Intravenous MELAtonin for prevention of Postoperative Agitation and Emergence Delirium in children (MELA-PAED)

A protocol and statistical analysis plan for a randomized clinical trial

Garioud, Anne Louise de Barros; Andersen, Lars Peter Kloster; Jensen, Aksel Karl Georg; Do, Hien Quoc; Jakobsen, Janus Christian; Holst, Lars Broksø; Rasmussen, Lars Simon; Afshari, Arash

Published in:
Acta Anaesthesiologica Scandinavica

DOI:
10.1111/aas.14342

Publication date:
2024

Document version:
Final published version

Received: 25 September 2023 | Accepted: 3 October 2023

DOI: 10.1111/aas.14342

RESEARCH ARTICLE

acta Anaesthesiologica Scandinavica

Intravenous MELAtonin for prevention of Postoperative Agitation and Emergence Delirium in children (MELA-PAED): A protocol and statistical analysis plan for a randomized clinical trial

Anne Louise de Barros Garioud[1,2] | Lars Peter Kloster Andersen[2,3] | Aksel Karl Georg Jensen[4] | Hien Quoc Do[1] | Janus Christian Jakobsen[5,6] | Lars Broksø Holst[1] | Lars Simon Rasmussen[7] | Arash Afshari[1,2]

[1]Department of Anesthesiology, Juliane Marie Center, Copenhagen University Hospital—Rigshospitalet, Copenhagen, Denmark

[2]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

[3]Department of Anesthesiology, Zealand University Hospital, Køge, Denmark

[4]Section of Biostatistics, Department of Public Health, University of Copenhagen, Copenhagen, Denmark

[5]Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark

[6]Department of Regional Health Research, The Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark

[7]Danish Ministry of Defence Personnel Agency, Copenhagen, Denmark

Correspondence
Anne Louise de Barros Garioud, Department of Anesthesiology, Juliane Marie Center, Copenhagen University Hospital—Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark.
Email: annelouise.garioud@icloud.com

Funding information
Dagmar Marshalls Fond; DASAIMs Forskningsinitiativ; Kong Christian den Tiendes Fond; Lægeforeningens Forskningsfond; Lippmann Fonden; Oberstinde Kirsten Jensa la Cours Legat; Rigshospitalet

Abstract

Background: Emergence agitation and delirium in children remain a common clinical challenge in the post-anesthetic care unit. Preoperative oral melatonin has been suggested as an effective preventive drug with a favorable safety profile. The oral bioavailability of melatonin, however, is low. Therefore, the MELA-PAED trial aims to investigate the efficacy and safety of intraoperative intravenous melatonin for the prevention of emergence agitation in pediatric surgical patients.

Methods: MELA-PAED is a randomized, double-blind, parallel two-arm, multi-center, superiority trial comparing intravenous melatonin with placebo. Four hundred participants aged 1–6 years will be randomized 1:1 to either the intervention or placebo. The intervention consists of intravenous melatonin 0.15 mg/kg administered approximately 30 min before the end of surgery. Participants will be monitored in the post-anesthetic care unit (PACU), and the Post Hospitalization Behavior Questionnaire for Ambulatory Surgery (PHBQ-AS) will be performed on days 1, 7, and 14 after the intervention. Serious Adverse Events (SAE) will be assessed up to 30 days after the intervention.

Results: The primary outcome is the incidence of emergence agitation, assessed dichotomously as any Watcha score >2 during the participant's stay in the post-anesthetic care unit. Secondary outcomes are opioid consumption in the post-anesthetic care unit and adverse events. Exploratory outcomes include SAEs, postoperative pain, postoperative nausea and vomiting, and time to awakening, to first oral intake, and to discharge readiness.

Conclusion: The MELA-PAED trial investigates the efficacy of intravenous intraoperative melatonin for the prevention of emergence agitation in pediatric surgical

Trial registration: EudraCT number: 2021-006464-24, Clinicaltrials.gov: NCT05541276.

patients. Results may provide further knowledge concerning the use of melatonin in pediatric perioperative care.

