2003) 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 31: 1250-1256.
73. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, et al. (2001) Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 29: 1303-1310.
74. Escames G, Acuña-Castroviejo D, López LC, Tan DX, Maldonado MD, et al. (2006) Pharmacological utility of melatonin in the treatment of septic shock: experimental and clinical evidence. *J Pharm Pharmacol* 58: 1153-1165.
75. Golombek DA, Martini M, Cardinali DP (1993) Melatonin as an anxiolytic in rats: time dependence and interaction with the central GABAergic system. *Eur J Pharmacol* 237: 231-236.
76. Papp M, Litwa E, Gruca P, Mocaër E (2006) Anxiolytic-like activity of agomelatine and melatonin in three animal models of anxiety. *Behav Pharmacol* 17: 9-18.
77. Srinivasan V, Pandi-Perumal SR, Trahkt I, Spence DW, Poeggeler B, et al. (2009) Melatonin and melatonergic drugs on sleep: possible mechanisms of action. *Int J Neurosci* 119: 821-846.
78. Steinhilber D, Brungs M, Werz O, Wiesenberg I, Danielsson C, et al. (1995) The nuclear receptor for melatonin represses 5-lipoxygenase gene expression in human B lymphocytes. *J Biol Chem* 270: 7037-7040.
79. Li B, Zhang H, Akbar M, Kim HY (2000) Negative regulation of cytosolic phospholipase A(2) by melatonin in the rat pineal gland. *Biochem J* 351 Pt 3: 709-716.
80. Deng WG, Tang ST, Tseng HP, Wu KK (2006) Melatonin suppresses macrophage cyclooxygenase-2 and inducible nitric oxide synthase expression by inhibiting p52 acetylation and binding. *Blood* 108: 518-524.
81. Sewerynek E, Melchiorri D, Reiter RJ, Ortiz GG, Lewinski A (1995) Lipopolysaccharide-induced hepatotoxicity is inhibited by the antioxidant melatonin. *Eur J Pharmacol* 293: 327-334.
82. Yerer MB, Aydogan S, Yapislir H, Yalcin O, Kuru O, et al. (2003) Melatonin increases glutathione peroxidase activity and deformability of erythrocytes in septic rats. *J Pineal Res* 35: 138-139.
83. Carrillo-Vico A, Lardone PJ, Naji L, Fernández-Santos JM, Martín-Lacave I et al. (2005) Beneficial pleiotropic actions of melatonin in an experimental model of septic shock in mice: regulation of pro-/anti-inflammatory cytokine network, protection against oxidative damage and anti-apoptotic effects. *J Pineal Res* 39: 400-408.
84. Di WL, Kadva A, Johnston A, Silman R (1997) Variable bioavailability of oral melatonin. *N Engl J Med* 336: 1028-1029.
85. Mistraretti G, Sabbatini G, Taverna M, Figini MA, Umbrello M, et al. (2010) Pharmacokinetics of orally administered melatonin in critically ill patients. *J Pineal Res* 48: 142-147.
86. Nordlund JJ, Lerner AB (1977) The effects of oral melatonin on skin color and on the release of pituitary hormones. *J Clin Endocrinol Metab* 45: 768-774.
87. Jahnke G, Marr M, Myers C, Wilson R, Travlos G, et al. (1999) Maternal and developmental toxicity evaluation of melatonin administered orally to pregnant Sprague-Dawley rats. *Toxicol Sci* 50: 271-279.
88. Shaw KM, Stern GM, Sandler M (1973) Melatonin and parkinsonism. *Lancet* 1: 271.