Effect of melatonin in patients with low anterior resection syndrome (MELLARS): a study protocol for a randomised, placebo-controlled, crossover trial

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ABSTRACT

Introduction After rectal cancer surgery, a majority of patients suffer from sequelae known as low anterior resection syndrome (LARS). It is a collection of symptoms consisting of flatus and/or stool incontinence, evacuation frequency, re-evacuation and urgency. The circadian hormone, melatonin, has shown to possess anti-inflammatory properties, and in high doses, it reduces bowel movements. The aim of the study is to investigate if locally administered melatonin has an alleviating effect on LARS. Secondly, the effect of melatonin on bowel movements, other patient-reported symptoms, quality of life, depression, anxiety, sleep disturbances, motilin levels and rectal mucosa histology will be examined.

Methods and analysis This is a randomised, placebo-controlled, double-blinded, two-period crossover trial. The participants are randomised to 28 days of 25 mg melatonin administered rectally via an enema daily (or placebo) followed by a 28-day washout and then 28 days of placebo (or melatonin). Three participants will be included in an internal feasibility test. They will receive 25 mg of melatonin daily for 28 days. Data from these participants will be used to assess the feasibility of the rectally administered melatonin and to analyse the course of recruitment and outcome measurements. Afterwards, 18 participants will be included in the crossover trial. The severity of the LARS symptoms will be evaluated using the LARS Score on the first and last day of each treatment period.

Ethics and dissemination The Regional Ethics Committee, the Danish Medicines Agency and the Data and Development Support in Region Zealand approved this study. The study will be performed according to the Helsinki II declaration. Written informed consent will be obtained from all participants. The results of the study will be submitted to peer-reviewed journals for publication and presented at congresses.

Trial registration numbers EudraCT Registry (2020-004442-11) and ClinicalTrial.gov Registry (NCT05042700).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The trial uses a randomised, placebo-controlled, double-blinded, crossover design.
⇒ The trial investigates the effect of melatonin in the treatment of low anterior resection syndrome (LARS).
⇒ The trial uses the LARS Score as a primary outcome, which is the validated tool for measuring LARS.
⇒ The trials provide both macroscopic and microscopic evaluation of the neorectum in patients with LARS.
⇒ Trial participations require extra visits to the hospital and daily dairy registration, which might be inconvenient and could result in dropouts and missing data.

INTRODUCTION

Background and rationale Advances in surgical techniques have enabled a rise in sphincter-preserving surgery. A total mesorectal excision is the current standard surgical procedure for rectal cancer, and more than 60% of the patients have restored bowel continuity after surgery. However, bowel continuity has not shown to improve post-surgical quality of life at least assessed by the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) C30, CR58 and SF-36 Questionnaires. After sphincter-preserving surgery, up to 90% of the patients suffer from bowel dysfunction of varying degrees, which is commonly known as low anterior resection syndrome (LARS). Unfortunately, LARS and the impact of the syndrome on patients’ quality of life persist over time.

LARS is a collection of symptoms consisting of flatus incontinence, liquid stool incontinence, evacuation frequency, re-evacuation and evacuation urgency. The syndrome can be diagnosed with a validated self-administered questionnaire, the LARS Score Questionnaire. Depending on the severity of these symptoms, the patients are divided into three groups: no LARS, minor LARS or major LARS. The consequences of suffering from LARS include toilet dependency, dissatisfaction with bowel function and an


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impact on one’s mental and emotional well-being. A recent population-bound study found that patients with major LARS had worsened quality of life, showing that the quality of life is closely related to the presence and severity of LARS.

The aetiology of LARS is considered to be multifactorial. Rectal compliance is reduced after resection, which is associated with bowel urgency, frequency, urge incontinence and decline in continence scores. Animal studies have shown that colon and rectal denervation results in increased peristaltic movements of the colon. Furthermore, studies have shown a persistent reduction in mean anal resting pressure after resection (reflecting internal anal sphincter dysfunction) and reduced maximum squeeze pressure (reflecting external anal sphincter dysfunction) caused by damage of rectal innervation and endoanal instrumentation. Patients with LARS present a decrease in the ability to discriminate between liquid and gas due to diminished sensitivity of the recto-anal transition affecting the mechanism of stool continence.

