Clinical trial results:
The anxiolytic effects of melatonin: A randomized, placebo-controlled, double-blinded clinical study.

Summary

EudraCT number	2014-003789-25
Trial protocol	DK
Global end of trial date	13 March 2021

Results information

Result version number	v1 (current)
This version publication date	01 July 2021
First version publication date	01 July 2021

Trial information

Trial identification

Sponsor protocol code	mela1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02386319
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Department of surgery, Herlev Hospital
Sponsor organisation address	Borgmester Ib Juuls Vej 1, Herlev, Denmark, 2730
Public contact	Dennis Bregner Zetner, Department of surgery, Herlev Hospital, 0045 27291376, dennis.bregner.zetner@regionh.dk
Scientific contact	Dennis Bregner Zetner, Department of surgery, Herlev Hospital, 45 27291376, dennis.bregner.zetner@regionh.dk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 March 2021
Global end of trial reached?	Yes
Global end of trial date	13 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study's main objective is to investigate melatonins anxiolytic effects in surgical patients (inguinal or umbilical hernia).

Protection of trial subjects:

Besides the study intervention, trial participants received standard care including a common anesthetic and analgesic regimen.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 October 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	27
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

56 patients were screened for inclusion. 6 of these patients did not meet the inclusion criteria. 20 patients were excluded due to unwllllingness to participate.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Melatonin

Arm description:

The group of patients receiving melatonin treatment related to surgery

Arm type	Experimental
Investigational medicinal product name	Melatonin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

4x10 mg melatonin. First dose of 10 mg 21:00 the night before surgery, second dose of 10 mg, 2 hours before surgery, third dose of 10 mg after surgery and final dose of 10 mg 21:00 the day of surgery

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One Oral tablet placebo x 4.
1st tablet. 21:00 the night before surgery
2nd tablet. 2 hours before surgery
3rd tablet. After surgery
4th tablet. 21:00 the day of surgery.

Number of subjects in period 1	Melatonin	Placebo
Started	18	18
Completed	16	17
Not completed	2	1
Consent withdrawn by subject	-	1
surgery cancelled	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Melatonin
Reporting group description:	
The group of patients receiving melatonin treatment related to surgery	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Melatonin	Placebo	Total
Number of subjects	18	18	36
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
median	57	60	
inter-quartile range (Q1-Q3)	45 to 62	50 to 69	-
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	18	18	36
Weight			
Units: kg			
median	87	90	
inter-quartile range (Q1-Q3)	73 to 95	81 to 94	-
Height			
Units: cm			
median	184	181	
inter-quartile range (Q1-Q3)	180 to 190	176 to 187	-
State anxiety			
STAI scale, state anxiety at enrolment			
Units: STAI			
median	27	27	
inter-quartile range (Q1-Q3)	22 to 34	23 to 31	-
Trait anxiety			
Baseline trait anxiety on the STAI scale			
Units: STAI			
median	30	27	

inter-quartile range (Q1-Q3)	23 to 34	24 to 30	-
VAS anxiety			
Visual Analogue Scale of anxiety at the time of enrolment			
Units: VAS			
median	5	5	
inter-quartile range (Q1-Q3)	0 to 10	1 to 14	-

End points

End points reporting groups

Reporting group title	Melatonin
Reporting group description: The group of patients receiving melatonin treatment related to surgery	
Reporting group title	Placebo
Reporting group description: -	

Primary: Preoperative anxiety (STAI), one hour before surgery

End point title	Preoperative anxiety (STAI), one hour before surgery
End point description:	
End point type	Primary
End point timeframe: Anxiety measured one hour before surgery	

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: STAI				
median (inter-quartile range (Q1-Q3))	27 (24 to 34)	28 (24 to 33)		

Statistical analyses

Statistical analysis title	Preoperative STAI
Comparison groups	Melatonin v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.814
Method	Wilcoxon (Mann-Whitney)

Secondary: VAS anxiety one hour before surgery

End point title	VAS anxiety one hour before surgery
End point description: Anxiety measured by Visual Analogue Scale, from 0 = no anxiety to 100= highest possible anxiety	
End point type	Secondary
End point timeframe: VAS anxiety one hour before surgery	

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: VAS				
median (inter-quartile range (Q1-Q3))	7 (0 to 28)	7 (1 to 13)		

Statistical analyses

Statistical analysis title	Preoperative VAS
Comparison groups	Melatonin v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.813
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)

Secondary: Day1, Sleep amout

End point title	Day1, Sleep amout
End point description:	

End point type	Secondary
End point timeframe:	
Night before surgery	

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: Hours				
median (inter-quartile range (Q1-Q3))	7 (6.5 to 8.3)	6.5 (6.3 to 7)		

Statistical analyses

Statistical analysis title	Sleep amount
Comparison groups	Melatonin v Placebo

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.165
Method	Wilcoxon (Mann-Whitney)

Secondary: Day1, Number of awakenings

End point title	Day1, Number of awakenings

End point description:

End point type	Secondary

End point timeframe:

Night before surgery

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: No. of awakenings				
median (inter-quartile range (Q1-Q3))	1 (1 to 2)	2 (1 to 3)		

Statistical analyses

Statistical analysis title	Day1, Awakenings
Comparison groups	Melatonin v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.725
Method	Wilcoxon (Mann-Whitney)

Secondary: Day 1, Time awake

End point title	Day 1, Time awake

End point description:

End point type	Secondary

End point timeframe:

Night before surgery

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: Minutes				
median (inter-quartile range (Q1-Q3))	7 (3 to 15)	10 (2 to 38)		

Statistical analyses

Statistical analysis title	Time awake
Comparison groups	Melatonin v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.415
Method	Wilcoxon (Mann-Whitney)

Secondary: Day 1, Karolinska sleepiness scale

End point title	Day 1, Karolinska sleepiness scale

End point description:

End point type	Secondary

End point timeframe:

Measured in the morning after sleep

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: Karolinska sleepiness scale				
median (inter-quartile range (Q1-Q3))	3 (2 to 3)	3 (2 to 3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Day 1, Karolinska sleepiness scale

End point title	Day 1, Karolinska sleepiness scale

End point description:

End point type	Secondary

End point timeframe:

In the morning after sleep

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: Karolinska Sleepiness Scale				
median (inter-quartile range (Q1-Q3))	3 (2 to 3)	3 (2 to 3)		

Statistical analyses

Statistical analysis title	Day 1, Karonlinska sleepiness
Comparison groups	Melatonin v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.652
Method	Wilcoxon (Mann-Whitney)

Secondary: Day 1, Fatigue

End point title	Day 1, Fatigue

End point description:

End point type	Secondary

End point timeframe:

Measured in the morning before surgery

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: 10 point scale				
median (inter-quartile range (Q1-Q3))	3 (2 to 3)	3 (2 to 4)		

Statistical analyses

Statistical analysis title	Day1, Fatigue
Comparison groups	Melatonin v Placebo

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.362
Method	Wilcoxon (Mann-Whitney)

Secondary: Day1, VAS sleep quality

End point title	Day1, VAS sleep quality
End point description: 0 Being best sleep quality and 100 being the worst	
End point type	Secondary
End point timeframe: Measured the morning before surgery	

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: VAS				
median (inter-quartile range (Q1-Q3))	24 (15 to 33)	34 (13 to 52)		

Statistical analyses

Statistical analysis title	Day1, VAS sleep quality
Comparison groups	Melatonin v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.346
Method	Wilcoxon (Mann-Whitney)

Secondary: Day 1, VAS comfort

End point title	Day 1, VAS comfort
End point description: 0 being very comfortable and 100 being very uncomfortable.	
End point type	Secondary
End point timeframe: Measured in the morning before surgery	

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: VAS				
median (inter-quartile range (Q1-Q3))	25 (15 to 33)	22 (15 to 29)		

Statistical analyses

Statistical analysis title	Day 1, VAS comfgort
Comparison groups	Melatonin v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.678
Method	Wilcoxon (Mann-Whitney)

Secondary: Day2, Sleep amount

End point title	Day2, Sleep amount

End point description:

End point type	Secondary

End point timeframe:

Measured in the morning the day after surgery

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: Hours				
median (inter-quartile range (Q1-Q3))	7 (5 to 7.6)	6.3 (5.3 to 8.2)		

Statistical analyses

Statistical analysis title	Day2, Sleep amount
Comparison groups	Melatonin v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.925
Method	Wilcoxon (Mann-Whitney)

Secondary: Day2, no. of awakenings

End point title	Day2, no. of awakenings

End point description:

End point type	Secondary

End point timeframe:

Measured in the morning the day after surgery

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: no. of awakenings				
median (inter-quartile range (Q1-Q3))	3 (2 to 4)	3 (1 to 5)		

Statistical analyses

Statistical analysis title	Day2, No. of awakenings
Comparison groups	Melatonin v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.664
Method	Wilcoxon (Mann-Whitney)

Secondary: Day2, time awake during night

End point title	Day2, time awake during night

End point description:

End point type	Secondary

End point timeframe:

Measured in the morning the day after surgery - questionnaire data

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: minutes				
median (inter-quartile range (Q1-Q3))	45 (10 to 100)	25 (5 to 50)		

Statistical analyses

Statistical analysis title	Day2, Time awake during night
Comparison groups	Melatonin v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.257
Method	Wilcoxon (Mann-Whitney)

Secondary: Day2, Karolinska sleepiness scale

End point title	Day2, Karolinska sleepiness scale

End point description:

End point type	Secondary

End point timeframe:

Measured by questionnaire the morning the day after surgery

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: Karolinska sleepniess scale				
median (inter-quartile range (Q1-Q3))	3 (2 to 7)	3 (3 to 6)		

Statistical analyses

Statistical analysis title	Day2, Karonlinska sleepiness
Comparison groups	Melatonin v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.984
Method	Wilcoxon (Mann-Whitney)

Secondary: Day2, Fatigue

End point title	Day2, Fatigue

End point description:

