CPPopt Guided Therapy: Assessment of Target Effectiveness

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Main aim: We will assess whether the new intervention protocol provides a greater percentage of time during which CPP is within 5 mmHg of calculated individual and flexible CPP (CPPopt). This window has been chosen based on past studies which show…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Increased intracranial pressure and hydrocephalus
Study type	Interventional

Summary

ID

NL-OMON47355

Source
ToetsingOnline

Brief title
COGITATE

Condition

- Increased intracranial pressure and hydrocephalus

Synonym
severe traumatic brain injury (TBI); severe cerebral contusion

Research involving
Human

Sponsors and support

Primary sponsor: Intensive Care
Source(s) of monetary or material Support: European Society of Intensive Care Medicine

Intervention

Keyword: Cerebral autoregulation, Cerebral monitoring, Cerebral perfusion management, Traumatic brain injury

Outcome measures

Primary outcome

Percentage of monitoring time with measured CPP within 5 mmHg of calculated individual and flexible CPP (CPPopt).

Time Frame: First 5 days during intensive care unit admission

In pilot studies, we showed that, on average, patients spent a mean (+SD) of 30% (8%) of their monitored time with measured CPP within 5 mmHg of CPPopt. The study will be powered to target an increase in this metric to 50% of monitored time.

Secondary outcome

Main secondary endpoint: Daily Treatment Intensity Level (TIL) score (0-48 points).

Time Frame: First 5 days during intensive care unit admission.

A change in daily TIL score of > 3 is representative of a clinical significant escalation of TBI treatment from basic ICP management to second tier therapies known to carry risk of harm and therefore is expected to represent a clinically significant potentially harmful effect of CPPopt guided management.

Other secondary endpoints: data like systemic (like arterial blood pressure)

and cerebral physiological values (like intracranial pressure and autoregulation status), used medications, (laboratory) markers of organ damage (heart, kidney, lungs), electrocardiograms, daily lung x-rays and diagnostic follow up imaging (mainly CT cerebrum) are collected for effectiviness and safety endpoints. For these secondary endpoints no extra measurements (blood results/scans) have to be done (already part of clinical routine).

Study description

Background summary

Traumatic brain injury (TBI) is a global health problem. Despite improvements in Intensive Care management, one-fourth of the patients will not survive, or survives with major handicaps (60%). Many severe TBI patients develop life-threatening brain swelling. Medical/surgical interventions aim to control the swelling and maintain adequate brain perfusion. Continuous monitoring of intracranial pressure (ICP) and cerebral perfusion pressure (CPP = arterial blood pressure (ABP) minus ICP) is therefore widely practised. However, treatment failure, apparent from ischemia or oedema, is common. Novel strategies are thus urgently needed to optimize perfusion and improve patient outcome.

Currently, clinicians apply just one brain perfusion target for all patients during their whole admission. It is becoming increasingly clear that this *one size fits all* guideline is inadequate, because perfusion varies between individuals and changes over time. Moreover, the self-protective autoregulation mechanism of the brain is impaired after severe TBI, which further affects perfusion. Cerebral autoregulation is an unique and complex mechanism of the cerebral arterioles.

Together with the well-known brain physics monitoring group in Cambridge an advanced TBI monitoring algorithm was developed that calculates the CPP level at which individual autoregulation works best (CPPopt), allowing optimal perfusion. Importantly, retrospective data showed that deviation from the calculated CPPopt value (relative hypo- or hyperperfusion) was related to poor outcome. Patients with perfusion levels close to the individual and flexibleCPP had a more favourable outcome. However there is no prospective evidence to support its use and observational data is insufficient to draw firm conclusions as to how to operationalize the use of autoregulation measurements as part of

daily treatment. Despite this, the concept of individual and flexible CPP is already being used clinically in two European centres.

The physiological effect of targeting individual and flexible CPP has not been prospectively established. Optimal autoregulation often occurs at CPPs somewhat higher than the (recent adjusted) recommended range of 60-70 mmHg given by the brain trauma foundation (BTF) guidelines, although these are based on weak evidence. It is unknown whether augmenting CPP to benefit cerebral perfusion may instead drive further oedema or contusion expansion over the next days or lead to excess respiratory, renal or myocardial injury.

The bottom line is that the physiological effect of targeting individual and flexible CPP must first be established as a prerequisite for any future clinical outcome study. At the same time, a feasibility study employing randomisation would also have the benefit of providing information on the down-stream physiological effects of targeting CPPopt and the feasibility of doing this.

Study objective

Main aim: We will assess whether the new intervention protocol provides a greater percentage of time during which CPP is within 5 mmHg of calculated individual and flexible CPP (CPPopt). This window has been chosen based on past studies which show significant impacts on outcome with greater variation from CPPopt, and on an initial feasibility study across participating centres. Therefore, the major endpoint of this study is to evaluate whether a CPPopt monitor, along with a CPP targeting protocol, is effective in reducing the difference between patient*s CPP and target *optimal* CPPopt (mainly by changing the patient*s blood pressure).

Secondary aim: Worsening of ICP is likely to be a poor primary endpoint for a safety study, as neuro-intensive care will attempt to control this and keep it constant with escalating levels of (potentially harmful) therapeutically intense interventions. Thus one of the secondary endpoints for this proposed study will be a change in daily TBI Therapeutic Intensity Level (TIL) score. The TIL score is a global summary measure of therapy intensity for control of intracranial pressure. We know that increasing TIL score involves therapies with increasing risk of harm. We will assess if targeting individual and flexible CPP in TBI patients causes a significant increase in daily TIL score.

Study design

Randomized, controlled, non-blinded, multicentre, intervention study

Intervention

Control group: Standard care.
This means: Patients are managed according to recent international trauma foundation guidelines with keeping CPP between 60 and 70 mmHg. Individual and flexible CPP information is recorded but hidden for the treating clinicians.

Intervention group: Patients are managed according to recent trauma foundation guidelines, except for CPP where the individual and flexible CPP is targeted. Individual and flexible CPP is calculated by an algorithm published in the literature since 2012 and already applied (of label) in 2 intensive care units in Europe (adult patients).

Study burden and risks

Benefit: Severe TBI patients have a high risk of not surviving the ICU admission or survive with major handicaps. Individual and flexible CPP guided management might decrease the changes of secondary brain damage during the ICU admission and eventually improve the functional patient outcome.

Risks: Individual and flexible CPP guided management might cause increased swelling of cerebral parenchyma, enlargements of cerebral contusions and areas with cerebral ischemia. Due to changes in arterial blood pressure levels and use of vaso-active medications damage to other organs like the lungs, heart and kidneys might occur. The potential role of improving neurological outcome is large enough to accept these risks.

Burden: During the research period the patients are comatose or sedated and not expected to suffer from changes in CPP management. ICU and hospital admission is not expected to be extended by inclusion in this study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Any adult severe TBI patient requiring ICP monitoring and ICP/CPP directed therapy for at least 24 hrs on the assessment of the recruiting team
- Start randomization within 24 hrs after ICU admission

Exclusion criteria

- Patients < 18 years old.
- Known pregnancy.
- Moribund at presentation (e.g. bilaterally absent pupillary responses)
- Patients with a primary decompressive craniectomy.
- Patients already enrolled in one other intervention research study.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-03-2018
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO Date:	29-12-2017
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	06-02-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT02982122
CCMO	NL60173.068.17