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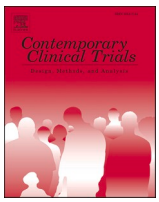
Contemporary Clinical Trials 154 (2025) 107927

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial



Effect of cyclic daytime versus continuous enteral nutrition on circadian rhythms in critical illness (CIRCLES): Study protocol for a randomized controlled trial

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ARTICLE INFO

Keywords:
Critical care
Intensive care unit
Circadian rhythm
Enteral nutrition

ABSTRACT

Background: Circadian rhythms and sleep are often disrupted in critically ill patients in the intensive care unit (ICU), which has been linked to poor clinical outcomes. Feeding-fasting cycles serve as a synchronizing cue for the circadian timing system, indicating that optimizing these cycles in the ICU could reinforce circadian rhythms. The CIRCLES trial evaluates whether cyclic daytime enteral nutrition improves 24-h rhythms in critically ill patients compared to continuous enteral nutrition.
Objective: To describe the study protocol for the CIRCLES study.
Study design: The CIRCLES study is an investigator-initiated randomized controlled trial in a tertiary care ICU in the Netherlands. Patients (aged ≥18 years) admitted to the ICU with an expected stay ≥48 h receiving or with intention to start enteral nutrition are eligible for inclusion. Patients ($n = 60$) are randomized to the *continuous* enteral nutrition (nutrition around the clock) or *cyclic* daytime enteral nutrition group (nutrition between 08:00 h to 20:00 h).
Main outcome measures: The primary outcome is the amplitude of 24-h rhythms in core body temperature. Secondary outcomes include 24-h rhythms in heart rate, mean blood pressure heart rate variability, melatonin and gene expression, glucose regulation, insulin administration, caloric intake and feeding intolerance.
Conclusion: We hypothesize that a cyclic daytime feeding strategy will result in a higher amplitude of 24-h rhythms in vital signs, heart rate variability, and melatonin, compared to continuous feeding, thereby suggesting improved circadian rhythm strength. This study aims to provide insight into strategies to optimize circadian rhythms in ICU patients.
Trial registration: Registered at ClinicalTrials.gov (NCT05795881), April 2023.

1. Introduction

Critically ill patients in the intensive care unit (ICU) often experience profoundly disrupted circadian rhythms and sleep/wake cycles, which has been linked to adverse clinical outcomes. [1] Circadian rhythms are approximately 24-h cycles in many physiological processes that are produced by the circadian timing system. Thereby, the circadian timing system regulates optimal functioning of cells, organs and systems by synchronization of human behavior and physiology with the predictable environmental changes of day and night. The circadian system is controlled by the central clock within the hypothalamus called the suprachiasmatic nucleus (SCN) and peripheral clocks in nearly every tissue in the body. [2] The circadian system functions autonomously (i.e. in absence of cues from the external environment). However, it requires external timing cues, called 'zeitgebers', in order to synchronize to the environment. Although the light-dark cycle is the primary synchronizing cue for the circadian system, feeding-fasting cycles, and related nutritional and hormonal signals, also serve as a synchronizing cue, primarily to peripheral clocks. [3] Disruption of circadian rhythms is associated with disturbances in immune function, hormonal and metabolic processes and cognitive disorders. [4]

The ICU environment and practices present a unique challenge to the

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https://doi.org/10.1016/j.cct.2025.107927
Received 20 December 2024; Received in revised form 18 April 2025; Accepted 25 April 2025
Available online 27 April 2025

circadian timing system, offering weak (i.e., low-intensity) and conflicting (i.e., altered timing) timing cues to the circadian system of ICU patients. Factors such as persistent exposure to dim light, noise, frequent patient care interaction and immobility all contribute to disruption of circadian rhythms in ICU patients. In addition, the delivery of continuous enteral nutrition across the 24-h cycle, a common practice in ICUs over the world, may exacerbate circadian disruption and thereby adversely affect patient outcomes. [5,6]