KEYWORDS
children, emergence agitation, emergence delirium, melatonin, sevoflurane

1 | INTRODUCTION

Agitation and delirium are common complications during emergence from anesthesia in preschool-aged children. Several risk factors have been identified including age, sex, choice of anesthetic, type of surgery, and preoperative behavioral traits.[1] The clinical features of emergence agitation include squirming, inconsolable crying, non-purposeful movements, and averted eye gaze. In addition to the discomfort experienced by the child, the condition may require medical interventions in the post-anesthetic care unit (PACU), which can be associated with prolonged postoperative stay and ultimately adverse effects. Furthermore, some studies have suggested an association with new-onset postoperative maladaptive behavior.[1,2]

There are still no consensus recommendations regarding preventive measures for emergence agitation. Therefore, the strategy in clinical practice remains at the discretion of the responsible anesthesiologist. Preventive strategies include total intravenous anesthesia and administration of prophylactic adjunctive agents such as midazolam, opioids, or alpha-2 agonists. More recently, studies have investigated the preventive effect of melatonin or melatonin receptor agonists on emergence agitation.[3–9] Most studies demonstrated some effect of melatonin[3–6,8] and interestingly, one study found a dose–response relationship with the most substantial effect of 0.4 mg/kg (maximum 20 mg) compared with 0.05 and 0.2 mg/kg.[4]

Short-term use of melatonin in doses ranging from 0.3 to 20 mg has been studied in pediatric populations without adverse effects.[10,11] The half-life of exogenous melatonin is approximately 45 min. However, the bioavailability of oral solutions is only approximately 15% with substantial inter-individual variation due to considerable first-pass metabolism.[12] While there is currently no commercially available intravenous melatonin solution, such a drug formulation would present the advantage of more accurate dosing and could hence prove ideal in a pediatric perioperative setting.

This trial aims to investigate the efficacy of intravenous intraoperative melatonin for preventing emergence agitation in children after general anesthesia. We hypothesize that intravenous melatonin can reduce the incidence of emergence agitation in children compared with placebo.

2 | METHODS

The MELA-PAED trial is designed as an investigator-initiated, randomized, controlled, double-blind, multicenter superiority trial with two parallel groups. The groups will be allocated 1:1 to melatonin and placebo, respectively. The primary outcome is the occurrence of emergence agitation during the stay in the PACU.

This trial protocol was developed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[13] The trial will adhere to this protocol, international Good Clinical Practice (GCP) guidelines,[14] the Helsinki Declaration,[15] and current Danish legislation and regulations. Participants will only be enrolled after the publication of the trial protocol and statistical analysis plan. The results of the trial will be reported according to Consolidated Standards of Reporting Trials (CONSORT).[16] Sponsor-investigator on this investigator-initiated trial is the Department of Anesthesiology, Juliane Marie Center, Copenhagen University Hospital—Rigshospitalet, Denmark.

In addition to the main trial, data will be collected for three pre-planned sub-studies, the results of which will be reported separately:

- Pharmacokinetic properties of intravenous melatonin in children aged 1–6 years. A pharmacokinetic open-label sub-study with participants enrolled in parallel with the randomized trial.
- A comparative study of two emergence agitation assessment tools, the Watcha and PAED scales, assessed in a sub-population of the main trial.
- New-onset postoperative maladaptive behavioral changes, characterized as the incidence of behavioral changes such as temper tantrums, nightmares, and sleep disturbances at days 1, 7, and 14 after the intervention.

2.1 | Participants

The trial will enroll 400 participants aged 1–6 years from departments of anesthesiology in academic hospitals with expertise in pediatric anesthesia. Participants will be enrolled from multiple sites including the Department of Anesthesia, Juliane Marie Center, Rigshospitalet, and Sygehus Lillebælt, Vejle. Participants enrolled at the Juliane Marie Center site will be assessed for emergence agitation and delirium employing both the Watcha and the PAED scales and will as such be contributing to the comparative sub-study of the two assessment tools. Twenty additional participants will be enrolled in the pharmacokinetic sub-study in parallel with the main trial. Because of feasibility aspects, the trial will primarily enroll Danish sites. The list of study sites will be updated on clinicaltrials.gov (NCT05541276). Each site's surgical schedules will be screened for trial recruitment, and enrollment will necessitate written consent from legal representatives after providing both written and oral trial information.

Inclusion criteria:

- Patients, 1–6 years of age.
- Elective surgical procedure of an expected duration of at least 30 min in general anesthesia maintained with sevoflurane.

Exclusion criteria:

- Any known allergy or contraindication to study treatment or excipients.
- Current daily medication with melatonin.