Melatonin, in addition to primarily being known as the circadian hormone, has also been known as a potent antioxidant with immune-enhancing effects and investigated for having antidepressant effects. Melatonin is not only produced by the pineal gland, but it is also produced in the enterochromaffin cells of the digestive mucosa. The levels of melatonin in the gastrointestinal tract surpass those in the blood 10-fold to 100-fold. Melatonin has several intestinal functions. First, melatonin regulates gastrointestinal motility; murine studies have found that administration of low-dose exogenous melatonin increases the gastrointestinal motility, whereas higher doses decrease the motility. In humans, studies have shown that 3 mg of oral exogenous melatonin increases colonic transit time in healthy subjects as well as in patients with irritable bowel syndrome (IBS). In an another study, 50% of the patients with constipation-dominant IBS showed self-reported improvement in symptom severity after treatment with 3 mg melatonin. Thus, it seems that even low doses of oral exogenous melatonin in humans increase gastrointestinal motility. Second, melatonin has anti-inflammatory properties; melatonin reduces the severity of intestinal inflammatory pathologies in animal models. Melatonin increases natural killer cell activity, increases Th2 cell-mediated immune responses, inhibit macrophages, and scavenge reactive oxygen species. Lastly, melatonin may moderate visceral sensation; patients with functional abdominal pain had lower urinary excretion of 6-sulfatoxymelatonin, the major metabolite of melatonin, and a lower amplitude of circadian rhythm when compared with healthy controls. Different administration routes of melatonin have been investigated showing that melatonin can be administered orally, intranasally, intravenously, intravesically, rectally, transdermally and vaginally. Time to maximum concentration for orally administered immediate-release melatonin is about 50 min, and the elimination half-life is about 45 min for both orally and intravenously administered melatonin. In a recent study, time to maximum concentration for rectally administered melatonin was shown to be 24 min and the elimination half-life to be 60 min. Thus, rectally administration is faster to reach maximum concentration and has a longer elimination half-life than orally administered immediate-release melatonin. Furthermore, the bioavailability of rectally administered melatonin was found to be 36%, whereas the bioavailability of orally administered melatonin was found to be only 15%. This could presumably be explained by less first pass effect associated with rectal administration, and as such rectal administration holds promise if one wishes to achieve a fast effect with high bioavailability. It is expected that the best effect of melatonin would be to administrate it locally in order to have a high concentration in the bowel wall in addition to have melatonin being absorbed into the systemic circulation in order to induce its sleep-promoting effects. The high local concentration would be expected to have a stabilising effect in the neorectum and probably the bowel wall-related pain would be better inhibited.

The effect of melatonin in patients with LARS has never been investigated before. The effects of melatonin in the gastrointestinal tract may improve the bowel-related quality of life due to the intestinal effects described earlier. Our hypothesis is that high-dose melatonin, which is safe to use, increases the colonic transit time, alleviates intestinal inflammation and might also have a mild analgesic effect in patients with LARS and thus reduces incon tinence, frequency, incomplete bowel movements and tenesmus. Bowel-related quality of life is decreased due to evacuation frequency, urgency, secondarily insomnia and abdominal pain. Melatonin might be an effective and very promising treatment possibility in these patients. In addition to its direct effects within the bowel, melatonin potentially also alleviates patients’ symptoms due to restoration of sleep and its possible analgesic effects.

Objectives
The primary objective of the study is to investigate whether treatment with melatonin has an alleviating effect on LARS symptoms. Secondarily, the effect of the treatment on bowel movements, other patient-reported symptoms, quality of life, depression, anxiety, sleep disturbances, motilin levels and microscopic changes in rectal mucosa will be investigated.

METHODS AND ANALYSIS
Trial design
The effect of melatonin in patients with low anterior resection syndrome (MELARS) trial is a multicentre, randomised, placebo-controlled, double-blinded, crossover trial investigating the effect of 25 mg exogenous melatonin (intervention) against placebo (control) administered 1 hour before bedtime. The trial has a
duration of 12 weeks for the patients, and outcomes are assessed throughout the study.