Interventions aimed at restoring rhythmic timing cues to the circadian system have the potential to improve patient outcomes. [7] Given the bidirectional relationship between nutrition and the circadian timing system, daytime cycles of enteral nutrition, as compared to continuous nutrition, may be a promising intervention. Daytime cycles of enteral nutrition are likely more physiologic, as they mimic natural eating behaviors more than continuous enteral nutrition. Indeed, rhythmic feeding-fasting cycles have been shown to serve as a powerful synchronizing cue for the circadian clock, capable of restoring dampened circadian rhythms in both physiological and metabolic processes in experimental animal models and human studies. [8–11] As robust evidence from human studies lacks, there is still a worldwide predominant practice of continuous enteral feeding, which is expected to exacerbate circadian disruption. Additionally, non-continuous (including cyclic, bolus and intermittent feeding schedules) enteral nutrition has been suggested to offer potential benefits over continuous feeding in terms of glycemic control, gastric intolerance, achieving nutritional goals, and muscle mass maintenance, although the evidence remains limited and inconclusive. [5,12,13] The optimal feeding strategy for critically ill patients continues to be a subject of ongoing debate in critical care nutrition, and has been listed as one of the top 10 priorities in the intensive care medicine research agenda in nutrition and metabolism. [14]

Clearly, understanding how different feeding patterns—particularly the impact of daytime feeding and overnight fasting—affect circadian rhythms in ICU patients is essential, and could potentially enhance patient recovery and improve clinical outcomes. In the CIRCLES trial, we aim to assess the effect of a cyclic daytime feeding schedule compared to a continuous feeding schedule on circadian rhythms in critical illness. Additionally, we will explore the effect of cyclic feeding on glucose regulation, nutritional goals, gastrointestinal intolerance, and clinical outcomes. Here, we present the protocol and statistical analysis plan for the CIRCLES trial.

2. Methods

2.1. Trial design and setting

The CIRCLES trial is an investigator-initiated, single center, open-label, parallel group randomized controlled trial, comparing the effect of cyclic daytime enteral nutrition versus continuous enteral nutrition on circadian rhythms in ICU patients (Fig. 1). The study is conducted in a tertiary care ICU in the Netherlands (Leiden University Medical Center). The first patient was randomized in June 2023, and patient recruitment is estimated to be completed in May 2025. An outline of the study procedure is provided in Fig. 2.

2.2. Study population

2.2.1. Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria (at the time of inclusion):

- Age ≥ 18 years old
- Receiving of or intention to start enteral nutrition via nasogastric or nasoduodenal tube
- Arterial line*
- Expected duration of ICU admission >48 h

*An arterial line is required to enable arterial blood sampling without subjecting patients to additional needle sticks. Arterial lines are part of the standard of care in our ICU."

2.2.2. Exclusion criteria

A potential subject who meets any of the following criteria at the time of inclusion is excluded from participation in this study:

- Receiving parenteral nutrition
- Oral intake
- Prior night-time (20:00 h – 8:00 h) enteral or parenteral nutrition within the same hospitalization before study inclusion
- Readmission to ICU with prior study inclusion

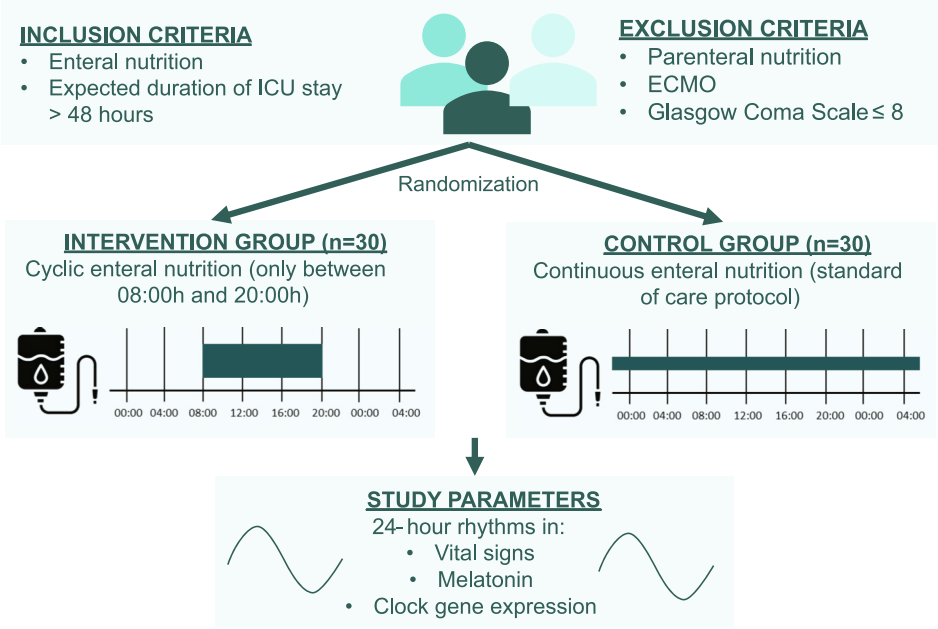

Fig. 1. Overview of the CIRCLES study.