2.2 | Intervention

The Investigational Medicinal Product (IMP) will be administered intravenously 30 min before the end of the surgical procedure. The experimental arm will receive melatonin (solution 1 mg/mL) 0.15 mg/kg body weight (maximum dose 5 mg). The comparator arm (placebo) will receive isotonic sodium chloride solution 9 mg/mL in a corresponding volume that is, 0.15 mL/kg body weight (maximum 5 mL).

The melatonin solution for intravenous injection is not commercially available. A new solution has been developed specifically for this trial in cooperation with Glostrup Apotek, Glostrup, Denmark. Since we will recruit pediatric patients in the trial, ethanol as a co-solvent was avoided.[17] Glostrup Apotek has adhered to Good Manufacturing Practice[18,19] in the development of the drug and the Danish Medicines Agency has approved the process. Packaging and labeling of IMP will be performed by Glostrup Apotek according to the centrally generated allocation list and allocated batch numbers. Handling of IMP will only be done by dedicated and trained site staff specified in the delegation log.

The dosage of 0.15 mg/kg (maximum 5 mg) is based on previous pediatric perioperative trials administering oral melatonin 0.05–0.5 mg/kg.[3–6,8] One trial demonstrated a dose–response relationship from 0.05 to 0.4 mg/kg administered orally.[4] Several clinical trials on infants have studied the administration of repeated doses of intravenous melatonin of 10 mg/kg (up to 10 times) without detecting adverse effects.[11] The main benefit of intravenous administration of melatonin is that bioavailability is optimal. Additionally, when the child is under general anesthesia, an intravenous catheter will be in place, thus allowing accurate drug dosage control and timing of drug administration without any inconvenience to the child.

No other prophylactic agitation treatment will be administered for participants in the trial, Participants will receive agitation treatment (rescue medication) based on a standardized algorithm if emergence agitation occurs in the PACU.

2.3 | Outcomes

All outcomes will be assessed from the end of anesthesia until discharge readiness from the PACU.

Primary outcome:

Emergence agitation: The incidence of emergence agitation will be evaluated according to observations on the Watcha score[6] assessed every 15 min from the end of anesthesia and during the PACU stay. The emergence agitation endpoint is defined as any Watcha score >2.

Secondary outcomes:

- *Opioid consumption*: The total amount of opioids administered for postoperative pain in the PACU will be evaluated as units of morphine equivalents per kg body weight (BW).
- *Non-serious adverse events (AE)*: Any untoward medical occurrence not considered serious (as defined below) from the intervention until 24-h follow-up.

Exploratory outcomes:

- Readmission(s) within 30 days.
- Serious Adverse Events (SAE) according to ICH definition.[20]
- Postoperative pain assessed on the FLACC scale.[21]
- PONV (postoperative nausea and vomiting) dichotomously.
- Time to first administration of opioid in PACU.
- Need for rescue medication according to agitation treatment algorithm.
- Time to awakening in PACU.
- Time to first postoperative oral intake.
- Time for discharge readiness according to national guidelines.
- Emergence delirium on the PAED scale.[22,23]

2.4 | Participant timeline and study procedures

The surgical schedules at participating sites will be screened for potential participants according to the trial's eligibility criteria. After obtention of informed consent, participants will be assigned a screening number. On the day of surgery, participants will be assigned a randomization number. Premedication with oral midazolam and/or topical local anesthetics will be administered if needed. Anesthesia will be induced with sevoflurane or intravenous anesthetics and maintained with sevoflurane and opioids. Paracetamol, nonsteroidal anti-inflammatory drugs, as well as peripheral or central nerve blocks can be administered according to clinical indication. No other sedative or analgesic drugs can be administered intra-operatively, including propofol beyond the induction dose. All drugs will be documented in the participants' medical charts.

During the surgical procedure, vital signs including blood pressure, heart rate, oxygen saturation, and respiratory rate will be continuously monitored according to local guidelines. In the PACU, participants will be monitored with continuous pulse oximetry. Assessment of PACU outcomes will be performed every 15 min by delegated trial personnel.

Table 1 outlines the timeline of study procedures and assessments for each participant.

TABLE 1 Scheduled study procedures and assessments.