**Study setting**

The study will be conducted at Zealand University Hospital (ZUH), Amager and Hvidovre Hospital and Aarhus University Hospital at departments of surgery. Patients with LARS treated at the involved trial centres will be screened for major LARS. Healthcare professionals will introduce the patients who are eligible for enrolment to the study, and if they consent to being contacted, the investigators will contact them and present the study.

**Eligibility criteria**

Participants will be screened for eligibility to enter the study by the investigators. The inclusion criteria and exclusion criteria are listed in **Table 1**.

If patients are eligible for inclusion, an investigator will obtain informed consent from trial participants (online supplemental appendix 1). Participants will be asked to sign a consent form on sharing their data and biological specimen with relevant external study partners such as laboratories.

**Interventions**

Each participant will receive treatment with melatonin and with placebo. The treatments will be given as enemas, which the participants administer themselves. Patients will be given thorough instruction at the inclusion meeting on how to use the enema to ensure better compliance. Each treatment phase will be of 28 days and separated by a 28-day washout phase. The 25 mg melatonin will be administered as 2.5 mL of a 10 mg/mL fluid (consisting of 25 mg of melatonin dissolved in 2.5 mL of a 20% w/w glycofurol and 40% w/w dimethyl sulfoxide (DMSO) solution in water). The placebo enema will not contain melatonin and DMSO. Patients will be instructed to administer the enema every evening during the treatment periods approximately 1 hour before bedtime. All concomitant care is permitted, and no drugs are prohibited during the trial. Patients’ regular medication will not be affected by the study.

There are no criteria set for discontinuing the intervention during the treatment phase; however, if a patient has not taken at least 75% of the medication during the first treatment phase, then the patient will be excluded from

<table>
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<th>Inclusion criteria</th>
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<tr>
<td>▶ Participants should have major LARS (LARS Score &gt;29)</td>
<td>▶ Known allergic reaction to melatonin</td>
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<td>▶ Participants should have undergone bowel continuity restoring surgery in relation to a surgical removal of a rectal tumour between the last 3 months and 24 months</td>
<td>▶ Dementia as determined by Mini-Mental State Examination Score &lt;24</td>
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<td>▶ Participants should be 18 years or older</td>
<td>▶ Participation in another pharmacological intervention trial at the point of inclusion</td>
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<td>▶ Participants must sign an informed consent form</td>
<td>▶ Completed any adjuvant oncological treatment within the last 3 months prior to inclusion</td>
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<td>▶ Rotor or Dubin-Johnson syndrome, epilepsy, systemic lupus erythematosus, rheumatoid arthritis, Parkinson’s disease, spinal cord injury and multiple sclerosis</td>
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<td>▶ Severe liver disease is defined as transaminases above three times the normal levels, and severe kidney disease is defined as eGFR below 40 mL/min.</td>
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<td>▶ Daily ongoing hypnotic treatment</td>
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<td>▶ Pre-existing medical sleep disorder diagnosed before the diagnosis of rectal cancer (ie, sleep apnoea, restless legs, narcolepsy)</td>
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<td>▶ Predictable poor compliance (due to pre-existing psychiatric disease, dementia or not able to read or speak sufficient Danish)</td>
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<td>▶ Pregnant or breast feeding</td>
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<td>▶ Severe, life-threatening medical condition, which implies that patients cannot participate in the study course (eg, metastatic disease, local recurrence, stroke, AMI)</td>
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<td>▶ Women not in menopause (defined as no menstruation during the last 12 months) should not be pregnant. Furthermore, reproductive women should use a secure birth control (intrauterine devices, hormonal contraceptives including oral pills, patches, vaginal rings and injections) during the entire period of the trial.</td>
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AMI, acute myocardial infarction; eGFR, Estimated Glomerular Filtration Rate; LARS, low anterior resection syndrome.
the study and will not receive the second treatment phase. There is no provision for after-trial care. Melatonin has a half-life of approximately 60 min when administered rectally.39 When a participant for any reason is terminated in the study, the patient will be followed for side effects for a period equal to five times the plasma half-life of melatonin after the last administration. No strategy to improve adherence to the interventions is planned in the study; however, adherence will be monitored closely as patients will be given a diary and patients will be asked to bring all used and unused enemas back. It is expected that this will strengthen the adherence to the protocol, as the diary also serves as a continuous reminder of trial participation.

