ISRCTN18296119 https://doi.org/10.1186/ISRCTN18296119

Melatonin for Anxiety prior to General anaesthesia In Children (MAGIC)

Submission date
08/01/2019

Recruitment status
No longer recruiting

Registration date
10/01/2019

Overall study status
Completed

Last Edited
25/02/2025

Condition category
Surgery

[X] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Current plain English summary as of 23/10/2020:

Background and study aims
Midazolam is an effective premedication in anxious children undergoing general anaesthesia, but it can have considerable side effects including respiratory suppression (slow and ineffective breathing), agitation, sedation, delayed recovery, sleep disturbance and nausea/vomiting. There is therefore a need for a safer medication which is as effective at reducing anxiety as midazolam. Melatonin has been found to be as effective as midazolam in the management of pre-operative anxiety in adults, although its effectiveness in children is not confirmed. A major flaw in previous trials relates to comparing a general pre-operative child group rather than selecting for specifically-anxious children; the effects of both melatonin and any comparator are therefore weakened by those children who would not have normally been selected for premedication ahead of surgery. Melatonin has an excellent side-effect profile, and may have further advantages over midazolam in that it reduces anxiety without sedation, reduces pain and improves post-discharge sleep disturbance. The aim of this study is to assess melatonin's effectiveness in anxious children ahead of general anaesthesia comparing it against the current standard, midazolam.

Who can participate?
Children aged 3-14 years undergoing elective dental, ophthalmological or ENT surgery under general anaesthesia, and assessed by healthcare professionals as requiring premedication

What does the study involve?
Following consent both a parent/guardian and the child complete separate questionnaires about how they feel. If the child is eligible to take part in the study, and this has been agreed by the hospital research team, then they are randomly allocated by a computer to one of the two treatment options: midazolam or melatonin. About 30 minutes before the participant is due to undergo general anaesthetic they receive their pre-medication (midazolam or melatonin). The participant is accompanied by a companion nurse during their trip from the ward into the anaesthetic room. Surgery happens as per usual care. The companion nurse sits with the parent /guardian(s) and child throughout their recovery from the surgery. They monitor the child's recovery and check with the child as to how they are feeling. At 14 days after surgery a research

nurse calls the parent/guardian(s) to ask a few simple questions about how they got on after discharge from hospital. Their child is asked to complete the same questionnaire that they completed before receiving their pre-medication.

What are the possible benefits and risks of participating?
There is a possibility that melatonin might not be as effective as midazolam at reducing anxiety, although early clinical trials have suggested that the effects of both medicines on anxiety are similar. On the day, should the child feel they cannot go ahead with the operation, the operation would be re-arranged for another day, and the child's anaesthetist will decide which pre-medication to give them at that time as part of standard of care as they will no longer be in the study. Midazolam is known to have some serious side effects. These are the most common ones (between 1/100 and 1/10 people): sedation, sleepiness, lower levels of consciousness, respiratory depression, nausea and vomiting. Midazolam is a commonly used drug for children undergoing general anaesthesia. It is likely an anxious child would still receive this even if they don't take part in the trial to reduce their anxiety. Melatonin is considered a very safe medicine and has no known serious side effects at the dose that will be used in this study; this is the main reason why this study is testing whether it can replace Midazolam as a pre-medication. However, all drugs have the potential to have side effects and so we could find a side effect that hasn't been seen before. If melatonin does not sufficiently reduce the participant's anxiety they may not be able to have their surgery on the day. This means it may need to be rearranged if not successful and the child's anaesthetist will decide which pre-medication to give them at that time as part of standard of care as they will no longer be in the study. If the participant receives melatonin and it is successful in reducing anxiety, then it is possible that the participant will have avoided some of the known side effects of midazolam – these include breathing problems, taking longer to recovery from the anaesthetic and occasionally becoming overexcited rather than calmed. The participants will also be contributing to research that will help children who need similar medication in the future.