	Study period					
	Screening	Allocation	Post-allocation	Follow-up		
Timepoint	−21 days to Day 0	Day 0 (day of surgery), T0	Day 0, T0 + 4 h	Day 1	Days 7 and 14	Day 30
Enrollment						
Eligibility screening	X					
Informed consent	X					
Medical history	X					
Concomitant medication	X					
Physical examination	X					
Height and weight	X					
Screening number	X					
Randomization number		X				
Intervention		X				
Assessments						
Vital signs		X	X			
(Blood samples)			(X)[a]			
Emergence agitation			X			
Opioid consumption		X	X	X		
Post-operative pain			X	X		
PONV			X			
Rescue medication			X			
Awakening			X			
Oral intake (time)			X			
Discharge readiness			X			
Emergence delirium			X			
PHBQ-AS[b]				X	X	
Adverse events		X	X	X	X[c]	X[c]

[a]Participants in pharmacokinetic sub-study only.
[b]PHBQ-AS: Post Hospitalization Behavior Questionnaire for Ambulatory Surgery.
[c]Assessment of Serious Adverse Events only.

2.5 | Sample size

Primary outcome:

With 200 participants in each treatment group that is, a total of 400 participants, we will have a power of 80% to detect a 30% relative risk reduction, with $\alpha = .05$, provided that the incidence of emergence agitation in the control group is 45%. Notably, a 30% relative risk reduction corresponds to an incidence of emergence agitation of 32% in the intervention group. The anticipated incidence of emergence agitation in the control group is based on the incidence of 47% found in a recent trial on a similar patient population.[24] We consider a relative risk reduction of 30% as a patient-important difference following the results of previous clinical trials.[3–6,8]

Secondary outcomes:

- Opioid consumption: With an alpha of .05 and a standard deviation of 35 μg/kg, we will have a power of approximately 92% to detect a difference of 20 μg/kg in postoperative opioid consumption. We have estimated that no more than 35% of the population will receive opioids based on data from a recent trial with a similar population.[24]
- Adverse events: With an alpha of .05 and a proportion of 25% in the control group (based on data, including PONV, from a recent trial with a similar population[24]), we will have a power of approximately 70% to detect a relative risk reduction of 40% on adverse events, assuming a reduction in, for example, PONV and pain-related events. Although we have limited power to assess this outcome, we will keep it as a secondary outcome due to its importance in balancing beneficial and harmful effects in a pediatric clinical drug trial.

2.6 | Data collection and management

Data will be collected and managed using REDCap (Research Electronic Data Capture) tools hosted at Capital Region, Denmark as

described in the Data Management and Statistical Analysis Plan, Appendix S1.[25] Source data will be extracted from participants' electronic medical records as well as paper Case Report Forms (CRF), when necessary. A detailed list of recorded variables can be found in Appendix S1. Range checks and the "Data Quality" module in REDCap will be used to promote data quality and flag missingness or untimeliness for specific values and variables.

2.7 | Randomization and blinding

All patients included in the trial will be randomized 1:1 to either intervention or control group according to a computer-generated allocation sequence stratified by site, age group (<2 vs. ≥2 years of age), and sex (male vs. female) using permuted blocks of random sizes. Study staff will be blinded to the sequence and block size. Only designated personnel will have access to perform the randomization. The process of randomization will be performed directly in REDCap.

Investigators, clinical staff, outcome assessors, participants, data managers, the data safety monitoring committee, statisticians, and conclusion makers will be blinded. The intervention and placebo will both be colorless and administered in equal volumes according to weight. Preparation of the IMP will be handled by separate trained staff without contact with the participant. Blinded data will be entered into the REDCap trial database for subsequent blinded data management. The statistical analyses will be conducted by a blinded statistician under the supervision of the Section of Biostatistics, Department of Public Health, University of Copenhagen, with the intervention groups coded as "A" and "B." The steering committee will write and agree on two abstracts while the blinding is intact; one assuming the intervention group is "A" and the control group is "B," and the other assuming the opposite. After this, the randomization code will be broken.

In case of an emergency, an investigator may request for an emergency unblinding when deemed necessary for the participant's safety. The unblinding will be performed directly in REDCap. For cases of system breakdown, a paper version of the allocation list will be kept securely with a person outside of the study team. Only the investigator and participant's code will be unblinded. Sponsor must be notified as soon as possible, but their approval is not necessary for unblinding in case of emergency. The participant will continue to be monitored in the trial after unblinding.

2.8 | Statistical methods

The full analysis set (intention to treat population defined as all randomized participants with useful data) will be used as the primary population for efficacy analyses. The primary efficacy analysis will be repeated within the per-protocol population for comparison. The per-protocol population will be defined as all participants who did not substantially deviate from the protocol that is:

- Received the intervention according to the allocation.
- Did not receive propofol more than 5 min after induction.
- Did not receive clonidine before arrival in PACU.
- Adhered to a minimum of 80% of outcome assessment scores for the primary outcome.