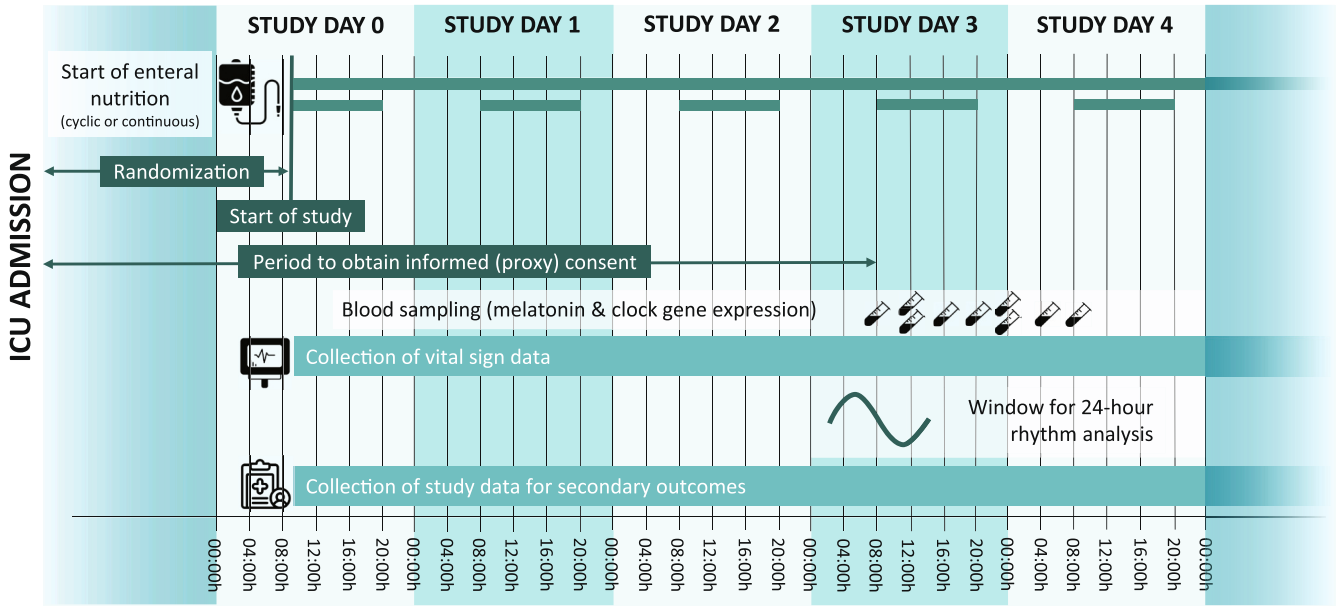

Fig. 2. Outline of the study procedure.

- Chronic enteral tube feeding prior to current admission
- Presence of one or more contraindications of enteral feeding and/or at significant risk for gastrointestinal intolerance according to standard protocol (including but not limited to gastrointestinal hemorrhage, intestinal ischemia or necrosis, impaired digestive tract integrity due to obstruction or perforation, gastrectomy, enterectomy, history of gastroparesis or esophageal dysmotility or expected surgery within 24 h)
- Patients with glycemic emergency (including but not limited to hyperglycemic hyperosmolar nonketotic coma, diabetic ketoacidosis, severe hypoglycemia resulting in ICU admission) or patients controlling their glucose levels and insulin dosing via continuous glucose monitoring
- Treatment with extracorporeal membrane oxygenation
- Severe neurological damage (significant neurological abnormalities such as bleeding, ischemia, neurotrauma or severe encephalopathy with Glasgow Coma Scale $\leq$8)
- Suspected or confirmed pregnancy

2.3. Randomization and treatment allocation

Patients are randomly assigned to receive either continuous enteral feeding or cyclic daytime enteral feeding (between 08:00 h – 20:00 h), without stratification. Randomization is performed using a dedicated and password protected clinical trial platform (CastorEDC). Due to the nature of the treatment, blinding is not possible. Each patient will be allocated a unique patient randomization number.