Where is the study run from?
University of Sheffield (UK)

When is the study starting and how long is it expected to run for?
March 2018 to December 2023

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
Marie Hyslop, m.c.hyslop@sheffield.ac.uk

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Previous plain English summary as of 05/08/2020:

Background and study aims
Midazolam is an effective premedication in anxious children undergoing general anaesthesia, but it can have considerable side effects including respiratory suppression (slow and ineffective breathing), agitation, sedation, delayed recovery, sleep disturbance and nausea/vomiting. There is therefore a need for a safer medication which is as effective at reducing anxiety as midazolam. Melatonin has been found to be as effective as midazolam in the management of pre-operative anxiety in adults, although its effectiveness in children is not confirmed. A major flaw in previous trials relates to comparing a general pre-operative child group rather than selecting for

specifically-anxious children; the effects of both melatonin and any comparator are therefore weakened by those children who would not have normally been selected for premedication ahead of surgery. Melatonin has an excellent side-effect profile, and may have further advantages over midazolam in that it reduces anxiety without sedation, reduces pain and improves post-discharge sleep disturbance. The aim of this study is to assess melatonin's effectiveness in anxious children ahead of general anaesthesia comparing it against the current standard, midazolam.

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Where is the study run from?
1. Sheffield Childrens Hospital

2. Royal Aberdeen Children's Hospital
3. Royal Bolton Hospital
4. Barnsley Hospital
5. Royal Stoke University Hospital, Stoke-on-Trent
6. Doncaster Royal Infirmary
7. Lister Hospital, Stevenage
8. Tayside Childrens Hospital
9. Royal Hospital for Children, Glasgow
10. University Hospital Crosshouse, Kilmarnock
11. Alder Hey Children's Hospital
12. Royal Manchester Children's Hospital
13. The James Cook University Hospital
14. Royal Victoria Infirmary
15. Newcastle Dental Hospital
16. Sunderland Royal Hospital

When is the study starting and how long is it expected to run for?
March 2018 to July 2022

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
Marie Hyslop, m.c.hyslop@sheffield.ac.uk

Previous plain English summary:

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Midazolam is an effective premedication in anxious children undergoing general anaesthesia, but it can have considerable side effects including respiratory suppression (slow and ineffective breathing), agitation, sedation, delayed recovery, sleep disturbance and nausea/vomiting. There is therefore a need for a safer medication which is as effective at reducing anxiety as midazolam. Melatonin has been found to be as effective as midazolam in the management of pre-operative anxiety in adults, although its effectiveness in children is not confirmed. A major flaw in previous trials relates to comparing a general pre-operative child group rather than selecting for specifically-anxious children; the effects of both melatonin and any comparator are therefore weakened by those children who would not have normally been selected for premedication ahead of surgery. Melatonin has an excellent side-effect profile, and may have further advantages over midazolam in that it reduces anxiety without sedation, reduces pain and improves post-discharge sleep disturbance. The aim of this study is to assess melatonin's effectiveness in anxious children ahead of general anaesthesia comparing it against the current standard, midazolam.

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Where is the study run from?
1. Sheffield Childrens Hospital
2. Royal Aberdeen Children's Hospital
3. Royal Bolton Hospital
4. Addenbrookes Hospital
5. Croydon University Hospital
6. Doncaster Royal Infirmary
7. Darlington Memorial Hospital
8. Tayside Childrens Hospital
9. Royal Hospital for Children, Glasgow
10. University Hospital Crosshouse
11. Alder Hey Children's Hospital
12. Royal Manchester Children's Hospital
13. Medway Maritime Hospital, Medway
14. The James Cook University Hospital

15. Royal Victoria Infirmary
16. Newcastle Dental Hospital
17. Sunderland Royal Hospital

When is the study starting and how long is it expected to run for?
March 2018 to July 2021

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
Dr Anna Thomason
a.l.thomason@sheffield.ac.uk

Study website
https://www.sheffield.ac.uk/scharr/research/centres/ctru/magic

Contact information

Type(s)
Scientific

Contact name
Ms Marie Hyslop

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Clinical Trials Research Unit
ScHARR
University of Sheffield
Regent Court
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Sheffield
United Kingdom
S1 4DA
+44 (0)114 222 4347
m.c.hyslop@sheffield.ac.uk

Additional identifiers

EudraCT/CTIS number
2018-000991-13

IRAS number
228234

ClinicalTrials.gov number

Secondary identifying numbers
CPMS 40234, IRAS 228234

Study information

Scientific Title
The MAGIC trial (Melatonin for Anxiety prior to General anaesthesia In Children): A Multicentre, Parallel Randomised Controlled Trial of Melatonin Versus Midazolam in the Premedication of Anxious Children Attending for Elective Dental, Ophthalmologic or ENT Surgery Under General Anaesthesia