Outcomes

The primary outcome of the study is the LARS Score. It is a simple validated 5-item self-rating scoring system that assesses the severity of LARS.7 The score was created to facilitate the monitoring of relevant functional low anterior resection outcomes. The 5-item questionnaire is based on a 27-item questionnaire40 and measures the most important characteristics of LARS, as the selection of the 5 items was only based on patients’ perceptions of the influence of bowel function on quality of life—and not on the opinions of professionals. The questions cover five symptoms: incontinence for flatus, incontinence for liquid stools, frequency, clustering and urgency. The range of the score is from 0 to 42 and divided into three groups: no LARS (0–20), minor LARS (21–29) and major LARS (30–42). For the purpose of the current study, the LARS Score will be used as a diagnostic tool at baseline with regard to the eligibility (inclusion criterion no. 1) of the participants. During the study, the LARS Score will be used as a rating scale to evaluate the severity and change of the syndrome.

The secondary outcomes are the following: daily bowel function using a diary, quality of life measured by the EORTC Quality of Life Questionnaires (QLQ-C30 and QLQ-CR29),41 42 patient-reported symptoms using the Measure Yourself Medical Outcome Profile 2 (MYMOP2) Questionnaire,43 anxiety and depression using the Hospital Anxiety and Depression Scale,44 insomnia using the Insomnia Severity Index,45 subjective and objective sleep outcomes measured by using a sleep diary and an actigraph, plasma levels of melatonin, levels of motilin and motilin receptors in blood and biopsies, difference in gene expression in whole blood and biopsies, and pathological assessment of the rectal mucosa. The biopsies are taken during a sigmoidoscopy, which takes less than 15 min, and most patients manage the discomfort without use of pain relief or sedation. Patients will be given an enema to clean the bowel prior to the sigmoidoscopy.

As melatonin administration with a rectal enema has not been used with the aim of treating LARS before, the first three patients will be included in a small internal feasibility test. The aim of this feasibility test is to assess the feasibility of the melatonin administration with the rectal enema, to analyse the course of recruitment, the outcome measurements, and the analysis techniques of collected biological specimens. The internal feasibility test will not be blinded nor randomised. The three patients will be recruited from ZUH and will receive 28 days of treatment with 25 mg of melatonin enema and undergo the same measurement and examinations as in the randomised controlled trial. They will not receive any placebo treatment nor have any washout period. The preliminary results from the internal feasibility test will allow us to assess potential difficulties related to the administration or design, which then will be able to be corrected before the randomisation part is initiated. Furthermore, it allows us to evaluate the secondary outcomes, the feasibility of running the different questionnaires and examinations, and the overall protocol adherence.

Participant timeline

The patients are included in the study on day 0. The trial consists of two treatment periods and one washout period (figure 1). Each period is 28 days long (±4 days). The patients start with a treatment period, then enter the washout period and lastly enter another treatment period. The patients finish the study on day 84. Before entering both treatment periods, the patients will answer all questionnaires and will be given the app/paper dairy for daily registrations. On the last day of both treatment periods, the patients will again answer all questionnaires, stop the use of the app/return the paper diary, and we will collect blood samples and biopsies (figure 1).

Figure 1 Participant timeline in the MELLARS study. HADS, Hospital Anxiety and Depression Scale; ISI, Insomnia Severity Index; LARS, low anterior resection syndrome; MELLARS, melatonin in patients with low anterior resection syndrome; MMSE, Mini-Mental State Examination Score; MYMOP, Measure Yourself Medical Outcome Profile; QLQ, Quality of Life Questionnaire.
Sample size
The sample size calculation is based on data from a similar Scandinavian cohort, which showed a median LARS Score up to 12 months after surgery with early closure of an ileostomy to be 31 (IQR 22–36) and with late closure of an ileostomy to be 34 (IQR 28–39). Based on these IQRs, we have calculated the SD to be 10.5 in the population. We assume that the LARS Score can be reduced by 13 points, which is a clinical relevant difference as a patient with a maximum LARS Score of 42 would go from having major LARS to minor LARS. The power calculation is based on two-sided test, and with a power of 0.90 and a significance level of 5% (alpha=0.05), the required sample size is 15. Due to an expected attrition rate of 20%, the study will proceed until 18 patients have been enrolled. In addition, 3 patients will initially be included in an internal feasibility test of the study, thus a total of 21 patients will be included in the study.

