The analgesic effects of exogenous melatonin in humans

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Abstract: The hormone, *melatonin* is produced with circadian rhythm by the pineal gland in humans. The melatonin rhythm provides an endogenous synchronizer, modulating e.g. blood pressure, body temperature, cortisol rhythm, sleep-awake-cycle, immune function and anti-oxidative defense. Interestingly, a number of experimental animal studies demonstrate significant dose-dependent anti-nociceptive effects of exogenous melatonin. Similarly, recent experimental- and clinical studies in humans indicate significant analgesic effects. In *study I*, we systematically reviewed randomized studies investigating clinical effects of perioperative melatonin. Meta-analyses demonstrated significant analgesic- and anxiolytic effects of melatonin in surgical patients, equating reductions of 20 and 19 mm, respectively, on a VAS, compared to placebo. Profound heterogeneity between the included studies was, however, present. In *study II*, we aimed to investigate the analgesic, anti-hyperalgesic, and anti-inflammatory effects of exogenous melatonin in a validated human inflammatory pain model. The study was performed as a randomized, double blind placebo-controlled crossover study. Primary outcomes were pain during the burn injury and areas of secondary hyperalgesia. No significant effects of exogenous melatonin were observed with respect to primary or secondary outcomes, compared to placebo. *Study III* and *IV* estimated the pharmacokinetic variables of exogenous melatonin. Oral melatonin demonstrated a t_{max} value of 41 min. Bioavailability of oral melatonin was only 3%. $T_{1/2\ elimination}$ was approximately 45 min following both oral and intravenous administration respectively. High-dose intravenous melatonin was not associated with increased sedation in terms of simple reaction times, compared to placebo. Similarly, no other adverse effects were reported. In *Study V*, we aimed to re-analyze data obtained from a randomized analgesic drug trial by a selection of standard statistical test. Furthermore, we presented an integrated assessment method of longitudinally measured pain intensity and opioid consumption. Our analyses documented that the employed statistical method impacted the statistical significance of post-operative analgesic outcomes. Furthermore, the novel integrated assessment method combined two interdependent outcomes, lowered the risk of type 2 errors, increased the statistical power, and provided a more accurate description of post-operative analgesic efficacy. Exogenous melatonin may offer an effective and safe analgesic drug. At this moment, however, the results of human studies have been contradictory. High-quality randomized experimental- and clinical studies are still needed to establish a 'genuine' analgesic effect of the drug in humans. Other perioperative effects of exogenous melatonin should also be investigated, before melatonin can be introduced for clinical routine use in surgical patients. Despite promising experimental and clinical findings, several unanswered questions also relate to optimal dosage, timing of administration and administration route of exogenous melatonin.

The thesis is based on the following manuscripts.

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1. **Study I.** Andersen LP, Werner MU, Rosenberg J, Gögenur I. A systematic review of peri-operative melatonin. Anaesthesia 2014; 69: 1163–71.
2. **Study II.** Andersen LP, Gögenur I, Fenger AQ, Petersen MC, Rosenberg J, Werner MU. Analgesic and anti-hyperalgesic effects of melatonin in a human inflammatory pain model: a randomized, double-blind, placebo-controlled, three-arm crossover study. Pain 2015; 156: 2286–94.
3. **Study III.** Andersen LP, Werner MU, Rosenkilde MM, Harpsøe NG, Fuglsang H, Rosenberg J, Gögenur I. Pharmacokinetics of oral and intravenous melatonin in healthy volunteers. BMC Pharmacol Toxicol 2016; 17: 8.
4. **Study IV.** Andersen LP, Werner MU, Rosenkilde MM, Fenger AQ, Petersen MC, Rosenberg J, Gögenur I. Pharmacokinetics of high-dose intravenous melatonin in humans. J Clin Pharmacol 2016; 56: 324–9.
5. **Study V.** Andersen LP, Rosenberg J, Torup H, Gögenur I, Werner MU. Assessment of post-operative analgesic drug efficacy: method of data analysis is critical. Manuscript in preparation.