Acronym
MAGIC

Study objectives
Melatonin is not inferior to midazolam in reducing anxiety in children pre-GA with fewer side effects.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 16/01/2019, North West – Liverpool Central Research Ethics Committee (3rd Floor Barlow House, 4 Minshull Street, Manchester, M1 3DZ; +44 (0)207 104 8196; nrescommittee.northwest-liverpoolcentral@nhs.net), ref: 18/NW/0758

Study design
Randomized; Both; Design type: Process of Care, Drug, Qualitative

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Anxiety prior to general anaesthesia

Interventions
Current interventions as of 23/10/2020:

This study:
1. Has two arms: melatonin vs midazolam

2. Is a parallel design i.e. patients will be allocated at a 1:1 ratio between the two arms
3. Is double blinded whereby the anaesthetists, surgeons and observer nurses will be fully blinded, with patient allocation concealment. Pharmacists will be unblinded
4. Will recruit both parents and children for participation in the trial. Parents will be asked to complete questionnaires on their anxiety as part of their participation
5. Is multicentre

The study is comprised of the feasibility pilot (first 6 months of recruitment) and the main study (the remaining recruitment period). There will be a stop/go decision at the end of the pilot phase based on recruitment and retention of during the first 6 months. A traffic light system defines the levels of recruitment and retention required in order for the main trial to continue.

Qualitative interviews with parents, children and research staff shall also inform the trialists on the success of enrolment during the internal pilot, identify any problems encountered and assist recruitment during the main trial. Further qualitative interviews in the main trial shall provide insight into stakeholder and patient acceptability of melatonin.

Eligible patients will have the following assessments, typically all on the same day:
1. Consent: Candidates (children and their parents) candidates shall be approached for consent by a suitably qualified medical professional (including research nurses).
2. Randomisation
3. Baseline: On the morning of surgery, following consent and randomisation , the following assessments will be completed:
3.1. American Society of Anaestheiologists (ASA) physical status
3.2. State-Trait Anxiety Inventory (STAI)
3.3. Modified Yale Preoperative Anxiety Scale (mYPAS)
3.4. Child Health Utility 9D questionnaire (CHU9D)
3.5. Cooperation score and resource use
4. Drug administration: Drug will be administered 30 minutes prior to the patient transfer by a member of the team who has been delegated to do so
5. Transfer to Theatre Admissions Unit (TAU): Following administration, a second, blinded, assessor will accompany the patient on transfer to the TAU. The following information will be collected following transfer and prior to surgery:
5.1. mYPAS
5.2. Additional medication given
5.3. Adverse events
6. Surgery: During surgery the following information should be recorded:
6.1. Completion of surgery
6.2. Time of extubation
6.3. Additional medication given
6.4. Adverse events
7. Post-surgery: Post-surgery the following information should be recorded:
7.1. Additional medication given including analgesia usage
7.2. Adverse events
7.3. Time to Post Anaesthesia Care Unit (PACU)
7.4. Vital signs
7.5. Time to discharge readiness
7.6. Time to actual discharge
8. In Post Anesthesia Care Unit (PACU):
8.1. Patient reported Faces Pain Score – Revised (FPS-R) every 15 minutes in PACU until discharge /maximum 2 hours whichever is first
8.2. Observer reported FPS-R every 15 minutes in PACU until discharge/maximum 2 hours

whichever is first
8.3. Cooperation score every 15 minutes in PACU until discharge/maximum 2 hours whichever is first
8.4. Paediatric anaesthesia emergence delirium (PAED) index every 15 minutes in PACU until discharge/maximum 2 hours whichever is first
8.5. Vancouver Sedation Recovery Scale (VSR) every 15 minutes in PACU until discharge /maximum 2 hours whichever is first
9. 14 day follow up via phone: The following assessments should be completed:
9.1. Adverse events
9.2. PHBQ
9.3. CHU9D

The trialists are proposing to undertake a sub-study, using a Study With a Trial (SWAT) design to evaluate the effectiveness of a personalised text message including the recipient's name, versus a standard text message for prompting response in trial participants to answer and complete telephone follow-up questionnaires in MAGIC. Participants of the MAGIC trial who provide a mobile phone number will be randomly allocated to receive either a personalised or standard text message prior to their follow-up telephone call. This SWAT should not represent any further burden to participants. Data from the SWAT will contribute to the 'PROmoting THE Use of SWATs' (PROMETHEUS) Programme (hosted by York Trials Unit at the University of York and supported by funding from MRC (https://www.york.ac.uk/healthsciences/research/trials /research/swats/prometheus/) and will help to increase the evidence base on the recruitment of participants to trials.