Recruitment
To ensure that the needed sample size can be reached, recruitment will take place at three centres: ZUH, Amager and Hvidovre Hospital and Aarhus University Hospital. Patients with major LARS will be approached by an investigator and will be given information about the study and screened for eligibility. Patients will be given sufficient time to think about participation. If they agree to participate, an inclusion meeting will take place and they will be included in the study. Recruitment for the internal feasibility trial started in October 2021 and continue until the sample size is recruited.

Assignment of intervention
Glostrup Apotek, the pharmacy producing the study medication, will handle the randomisation process. Half of the patients will receive melatonin and then placebo, and the other half will receive placebo and then melatonin. The randomisation list/sequence will be made before the study starts by using dedicated online software by Glostrup Apotek. The randomisation will not be stratified or use block randomisation. Based on the randomisation list, Glostrup Apotek will apply the randomisation code and patient number on the study medication boxes. Likewise, batch numbers for the melatonin and placebo will be noted on a separate piece of paper correlated to the patient’s number. This will not be available to the investigators recruiting the participants.

Allocation concealment consists of two sets of code envelopes (opaque, sealed envelope for each patient, containing the randomisation code for each patient) produced by Glostrup Apotek. They will be sent to ZUH (sponsor’s centre) to be stored; one in the patient’s case report form (CRF) and the other in the trial master file. Thus, the blinding will be preserved for everyone including the sponsor, the investigators, clinicians and any external outcome assessor such as a pathologist. The participants are also blinded. Unblinding can be performed if a suspected unexpected serious adverse reaction occurs by the investigator via access to the code envelope in the patients’ CRF.

Data collection and management
Collected data will continuously be registered and filled into each patient’s electronic CRF (eCRF). The questionnaires are sent to the participants via e-mail with a unique generated link; however, the Mini-Mental State Examination and MYMOP2 will be filled out on paper and have data transferred to the eCRF later. By using the eCRF, the answered questionnaires become source data and will be transferred directly to the electronic database on completion. The paper worksheets will be stored identifiable in a locked cabinet at the respective research sites. At the point of inclusion, baseline demographics will be collected from the participants and their medical records. The eCRFs are created using the online platform Easytrial.com (Easytrial Aps, Glostrup, Denmark) and serve as the electronic data storage for the trial. Data will be stored as personally identifiable information for 10 years. The data will be stored in compliance with General Data Protection Regulation (GDPR). If a patient withdraws from the study or does comply with the intervention protocols, the data that have been collected will be used in an anonymous manner.

The data handling will be in accordance with the act on processing of sensitive personal information, the GDPR and the Data Protection Act.

Statistical methods
For the primary outcome, an intention-to-treat analysis will be performed as recommended by Consolidated Standards of Reporting Trials (CONSORT) and will be including all patients randomised into the study. The primary outcome is the difference in the change in the LARS Score between the melatonin treatment and the placebo treatment. Paired t-test or Wilcoxon rank sum test will be used to assess the primary outcome, depending on the distribution of the data. Log transformation will be applied if relevant and possible. A two-tailed p value of less than 0.05 will be considered statistically significant. Furthermore, a per-protocol analysis will be including only patients who have adhered to the protocol. Patients will adhere to the protocol if they take 75% or more of the prescribed project medicine. This will be monitored at each follow-up meeting in which patients will be asked to bring the medicine box with them. In case of missing data, it will first be assessed whether the missing data are missing at random, missing completely at random or missing not at random. Depending on this assessment, the missing data will be handled according to guidelines from Copenhagen Trial Unit. For the secondary exploratory outcomes, the same method will be applied for the outcome scores obtained on the first and last day of each treatment period.