End point type	Secondary

End point timeframe:

Measured by questionnaire the morning the day after surgery

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: 10 point scale				
median (inter-quartile range (Q1-Q3))	5 (3 to 6)	4 (3 to 5)		

Statistical analyses

Statistical analysis title	Day2, Fatigue
Comparison groups	Melatonin v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.565
Method	Wilcoxon (Mann-Whitney)

Secondary: Day2, VAS sleep quality

End point title	Day2, VAS sleep quality

End point description:

VAS scale 0= best sleep, 100= worst sleep

End point type	Secondary

End point timeframe:

Measured by questionnaire the morning the day after surgery

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: VAS				
median (inter-quartile range (Q1-Q3))	44 (22 to 57)	33 (14 to 53)		

Statistical analyses

Statistical analysis title	Day2, VAS sleep quality
Comparison groups	Melatonin v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.428
Method	Wilcoxon (Mann-Whitney)

Secondary: Day2, Comfort

End point title	Day2, Comfort
End point description: VAS scale, 0=Best comfort, 100= very uncomfortable	
End point type	Secondary
End point timeframe: Questionnaire the morning the day after surgery	

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: VAS				
median (inter-quartile range (Q1-Q3))	35 (22 to 63)	40 (29 to 61)		

Statistical analyses

Statistical analysis title	Day2, VAS comfort
Comparison groups	Melatonin v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.925
Method	Wilcoxon (Mann-Whitney)

Secondary: Propofol intraoperative use

End point title	Propofol intraoperative use

End point description:

End point type	Secondary

End point timeframe:

Noted after anaesthesia

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: milligram(s)				
median (inter-quartile range (Q1-Q3))	499 (401 to 517)	449 (410 to 486)		

Statistical analyses

Statistical analysis title	Propofol use
Comparison groups	Melatonin v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.101
Method	Wilcoxon (Mann-Whitney)

Secondary: Remifentanil intraoperative use

End point title	Remifentanil intraoperative use

End point description:

End point type	Secondary

End point timeframe:

Measured after anaesthesia

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: microgram(s)				
median (inter-quartile range (Q1-Q3))	1342 (1153 to 1725)	1330 (1045 to 1582)		

Statistical analyses

Statistical analysis title	Remifentanil use
Comparison groups	Melatonin v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.528
Method	Wilcoxon (Mann-Whitney)

Secondary: Opioid used in anaesthesia recovery

End point title	Opioid used in anaesthesia recovery
End point description:	
Peroral oxycodone usage.	
End point type	Secondary
End point timeframe:	
Measured from the end of general anaesthesia to the patient being discharged from hospital	

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: milligram(s)				
median (inter-quartile range (Q1-Q3))	5 (0 to 8)	0 (0 to 5)		

Statistical analyses

Statistical analysis title	Rescue oxycodone
Comparison groups	Melatonin v Placebo

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.182
Method	Wilcoxon (Mann-Whitney)

Secondary: Total oxycodone used 24 hours after surgery

End point title	Total oxycodone used 24 hours after surgery

End point description:

End point type	Secondary

End point timeframe:

Total opiod used 24 hours after surgery

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: milligram(s)				
median (inter-quartile range (Q1-Q3))	5 (5 to 15)	7.5 (5 to 10)		

Statistical analyses

Statistical analysis title	Total opioid 24 hours
Comparison groups	Melatonin v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.76
Method	Wilcoxon (Mann-Whitney)

Secondary: Length of stay

End point title	Length of stay

End point description:

End point type	Secondary

End point timeframe:

Measured from time between start surgery and hospital discharge

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: hours				
median (inter-quartile range (Q1-Q3))	3 (2.6 to 3.9)	3 (2.5 to 3)		

Statistical analyses

Statistical analysis title	Length of stay
Comparison groups	Melatonin v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.477
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse events were only monitored actively during the study period. Melatonin has an elimination half-life of 30-60 minutes.

Adverse event reporting additional description:

Information on adverse events were collected using an electronic questionnaire and by a telephone interview after each participant's completion of the trial.

However, no adverse event were described either during or after the trial.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24

Reporting groups

Reporting group title	Melatonin

Reporting group description:

The group of patients receiving melatonin treatment related to surgery

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Melatonin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Melatonin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Oral melatonin results in few and mild adverse effects. The few known adverse effects include drowsiness and dizziness. These are symptoms that are diffucult to distinguish from the normal effects of general anesthesia, and thus, we have not been able to record any adverse effects in the present study. Multiple previously pubslihed RCTs have reported no adverse effects of oral melatonin, even when administered in doses more than double of what was used in our study.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 October 2020	In the original protocol for this RCT, only female patients undergoing cosmetic breast enhancement surgery were eligible for inclusion. However, due to issues with patient recruitment, the protocol was amended in October 2020 to change the study population to male patients undergoing elective hernia surgery.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
30 April 2020	Due to issues with participant recruitment, the trial was put on a temporary hiatus and the protocol was amended to rectify these issues.	07 October 2020

Notes:

Limitations and caveats

None reported