2.4. Informed consent procedure

All patients admitted to the ICU of Leiden University Medical Center (Leiden, the Netherlands) are screened for inclusion. Informed consent is obtained in accordance with local legal regulations, and every effort is made to obtain informed consent from eligible patients before the initiation of enteral nutrition. Since patients are often unable to provide informed consent due to their critical condition, consent is sought from a proxy or legal representative in such cases. However, in the majority of cases, the time from inclusion to the start of the study intervention is short, and obtaining consent within this limited timeframe is not always feasible. Therefore, deferred consent can be used in those situations, allowing the study intervention to proceed, under the condition that consent is obtained as soon as possible, and no later than before the start of the additional measurements on day 3 after the start of enteral nutrition (Fig. 2). If consent is not obtained before this deadline, the patient will be withdrawn from the study. In case consent from a proxy or legal representative is obtained, every effort is made to obtain consent from the participant themselves as soon as their decisional capacity allows during their ICU stay. In case a participant dies before informed consent is obtained, the study data will still be used.

2.5. Study intervention

Patients are randomly allocated to either the *continuous* enteral nutrition (control) group or the *cyclic* daytime enteral nutrition (intervention). In the *continuous* group, nutrition is administered continuously over 24 h a day, according to the local standard of care protocol. In the *cyclic* group, administration of nutrition is restricted to a 12-h period during daytime hours (between 08:00 h and 20:00 h). The study intervention is followed until the enteral nutrition is stopped, discharge from the ICU or one of the discontinuation criteria are met, whichever came first.

2.5.1. Nutritional targets

In both groups, similar daily nutrition targets are pursued. Nutritional targets are determined individually for each patient based on their weight, according to the standard of care protocol (first week of ICU admission: 25 kcal/kg/day and 1,5 g/kg/day of protein, after first week of ICU admission: 30 kcal/kg/day and 1,5 g/kg/day of protein). The nutritional target is adjusted when high dosages of propofol (>300 mg/h) are administered (Supplementary Table 1).

2.5.2. Nutrition initiation scheme

According to the standard of care protocol, enteral nutrition should preferably be started within 24 h after ICU admission. In both study groups, enteral nutrition will be initiated by gradually increasing the administration rate every 4–6 h, if gastric residual volume is below 200 mL. This increase is continued until the target rate is reached, as soon as clinically feasible, depending on the patient's tolerance. Actions following gastric residual volumes >200 mL are similar in both groups and are outlined in Supplementary Fig. 1. In the *cyclic* group, the increase in administration rate per step is doubled relative to the *continuous* group (40 mL/h vs 20 mL/h increase per step, respectively) to

pursue equal nutritional intake (Supplementary Fig. 1). Also, in the *cyclic* group, the administration is interrupted between 20:00 h and 08:00 h, and is each morning resumed at the administration rate that was used before the nighttime interruption.

2.5.3. Gastric residual volume checks and treatment of feeding intolerance

After the target dosing rate of enteral nutrition is achieved, gastric residual volumes are checked every 4–6 h during feeding hours in both study groups by actively siphoning with a 50 mL syringe, following the standard of care protocol. Again, actions following the checks of gastric residual volume are equal between both study groups and are according to standard of care protocol. When gastric residual volumes are <200 mL, the full volume is returned. For feeding intolerance with gastric residual volumes >200 mL, treatment with metoclopramide (10 mg intravenously, three times daily) and erythromycin (100 mg intravenous, two times daily) is administered for a maximum of 5 days. A maximum of 200 mL is returned. If gastric residual volumes exceed 400 mL, the placement of a duodenal tube is considered. The actions following gastric residual volume checks are outline in Supplementary Fig. 1.

2.5.4. Glucose regulation

In both study groups, glucose levels are checked every 6 h in all patients to ensure glucose levels stay between 5 and 8 mmol/L, with more frequent checks on indication, in accordance with the standard of care protocol. In the *cyclic* group, an additional glucose check is performed 1 h after stopping the enteral nutrition. Blood samples are collected from the arterial line and analyzed using a blood gas analyzer (RAPIDPoint® 500, Siemens Healthcare Diagnostics, The Netherlands). When glucose levels exceed 8 mmol/L, insulin therapy is started. The insulin therapy protocol is outlined in Supplementary Table 2 and Supplementary Fig. 2. According to the standard of care protocol, insulin administration is stopped when enteral nutrition is stopped. Therefore, in the *cyclic* group, insulin is only administered during the daytime feeding hours. However, this does not apply to certain patients, including those with type 1 diabetes or post-pancreatectomy, in whom insulin will continue during the nighttime fasting period. Hypoglycemic events (<3.5 mmol/L) are treated intravenously with 50 mL of 40 % glucose, with an immediate cessation of insulin administration, and glucose levels are checked every 15 min until they exceed 5 mmol/L.