The primary outcome, a dichotomous assessment of emergence agitation, will be analyzed with a two-step approach as a reliable method for covariate adjustment producing a so-called "standardized" or "plug-in" estimator.[26–28] The first step fits a logistic regression model with treatment group, site, age group, and sex as factors. The second step involves creating two predictions (i.e., probabilities for experiencing the outcome) based on this model for each participant: one assuming the participant was assigned the intervention, the other assuming the participant was assigned to the control arm. A group-wise average based on predictions for intervention versus control will then provide the basis for an estimate of the marginal Risk Ratio (RR) of emergence agitation occurrence between the two arms. The estimated RR will be supplemented with bootstrapped 95% confidence intervals (CI) and a two-sided p-value for testing of the null hypothesis that the RR is equal to 1. The estimated marginal risks by treatment group and marginal risk difference including corresponding 95% CI will also be reported.

Other dichotomous variables will be analyzed with a similar statistical approach. Please find a detailed description of all planned statistical analyses in the statistical analysis plan, Appendix S1.

2.9 | Monitoring

An independent Data Safety Monitoring Committee (DSMC) will be established before the initiation of the trial. Members will include a chairman, a member with experience in clinical research, and a member with experience in clinical (pediatric) anesthesia.

After enrolling 50% of planned participants, that is, after the inclusion of 200 participants, the DSMC will review the trial's progress. Specifically, the DSMC will:

- Monitor safety data, incl. SAEs and SARs (serious adverse reaction).
- Provide recommendations regarding continued recruitment, enrollment of additional sites, or whether recruitment should be terminated for certain subgroups due to safety concerns.
- Assess data quality, including data completeness.

The trial will only be terminated early if deemed necessary due to safety concerns. Efficacy analyses will not be evaluated by the DSMC. In addition to the pre-planned meeting of the DSMC after the inclusion of 50% of participants, the DSMC may decide whether any other interim assessments are warranted.

The trial will adhere to GCP standards[14] and be monitored by regional GCP units.

3 | DISCUSSION

Emergence agitation constitutes a significant clinical challenge affecting up to 50% of pediatric patients undergoing surgery and general anesthesia.[29] Emergence agitation increases the risk of complications and may impose a negative behavioral impact beyond the perioperative course.[30] No single drug intervention is widely accepted as the standard of care for preventing emergence agitation in surgical pediatric patients. Furthermore, previously applied drugs demonstrate varying clinical effects and may induce a range of adverse effects.[30]

Previous randomized trials investigating oral preoperative melatonin have shown promising results.[3–6,8] However, some methodological limitations hinder robust conclusions. Therefore, this randomized controlled trial aims to investigate if intravenous intraoperative melatonin could reduce the risk of emergence agitation in surgical pediatric patients.

Intravenous administration possesses several advantages, including improved drug dosage control with optimal bioavailability. Additionally, intraoperative timing of administration provides optimal drug delivery during emergence from anesthesia and early recovery, thereby coinciding with the clinical time course of emergence agitation. These methods may prove ideal in a pediatric population to optimize clinical efficacy and reduce the risk of adverse effects.

We acknowledge that there are currently no commercially available intravenous formulations of melatonin, potentially limiting the reproducibility of our findings. We also recognize that the use of sevoflurane, the gender distribution in surgical patients in this age group, and the type of surgery might limit the generalizability of the results of the trial.

However, we find that a safe drug intervention for the prevention of emergence agitation in children is still needed. The findings of this study may provide further valuable knowledge concerning the use of melatonin within this indication and in this patient group. Further studies may investigate different dosing regimens or include other comparators.

Trial results will be uploaded as soon as possible on clinicaltrials.gov and the EudraCT database. Results—irrespective of their conclusions—will be submitted to an international peer-reviewed medical journal with open access. The author list will be based on contributions according to the International Committee of Medical Journal Editors (ICMJE) recommendations.[31] We will adhere to the CONSORT statement[16] for reporting.