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3.4. Child Health Utility 9D questionnaire (CHU9D)
3.5. Cooperation score and modified post-box test
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7.6. Time to actual discharge
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8.3. Cooperation score and modified post-box test
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Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Melatonin, midazolam

Primary outcome measure
Preoperative distress measured using the modified Yale Preoperative Anxiety Scale (mYPAS); Timepoint(s): baseline, start of transfer to TAU, entry to TAU, administration of anaesthesia

Secondary outcome measures
Safety:
1. Mortality measured using PAED assessment post-surgery
2. Post-surgical recovery measured using VSR and FPS-R post-surgery
3. Post-discharge behaviour measured using PHBQ at 14 days follow-up
4. Analgesia requirements and adverse events measured using the concomitant medication and adverse events collected pre-, during and post-surgery
5. Orientation and cognitive/psychomotor function measured using the cooperation score post-surgery
6. Serious adverse events reported at pre- and post-surgery and 14 days

Efficacy:
1. Anaesthetic turnaround time and recovery time measured using time of induction of anesthesia, time of surgery completion and time to discharge
2. Anaesthetic failure rate measured using anaesthesia abandonment cases pre-surgery

Qualitative:
1. Recruitment experiences and acceptability of the two drugs assessed using responses from interviews with patients and stakeholders at interviews held post the 14 days follow-up

Economic:
1. The cost-effectiveness of introducing melatonin, compared to midazolam, over the study period. A decision tree model will be developed to estimate cost-effectiveness and cost per QALY over a 1-year period

Overall study start date
01/03/2018

Completion date
31/12/2023

Eligibility

Key inclusion criteria
Current inclusion criteria as of 23/10/2020:

1. Children aged 3-14 years undergoing elective dental, ophthalmological or ENT surgery under general anaesthesia
2. Pragmatically assessed by healthcare professionals as requiring premedication as per local standard care for high/expected high levels of preoperative distress prior to elective dental/ENT /ophthalmological surgery under general anaesthetic, including known negative experiences, failed anaesthesia, parents displaying high levels of distress, additional/special needs or judged as unable to tolerate general anaesthetic without premedication
3. ASA grades I & II
4. Parent or person with parental responsibility able to give written, informed consent and child willing to assent

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Previous inclusion criteria:

1. Children aged 5-14 years undergoing elective dental, ophthalmological or ENT surgery under general anaesthesia
2. Pragmatically assessed by healthcare professionals as requiring premedication as per local standard care for high/expected high levels of preoperative distress prior to elective dental/ENT /ophthalmological surgery under general anaesthetic, including known negative experiences, failed anaesthesia, parents displaying high levels of distress, additional/special needs or judged as unable to tolerate general anaesthetic without premedication
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Participant type(s)
Patient

Age group
Child

Lower age limit
3 Years

Upper age limit
14 Years

Sex
Both

Target number of participants
Planned Sample Size: 1650; UK Sample Size: 1650; (child sample size: 624)

Total final enrolment
110

Key exclusion criteria
Current exclusion criteria as of 23/10/2020:

1. Not undergoing elective, day-case dental, ophthalmological or ENT surgery under general anaesthesia
2. Not displaying level of anxiety that would usually warrant premedication under the standard NHS care pathway
3. Reason for premedication other than anxiety
4. Current prescription of melatonin, midazolam or other non-permitted drug (please see protocol)
5. Obstructive sleep apnoea
6. ASA grades III, IV & V
7. Severe learning disability rendering child unable to communicate even with specialised support
8. Parent declines for their child to participate in the trial

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Previous exclusion criteria:

1. Not undergoing elective, day-case dental, ophthalmological or ENT surgery under general anaesthesia
2. Not displaying level of anxiety that would usually warrant premedication under the standard NHS care pathway
3. Reason for premedication other than anxiety
4. Current prescription of melatonin, midazolam or other non-permitted drug (please see section 7.11.2)
5. Obstructive sleep apnoea
6. ASA grades III, IV & V
7. Severe learning disability rendering child unable to communicate even with specialised support