2.6. Study measurements and data collection

2.6.1. Collection and analysis of blood samples

On study day 3 and 4, blood samples are drawn at approximately 4 h intervals for a 24-h period (around 08:00 h,12:00 h, 16:00 h, 20:00 h, 00:00 h, 04:00 h, 08:00 h) (Fig. 2). 4 mL of arterial blood is collected through the arterial line, most commonly placed in the radial artery, in K2-EDTA tubes. Additionally, around 12:00 h and 00:00 h, 2.5 mL arterial blood is collected in PAXgene blood RNA tubes. The blood samples in the K2-EDTA tubes are processed and centrifuged as soon as possible, after which blood plasma is transferred into opaque containers and stored at −80 °C. PAXgene tubes are kept at room temperature for at least 2 h and subsequently frozen at −20 °C. The processing and freezing of all blood samples is performed by the hospital's laboratory. Levels of melatonin in the blood plasma samples will be determined by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). Levels of circulating plasma metabolites will be determined by targeted metabolomics analysis. Genome-wide gene expression will be analyzed from the whole blood samples collected in the PAXgene RNA tubes using RNA-sequencing.

2.6.2. Routine clinical care data

Vital signs are measured as part of routine care, and are automatically stored from the monitoring system in a data warehouse at a sampling rate of 1 or 500 Hz for numeric or waveform data, respectively. Electrocardiogram, heart rate, core body temperature and mean blood pressure data will be extracted from the data warehouse. Data required to compute the secondary outcome measures (including blood glucose levels, insulin administration, gastric residual volumes and caloric intake) are collected as part of routine clinical care and are extracted from the electronic health record.

2.7. Strategies to enhance protocol compliance

Protocol compliance is enhanced by the implementation of reminders in the patient data management system for timely restarting and stopping the nutrition at 08:00 h and 20:00 h, respectively, calculation of the required nutritional intake and orders for blood sample draws. Additionally, daily checks by the research team ensure adherence to the protocol and allow for timely identification and prevention of protocol deviations. Compliance to the study intervention protocol is evaluated by the proportion of feeding hours in allocated feeding hours (08:00 h to 20:00 h in the *cyclic* group, 00:00 h to 00:00 h in the *continuous* group) and, only applicable in the *cyclic* group, fasting hours in allocated fasting hours.

2.8. Discontinuation of the study protocol

After inclusion, if any of the following criteria are met during study participation, the study protocol is discontinued in this patient:

- Receiving parenteral nutrition (also when administered in addition to enteral nutrition)
- Oral intake exceeding half of total caloric intake (also when in addition to enteral nutrition)
- Persistent feeding intolerance despite standard of care intervention (administration of prokinetics, duodenal tube placement) as decided by the treating physician in collaboration with the nursing staff and research team
- Treatment with extracorporeal membrane oxygenation
- Severe neurological damage (significant neurological abnormalities such as bleeding, ischemia, neurotrauma or severe encephalopathy with Glasgow Coma Scale ≤8)
- Decision of treating ICU physician

These criteria are assessed daily. After discontinuation of the study protocol, patients will receive the standard ICU care.

2.9. Co-enrolment

Co-enrolment in other clinical trials is allowed as long as the study outcomes and interventions do not interfere.

2.10. Withdrawal and replacement of individual subjects

Patients can leave the study at any time for any reason if they wish to do so without any consequences. The attending physician can decide to withdraw a subject from the study for medical reasons. After withdrawal, these patients will receive the standard ICU care. Subjects will be replaced when informed or deferred consent is not obtained after randomization, or the study protocol is not followed up to and including day 4 9:00 h of the study period. The replacement of the subject is done in the automated randomization scheme.

2.11. Outcome measures

The primary outcome is the amplitude of the 24-h rhythm of core body temperature, as determined by cosinor analysis at study day 3–4 (Fig. 2). Secondary outcomes include measures related to 24-h rhythms in mean blood pressure, heart rate, melatonin and clock gene expression, glucose regulation, nutrition and clinical outcomes. All primary and

secondary outcomes are listed in Table 1.