Monitoring
The study has no data monitoring committee, as it is unlikely to have the opportunity to make a difference.
 Likewise, no interim analysis is planned. The Good Clinical Practice unit from the University of Copenhagen will monitor the study. To monitor harms, investigators will interview the participants at each visit regarding possible adverse reactions and events. The Investigators’ Brochure for melatonin will function as reference documents in evaluation of adverse events. On the basis of the literature, the effects of melatonin the following known, usual side effects (1%–10%) and non-usual side effects (0.1%–1%) will not be registered as adverse events: light headache, light nausea, dyspepsia, minor symptoms of sleepiness and light morning drowsiness.

Patient and public involvement

Patients or the public were not involved in the design of the study. In the internal feasibility test, the three patients were able to give feedback on their experience with the study conduct, which could be taken into account before starting the randomised trial. All three patients in the feasibility phase were interviewed by the primary investigator in an unstructured interview regarding participation in the trial. Patients unanimously expressed satisfaction with trial participation and did not suggest any changes in the design or conduct of the study.

ETHICS AND DISSEMINATION

The Regional Health Committee (SJ-870), the Danish Medicines Agency (2020-004442-11) and the Data and Development Support in Region Zealand (REG-140-2020) have approved this study. The study will be performed in agreement with the Helsinki II declaration and Danish Law 593 of 2011 on the Research Ethics Committee’s practices regarding health research trials.

The Regional Health Committee and the Danish Medicines Agency will approve any important protocol amendments. After such an approval, the investigators will be contacted with the updates and relevant registries will be updated.

All study-related information will be stored in the respective regions in locked file cabinets in areas with limited access until the last patient is completed, then the data will be stored in the Region of Zealand. All laboratory specimens, reports, data collection, process and administrative forms will be identified with pseudo-anonymised participant ID numbers to maintain participant confidentiality. The key files to the pseudo-anonymisation will be kept on separate secure data site according to GDPR in the Region of Zealand. The data will be handled in the Region of Zealand.

The results of this study will be submitted to peer-reviewed journals for publication. The manuscript will follow the CONSORT statement and both positive, neutral and negative findings will be published. Furthermore, the results will also be reported on the EudraCT Registry. Authorship guidelines put forth by the ICJME will be applied for all publications originating from the current trial.

DISCUSSION

Management guidelines for LARS emphasise the large gap in knowledge about the treatment of LARS, as only a limited number of randomised controlled trials have been performed. Due to the lack of sound evidence, current recommendations are partly based on expert opinions.

To our knowledge, this is the first randomised controlled trial to evaluate whether treatment with melatonin has an alleviating effect on LARS symptoms. The study is adequately powered to test the main hypothesis regarding change in the LARS Scores. Furthermore, it has an extensive list of secondary outcomes to support the conclusion of the study, such as daily registrations of bowel movements, quality of life and both local and systemic inflammation. Incidence rates of colorectal cancer have been declining due to the increase in the colorectal cancer screening programmes. However, the incidence of colorectal cancer in younger age group–20–49 years–has been increasing in the last decade and will continue to do so in the next two decades causing colorectal cancer to become the second leading cancer in this age group. Thus, it is also expected that the incidence of LARS increases in younger patients in the future. Unfortunately, there is a sparse knowledge about the mental health and sleep quality in patients with LARS, but the results of this study will reduce the current knowledge gap in this area. Likewise, the knowledge about the histology of the neorectum in patients with LARS is limited, and the examination of the biopsies taken will improve our knowledge. Even though the trial is not designed to implement melatonin in the treatment of LARS, successful findings will contribute with a possible evidence-based treatment option for LARS and add-on to the increasing focus on the monitoring and treatment of LARS in patients after rectal cancer surgery. The melatonin enema has a great potential to not only alleviate LARS symptoms but also improve sleep and overall quality of life. If the findings are non-significant, the study result still has an effect on future research and treatments for LARS, as it will reduce the knowledge gap in regard to mental health, sleep and histology of neorectum in patients with LARS.

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MELLARS trial, revised the manuscript for important intellectual content, and read and approved the final manuscript.

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