AUTHOR CONTRIBUTIONS

Conceptualization: Anne Louise de Barros Garioud, Lars Peter Kloster Andersen, Arash Afshari. Funding Acquisition: Anne Louise de Barros Garioud, Lars Peter Kloster Andersen. **Methodology:** Anne Louise de Barros Garioud, Lars Peter Kloster Andersen, Aksel Karl Georg Jensen, Hien Quoc Do, Janus Christian Jakobsen, Lars Broksø Holst, Lars Simon Rasmussen, Arash Afshari. **Project Administration:** Anne Louise de Barros Garioud. **Supervision:** Lars Peter Kloster Andersen, Arash Afshari. **Writing – Original Draft Preparation:** Anne Louise de Barros Garioud. **Writing – Review and Editing:** Anne Louise de Barros Garioud, Lars Peter Kloster Andersen, Aksel Karl Georg Jensen, Hien Quoc Do, Janus Christian Jakobsen, Lars Broksø Holst, Lars Simon Rasmussen, Arash Afshari.

ACKNOWLEDGMENTS

Individual ICMJE disclosure forms can be found in the conflict-of-interest appendix, Appendix S2.

FUNDING INFORMATION

The trial has received unrestricted grants from Rigshospitalet Research Grants, Oberstinde Kirsten Jensa la Cours Legat, Lægeforeningens Forskningsfond, DASAIMs Forskningsinitiativ, Dagmar Marshalls Fond, Lippmann Fonden, and Kong Christian den Tiendes Fond.

DATA AVAILABILITY STATEMENT

Final de-identified data and statistical code supporting the findings of the trial will be made available to other researchers through a public open data repository.

ETHICS AND DISSEMINATION

The MELA-PAED trial has been registered in the European Clinical Trials Database (EudraCT 2021-006464-24), clinicaltrials.gov (NCT05541276), and the Knowledge Center for Data Review in the Capital Region (P-2022-782). It has been approved by the Danish National Committee on Health Research Ethics and the Danish Medicines Agency (EudraCT-nr 2021-006464-24). No trial procedure will be performed without prior signed informed consent from both legally acceptable representatives for the participant.

ORCID

Anne Louise de Barros Garioud https://orcid.org/0000-0003-1149-9946
Lars Peter Kloster Andersen https://orcid.org/0000-0003-0053-2560
Aksel Karl Georg Jensen https://orcid.org/0000-0002-1459-0465
Hien Quoc Do https://orcid.org/0000-0002-9124-8612
Janus Christian Jakobsen https://orcid.org/0000-0002-3642-2120
Lars Broksø Holst https://orcid.org/0000-0001-8951-9252
Lars Simon Rasmussen https://orcid.org/0000-0002-7480-3004
Arash Afshari https://orcid.org/0000-0001-5117-9715

REFERENCES

1. Kain ZN, Caldwell-Andrews AA, Maranets I, et al. Preoperative anxiety and emergence delirium and postoperative maladaptive behaviors. *Anesth Analg*. 2004;99(6):1648-1654.
2. Fortier MA, Del Rosario AM, Rosenbaum A, Kain ZN. Beyond pain: predictors of postoperative maladaptive behavior change in children. *Paediatr Anaesth*. 2010;20(5):445-453.
3. Samarkandi A, Naguib M, Riad W, et al. Melatonin vs. midazolam premedication in children: a double-blind, placebo-controlled study. *Eur J Anaesthesiol*. 2005;22(3):189-196.
4. Kain ZN, Maclaren JE, Herrmann L, et al. Preoperative melatonin and its effects on induction and emergence in children undergoing anesthesia and surgery. *Anesthesiology*. 2009;111(1):44-49.
5. Özcengiz D, Gunes Y, Ozmete O. Oral melatonin, dexmedetomidine, and midazolam for prevention of postoperative agitation in children. *J Anesth*. 2011;25(2):184-188.
6. Khalifa OSM, Hassanin AAM. Melatonin, ketamine and their combination in half doses for management of sevoflurane agitation in children undergoing adenotonsillectomy. *Egypt J Anaesth*. 2013;29(4):337-341.

