



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 unwillingness 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 | Subject, Investigator, Monitor, 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, Karolinska 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 opioid 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 difficult 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 published 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