2.12. Sample size calculation

The sample size calculation is based on the primary outcome variables in this study: the amplitude of the 24-h rhythm in core body temperature. We expect an average core body temperature amplitude of 0.33 °C in the *continuous* group [15] and of 0.41 °C in the *cyclic* group [16], and a standard deviation of 0.10 °C in both groups (preliminary analysis). Using an α of 0.05, we need 28 patients in each group to detect a difference with a power of 80 % using a parametric *t*-test. Consequently, we plan to include a total of 60 patients ($n = 30$ per group) who followed the study protocol up to and including day 4 09:00 h of the study period.

For reference, the amplitude of the 24-h rhythm in core body temperature in healthy individuals is approximately 0.5 °C. [17] Therefore, we consider this difference of 0.08 °C to be physiologically relevant, because core body temperature fluctuates in within a narrow range and is considered an important systemic timing cue capable of resetting peripheral circadian clocks, with small increases in amplitude leading to more efficient synchronization. [18]

2.13. Data processing

2.13.1. Vital sign data processing

The vital sign data processing will be done using Python programming language. All available vital sign values are extracted from the data warehouse. Vital sign values outside physiological ranges will be removed, as they are expected to result from erroneous measurements. Physiological ranges are defined as follows: 30 < heart rate < 240 bpm, 30 mmHg < mean blood pressure < 150 mmHg, 34 °C < core body temperature < 42 °C. Next, parts with rapid fluctuations that are assumed to be unphysiological are detected in the derivative of the vital sign time series and removed. Finally, the vital sign data will be downsampled from 1/s to 1/15 min by taking the median value per 15 min window.

2.13.2. Heart rate variability processing

HRV metrics will be retrieved from the raw ECG signal using Python programming language. To calculate the various HRV metrics, R-peaks will be detected using the Pan-Tompkins algorithm. [19] First, the ECG signal will be filtered with a first-order Butterworth bandpass filter, using cutoff frequencies of 5 Hz and 15 Hz. Next, R-peaks will be detected in the ECG signal using the BioSPPy toolbox. [20] Subsequently, artifacts and ectopic beats are removed from the data through the ADARRI method. [21] HRV metrics in time, frequency and nonlinear domain will then be calculated using the PyHRV toolbox. [22] HRV metrics will be computed per 5-min window every 15 min.

2.13.3. Cosinor analysis

Cosinor analysis will be performed using the Python package Scipy. [23] A cosine wave with a 24-h period will be fitted to the vital sign time series. Acrophase and amplitude are retrieved from the fitted cosine wave.

2.14. Statistical analysis

Statistical analysis will be performed using R and Python programming language. Continuous parameters will be presented using mean and standard deviation and will be compared between both study groups using a Student's *t*-test. If the distribution is not normal, median and interquartile range will be used to present the data and an appropriate data transformation or non-parametric alternative will be used. To compare acrophases of 24-h rhythms, the Rayleigh test will be used, as this test is suitable for circular data. Categorical data will be compared using Chi-squared tests. *P*-values of 0.05 will be used for statistical significance, and 95 % confidence intervals will be used to show the statistical uncertainty. No interim analysis will be performed. The following outcomes will be analyzed by per-protocol analysis: 24-rhythms of plasma melatonin, core body temperature, mean blood pressure, heart rate and heart rate variability, circulating metabolites and peripheral clock gene expression. The remaining outcomes will be analyzed by both intention-to-treat and per-protocol analysis.