Date of first enrolment
10/07/2019

Date of final enrolment
13/03/2023

Locations

Countries of recruitment
England

Scotland

United Kingdom

Study participating centre
Sheffield Childrens Hospital (lead centre)
Sheffield Children's Hospital
Clarkson St
Sheffield

United Kingdom
S10 2TQ

Study participating centre
Royal Aberdeen Children's Hospital
Westburn Rd
Aberdeen
United Kingdom
AB25 2ZG

Study participating centre
Royal Bolton Hospital
Minerva Rd
Farnworth
Bolton
United Kingdom
BL4 0JR

Study participating centre
Doncaster Royal Infirmary
Thorne Rd
Doncaster
United Kingdom
DN2 5LT

Study participating centre
Tayside Childrens Hospital
Ninewells Hospital & Medical School
United Kingdom
DD1 9SY

Study participating centre
Royal Hospital for Children
1345 Govan Road
Glasgow
United Kingdom
G51 4TF

Study participating centre

University Hospital Crosshouse Kilmarnock
Kilmarnock Rd
Crosshouse
Kilmarnock
United Kingdom
KA2 0BE

Study participating centre
Alder Hey Children's Hospital
E Prescot Rd
Liverpool
United Kingdom
L14 5AB

Study participating centre
Royal Manchester Children's Hospital
Oxford Rd
Manchester
United Kingdom
M13 9WL

Study participating centre
The James Cook University Hospital
Marton Rd
Middlesbrough
United Kingdom
TS4 3BW

Study participating centre
Royal Victoria Infirmary
Queen Victoria Rd
Newcastle upon Tyne
United Kingdom
NE1 4LP

Study participating centre
Newcastle Dental Hospital
Richardson Rd
Newcastle upon Tyne
United Kingdom
NE2 4AZ

Study participating centre
Sunderland Royal Hospital
Kayll Rd
Sunderland
United Kingdom
SR4 7TP

Study participating centre
Lister Hospital
Coreys Mill Lane
Hertfordshire
Stevenage
United Kingdom
SG1 4AB

Study participating centre
Barnsley Hospital
Gawber Road
Barnsley
United Kingdom
S75 2EP

Sponsor information

Organisation
Sheffield Teaching Hospitals NHS Foundation Trust

Sponsor details
c/o Alessia Dunn
Northern General Hospital
Herries Road
Sheffield
England
United Kingdom
S5 7AU
+44 (0)114 271 2550
alessia.dunn@sth.nhs.uk

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/018hjpz25

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: 16/80/08

Results and Publications

Publication and dissemination plan
Current publication and dissemination plan as of 16/02/2024:
Planned publication in high impact journal (BJA). Results were also disseminated to all patients and their parents who participated. This was done by trial summary leaflets (age-specific) sent directly via post.

Previous publication and dissemination plan:
The protocol will be available online via the MAGIC website once approvals have been received. The statistical analysis plan will not be made publicly available at this time.

Intention to publish date
31/07/2024

Individual participant data (IPD) sharing plan
Current IPD sharing plan as of 19/02/2024:
The dataset generated and analysed during the trial is available upon request. The dataset is stored at the University of Sheffield on a secure network.
1. The name and email address of the investigator/body who should be contacted for access to the datasets: Currently CI - Prof. Chris Deery (custodian) - c.deery@sheffield.ac.uk
2. The type of data that will be shared: anonymised dataset
3. Dates of availability: until 30th June 2048 (25 years after the end of the study)
4. Whether consent from participants was required and obtained: consent from particpants was obtained
5. Comments on data anonymization: all data will be anonymised

Previous IPD sharing plan:
The datasets generated during and/or analysed during the current study are/will be available upon request. The dataset will be stored at the University of Sheffield on a secure network. Details of the data-sharing requirements are not yet available. Various details of the dataset will be included in the publication.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Interim results article	qualitative internal pilot study	16/07/2021	19/07/2021	Yes	No
HRA research summary			28/06/2023	No	No
Results article		10/11/2023	13/11/2023	Yes	No
Other publications	embedded randomised controlled retention trial	07/02/2024	07/02/2024	Yes	No
Statistical Analysis Plan	version 3		16/02/2024	No	No
Protocol file	version 4.1	28/09/2020	20/02/2024	No	No
Results article	Acceptability qualitative interview study results	05/12/2024	11/12/2024	Yes	No
Other publications	Barriers and enablers to recruiting participants	04/02/2025	25/02/2025	Yes	No