7. Komazaki M, Mihara T, Nakamura N, Ka K, Goto T. Preventive effect of ramelteon on emergence agitation after general anaesthesia in paediatric patients undergoing tonsillectomy: a randomised, placebo-controlled clinical trial. *Sci Rep*. 2020;10(1):21996.
8. Singla L, Mathew PJ, Jain A, Yaddanapudi S, Peters NJ. Oral melatonin as part of multimodal anxiolysis decreases emergence delirium in children whereas midazolam does not. *Eur J Anaesthesiol*. 2021;38(11):1130-1137.
9. Jangra S, Ashok V, Sethi S, Ram J. Atomised intranasal dexmedetomidine versus oral melatonin in prevention of emergence delirium in children undergoing ophthalmic surgery with sevoflurane. *Eur J Anaesthesiol*. 2022;39(11):868-874.
10. Gitto E, Aversa S, Reiter RJ, Barberi I, Pellegrino S. Update on the use of melatonin in pediatrics. *J Pineal Res*. 2011;50(1):21-28.
11. Andersen LPH, Gögenur I, Rosenberg J, Reiter RJ. The safety of melatonin in humans. *Clin Drug Investig*. 2016;36(3):169-175.
12. Harpsøe NG, Andersen LPH, Gögenur I, Rosenberg J. Clinical pharmacokinetics of melatonin: a systematic review. *Eur J Clin Pharmacol*. 2015;71(8):901-909.
13. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med*. 2013;158(3):200-207.
14. European Medicines Agency (EMA). Guideline for good clinical practice E6(R2). *Comm Hum Med Prod*. 2016;6(December):1-68.
15. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194.
16. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *PLoS Med*. 2010;7(3):1-7.
17. European Medicines Agency (EMA). Information for the package leaflet regarding ethanol used as an excipient in medicinal products for human use information for the package leaflet regarding ethanol used as an excipient in medicinal products for human use Table of contents. *Comm Med Prod Hum Use*. 2022;31(September 2018):1-34.
18. European Commission Health and Consumers Directorate-General. *EudraLex—Volume 4—Good Manufacturing Practice (GMP) Guidelines* [Internet]. 2010 Accessed October 17, 2023. https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en
19. European Commision Enterprise and Industry Directorate-General. EudraLex: The Rules Governing Medicinal Products in the European Union. *EU GMP Annex 13: Investigational Medicinal Products*. 2010.
20. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2). *ICH Harmonised Guideline*. 2016 pp. 1–60.
21. Merkel SI, Voepel-Lewis T, Shayevitz JR, Malviya S. The FLACC: a behavioral scale for scoring postoperative pain in young children. *Pediatr Nurs*. 1997;23(3):293-297.
22. Sikich N, Lerman J. Development and psychometric evaluation of the pediatric anesthesia emergence delirium scale. *Anesthesiology*. 2004;100(5):1138-1145.
23. Bajwa SA, Costi D, Cyna AM. A comparison of emergence delirium scales following general anesthesia in children. *Paediatr Anaesth*. 2010;20(8):704-711.
24. Ydemann M, Nielsen BN, Henneberg S, et al. Intraoperative clonidine for prevention of postoperative agitation in children anaesthetised with sevoflurane (PREVENT AGITATION): a randomised, placebo-controlled, double-blind trial. *Lancet Child Adolesc Health*. 2018;2(1):15-24.
25. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381.
26. U.S. Department of Health and Human Services Food and Drug Administration. *Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products. Guidance Document* [Internet]. 2023 Accessed October 17, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adjusting-covariates-randomized-clinical-trials-drugs-and-biological-products
27. Steingrimsson JA, Hanley DF, Rosenblum M. Improving precision by adjusting for prognostic baseline variables in randomized trials with binary outcomes, without regression model assumptions. *Contemp Clin Trials*. 2017;54:18-24.
28. Morris TP, Walker AS, Williamson EJ, White IR. Planning a method for covariate adjustment in individually randomised trials: a practical guide. *Trials*. 2022;23(1):1-17.
29. Vlajkovic GP, Sindjelic RP. Emergence delirium in children: many questions, few answers. *Anesth Analg*. 2007;104(1):84-91.
30. Nair S, Wolf A. Emergence delirium after paediatric anaesthesia: new strategies in avoidance and treatment. *BJA Educ*. 2018;18(1):30-33.
31. International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals *[Internet]*. International Committee of Medical Journal Editors (ICMJE); 2023. p. 1. Accessed October 17, 2023. http://www.icmje.org/icmje-recommendations.pdf

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Garioud ALB, Andersen LPK, Jensen AKG, et al. Intravenous MELAtonin for prevention of Postoperative Agitation and Emergence Delirium in children (MELA-PAED): A protocol and statistical analysis plan for a randomized clinical trial. *Acta Anaesthesiol Scand*. 2024;68(2):280-286. doi:10.1111/aas.14342