Table 1

Study outcomes
Primary study parameter
• 24-h rhythm (amplitude) of core body temperature: cosinor analysis at study day 3–4
Secondary study parameters
Circadian rhythm
• 24-h rhythm (phase) of core body temperature: cosinor analysis at study day 3–4
• 24-h rhythm (amplitude & phase) in mean blood pressure: amplitude & acrophase cosinor analysis at study day 3–4
• 24-h rhythm (amplitude & phase) in heart rate: cosinor analysis at study day 3–4
• 24-h rhythm (amplitude & phase) in heart rate variability (HRV): cosinor analysis at study day 3–4. HRV metrics include: SDNN, pNN50, and LF:HF ratio
• 24-h rhythm (amplitude & phase) of plasma melatonin levels: time-of-day dependent changes in melatonin levels measured in plasma samples collected at timepoints 08:00 h,12:00 h, 16:00 h, 20:00 h, 00:00 h, 04:00 h, 08:00 h on study day 3–4
• Peripheral clock and clock-controlled gene expression: time of day-dependent difference in genome-wide gene expression in whole blood samples collected around 00:00 h and 12:00 h.
• 24-h rhythm in circulating metabolites: time-of-day dependent changes in circulating metabolites measured in plasma samples collected at 08:00 h,12:00 h, 16:00 h, 20:00 h, 00:00 h, 04:00 h, 08:00 h on study day 3–4
Glucose regulation
• Mean daily rate of hyperglycemia/hypoglycemia. Hypoglycemia is defined as glucose levels <3.5 mmol/L, hyperglycemia is defined as glucose levels >10 mmol/L.
• Mean daily time-weighted average of glucose levels
• Mean daily glucose variability: mean coefficient of variation of glucose levels
• Mean daily insulin administration (number of insulin units)
Nutrition
• Mean daily caloric intake (calories per kilogram that patient receives)
• Daily rates of gastric residual volume > 200 mL
Clinical Outcomes
• Incidence of delirium. Presence of delirium is defined as a positive Confusion Assessment Method for the ICU (CAM-ICU) score, or the use of haloperidol >2 days in combination with clinical documentation of delirium.
• Incidence of infections. Presence of infection is defined as a registered infection or non-prophylactic use of antibiotics >3 days in combination with a positive culture.
• ICU length of stay
• Days on invasive mechanical ventilation
• 28-day mortality

2.15. Data management

All source data is either captured in a dedicated and password protected clinical trial platform (CastorEDC), or will be directly extracted from the electronic health record or patient monitoring system. All patient identifying information is removed from the source data, and the data is coded with the allocated patient randomization number. The identification code and source data are stored digitally on a secure network drive, accessible only to authorized personnel with explicit access permissions, that is safeguarded by the principal investigator. All data will be stored for the length of the study and for 15 years afterwards, according to the local guidelines.

2.16. Ethical approval

The ethical approval has been granted by the local medical ethics committee of Leiden, Den Haag, and Delft in the Netherlands in December 2022 (reference number P22.080). The trial was registered at ClinicalTrials.gov (NCT05795881) in April 2023.

3. Summary

Increasing evidence suggests that disruption of circadian rhythms in critically ill patients in the ICU are linked to poor clinical outcomes. [1] Even though it is well-known that timing of nutrition is a crucial circadian timing cue, continuous enteral tube feeding is a predominant common practice is ICUs all over the world. However, the impact of cyclic nutrition on circadian rhythms, and other outcomes, in critically ill patients remains unclear. In the CIRCLES trial, we aim to assess the effect of a cyclic daytime feeding schedule compared to a continuous feeding schedule on circadian rhythms in critical illness. We hypothesize that a cyclic feeding strategy with a daytime feeding period will result in a higher amplitude of 24 h rhythms in vital signs, heart rate variability, and melatonin, compared to continuous feeding. This would suggest an improvement in circadian rhythm strength. In addition, we will explore the effect of cyclic feeding on clinically-relevant outcomes, such as glucose regulation and insulin administration, feeding intolerance and caloric intake and the incidence of delirium and infections. The CIRCLES trial will help to gain more insight into strategies to optimize circadian rhythms in critically ill patients. In addition, the results from our study will help to design a larger randomized controlled trial that is powered to assess the effect of the cyclic daytime feeding schedule on clinical outcomes.

CRediT authorship contribution statement

Floor W. Hiemstra: Writing – original draft, Visualization, Project administration, Methodology, Investigation. **Marit F. van Gent:** Writing – review & editing, Investigation. **Evert de Jonge:** Writing – review & editing, Methodology. **David J. van Westerloo:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Laura Kervezee:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Funding statement

This work was supported by a VENI grant (2020–09150161910128 to LK) from the Netherlands Organization for Health Research and Development (ZonMw), an institutional project grant from the Leiden University Medical Center (to LK and DJvW), a research grant from the Dutch Society for Intensive Care (NVIC) (to FWH) and the BioClock Consortium (project number 1292.19.077 to LK) funded by the research program NWA-ORC by the Dutch Research Council (NWO).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cct.2025.107927.

Data availability

No data was used for the research described in the article.

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