Circadian rhythms in critically-ill children

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Primary Objectives: To evaluate the status of the circadian rhythm of critically ill children in multiple facets and on multiple moments during their PICU stay. To describe the distributions of rhythmic parameters in the paediatric ICU and their...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON49654

Source
ToetsingOnline

Brief title
Critical Clock

Condition

- Other condition

Synonym
Critical illness

Health condition

Ernstige ziekte in het algemeen. Alle kinderen opgenomen op de intensive care, ongeacht onderliggende aandoening, komen in aanmerking

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: circadian rhythm, criticall illness, pediatrics

Outcome measures

Primary outcome

The main parameters of interest are the measures of circadian rhythmicity and

the related sleep characteristics.

- Melatonin:

o Baseline

o Amplitude

o Acrophase (the time of the peak)

- Cortisol:

o Bathyphase (the time of the trough level)

o Acrophase

o Amplitude

- Sleep characteristics:

o Total sleep time

o Sleep efficiency (with respect to sleep period time)

o Sleep quality

o Sleep fragmentation index

o Arousal index

o Proportion of sleep during nighttime

o Sleep onset time

o Sleep offset time

- Gene expression levels

o Circadian time shift

- Vital signs: amplitude and acrophase of:

o Heart rate

o Blood pressure

o Oxygen saturation

o Respiratory rate

o Body temperature

The endocrine markers, sleep characteristics and gene expression levels will be assessed on days 1, 3, 7, 14 and before discharge. Vital signs will be monitored continuously.

Secondary outcome

Variables influencing circadian rhythms

We will collect the following parameters to assess their association with circadian rhythms:

- Age

- Sex

- Tanner stage of puberty

- Diagnosis and diagnosis group

- PRISM-score upon admission

- Daily PELOD-score

- Light and sound levels

- Daily maximum level of ventilator support

- Nutrition type

- Sedation: medication type and sedation level

- Inotropic medication use

- Corticosteroid use

- Melatonin use

- Large procedures like surgery

- Whether a patient is admitted to a single-patient or a multi-patient room

Light will be recorded continuously with samples every minute through HOBO® Pendant temp/light sensors (Onset Computer Corporation, Bourne, MA, USA). Sound level will be recorded with Flus ET-958 sound level meters (Shenzhen Flus Technology Co, Shenzhen, China), with samples every two seconds.

Clinical outcome parameters

The main outcome parameter we want to predict is length of PICU-stay. This will be censored for deaths.

Furthermore, since delirium has a strong relation with sleep and deprivation thereof, we will assess the predictive value of both sleep and other circadian rhythm parameters on delirium scores (SOS-PD) and delirium incidence.

Study description

Background summary

In health, many physiological processes depend on intrinsic timekeeping mechanisms collectively called circadian rhythm. These synchronized variations are important for predictive homeostasis and the temporal segregation of conflicting processes. This rhythm is entrained by several external periodic time cues, the so-called Zeitgebers (*timegivers*). Examples of these Zeitgebers are daylight, social interaction, exercise, and environmental temperature. An intensive care unit (ICU) lacks these normal synchronizing cues, and contains several factors disturbing a patients rhythm, such as

medication, ventilation and care procedures. Additionally, a patient*s critical illness might also contribute to circadian disturbances.
In critically-ill adults the circadian rhythm has been shown to be disturbed, and these disturbances are associated with worse outcome. In critically ill children, some studies also suggest a disturbed circadian rhythm in during Pediatric Intensive Care Unit (PICU) stay, but these are only small-scale exploratory studies.
Furthermore, these studies have only studied individual facets of the circadian rhythm, whereas multifaceted monitoring has been proposed as the optimal method to identify circadian rhythm in a PICU setting. This approach of circadian rhythm monitoring of different physiological processes includes vital sign pattern recognition, evaluation of circadian rhythm in biomarkers (cortisol and melatonin), the registration of sleep-wake cycles using electrophysiology, and the rhythm of gene expression. The individual facets are indirect measures of circadian rhythmicity and controlled by more than just the circadian rhythm. This makes the individual measures vulnerable to bias, especially in the ICU environment with its many disturbing factors. Combining the facets reduces this vulnerability and provides a robust way of measuring a patients circadian rhythm.
Since these individual measures have only been described in small-scale studies and as individual facets, we firstly aim to study their rhythm or disturbances thereof in the PICU population, along with their correlations. We will then aim to construct a measure of a patient*s overall circadian rhythm from the combination of these facets and study its evaluate its determinants and clinical consequences. Lastly, to explore whether in the future, circadian rhythm monitoring may be performed real-time and non-invasively, we will study the potential of algorithms based on vital signs alone.

Study objective

Primary Objectives:
To evaluate the status of the circadian rhythm of critically ill children in multiple facets and on multiple moments during their PICU stay. To describe the distributions of rhythmic parameters in the paediatric ICU and their evolution during PICU stay.

Secondary Objectives:
1. To identify the correlations between different circadian rhythm parameters.
2. To construct a robust combined measure of circadian rhythmicity from these parameters, which is assumed to robustly reflect the underlying circadian rhythm of a patient.
3. To assess the accuracy of combinations of vital signs in determining underlying circadian rhythm with the constructed measure mentioned in secondary objective 2 as a reference in order to explore to what extent vital signs alone may be used to evaluate underlying circadian rhythm of a critically-ill child.
4. To determine the role of the circadian rhythm in critical illness and recovery by studying the associations between circadian rhythms in relation

with both patient and disease characteristics on one hand and outcome on the other.

Study design

This will be a prospective cohort study starting on admission to the PICU and ending upon death or discharge from PICU whichever comes first. All critically ill children (term neonates * 17 years of age) admitted to the PICU with an expected stay of more than 48 hours will be eligible for inclusion. 165 patients will be included in total.

During the length of the study we will perform the following measurements:
- Sleep registration on days 1, 3, 7, 14 and discharge
- Cortisol 7 times a day on days 1, 3, 7, 14 and the last day before discharge
- Melatonin 13 times a day on days 1, 3, 7, 14 and the last day before discharge
- Gene expression levels twice daily on days 1, 3, 7, 14 and the last day before discharge
- Vital signs continuously

The discharge measurements will provide a logistical challenge so will only be performed if discharge is foreseen with more than a 24 hour period, to make sure a full period of measurement is possible.
These measurements will only performed as long as a patient is admitted to the ICU. Measurements will vary based on weight. Additionally, we will record patient and disease characteristics and short-term outcomes.

Study burden and risks

Benefits and risks
During the informed consent process, it will be made clear that participation in this study will provide no direct benefits to the patient and that refusal to participate will have zero impact on the care received from any of the nursing medical staff. The burden will consist of additional blood samples, which will only be acquired during blood draws for clinical purposes as to not impose additional draws on subjects. Also on day 3, 7 and 14 patients will undergo EEG for 24 hours. We believe this burden to be negligible.
Group-relatedness
Biological rhythms in children are different than in adults, due to the developing brain and body. Therefore, this study requires this specific study group of critically ill children of a large age range.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- All children with an expected PICU-stay of at least two days.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- Preterm, i.e. postconceptional age of <37 weeks, on admission
- Hydrocortison use in the 3 days prior to admission
- Melatonin use within 24 hours prior to admission
- Transfer from another PICU or NICU
- Weight < 2.025 kg
- Previously included in this Critical Clock study

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-03-2021
Enrollment:	165
Type:	Actual

Ethics review

Approved WMO

Date:	03-11-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 20589
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL72597.078.20