The effect of proactive versus reactive treatment of hypotension on postoperative disability and outcome in surgical patients under anesthesia (PRETREAT): an adaptive, multicenter randomized controlled trial

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON55117

Source
ToetsingOnline

Brief title
PRETREAT

Condition

- Other condition
- Myocardial disorders
- Renal disorders (excl nephropathies)

Synonym
Hypotension; low blood pressure

Health condition

Postoperatief functioneren en kwaliteit van leven

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W,ZonMw (Goed Gebruik Geneesmiddelen)

Intervention

Keyword: Intraoperative hypotension, Organ damage, Postoperative disability, Proactive treatment

Outcome measures

Primary outcome

The primary outcome of the study is persistent functional disability at six

months after surgery, measured with the 12-item WHODAS 2.0 questionnaire

Secondary outcome

Secondary outcomes for the trial are: functional disability after 30 days

(WHODAS 2.0), quality of live after 30 days and six months (EQ-5D-5L

questionnaire), six-months mortality, in-hospital mortality, length of hospital

stay, and in-hospital complications, i.e. acute kidney injury, myocardial

injury, stroke, unexpected admission at the intensive care unit, and

postoperative use of non-prophylactic antibiotics.

Study description

Background summary

Over 1.4 million surgical procedures are performed every year in the Netherlands, of which one million under general or regional anesthesia. Unfortunately, surgery is not without complications. A risk factor for complications that commonly occurs during surgery under anesthesia is low blood pressure (hypotension). When a patient undergoes anesthesia, the body loses control over the compensatory mechanisms to regulate blood pressure and counteract hypotension. Hypotension, even for one minute, increases the risks of complications, such as myocardial infarction, renal failure, and postoperative death. Finding a solution for hypotension has therefore been prioritized in the 2018 TOP-10 research agenda of the Dutch Society of Anesthesiology.
Anesthesiologists have been using cardiovascular drugs since the emergence of large-scale anesthesia to fight hypotension, but despite those efforts, in more than 75% of surgical procedures (approximately 750.000 procedures per year) patients have one or more episodes of hypotension (a Mean Arterial Pressure (MAP) below 65 mmHg).
Anesthetic drugs, surgical manipulation and blood loss typically cause many fluctuations in a patient*s blood pressure. Not all patients are affected equally: the frequency and magnitude of blood pressure fluctuations depend on the type of surgery and on the patient*s comorbidity. Patients with more and greater blood pressure fluctuations have a greater chance of their blood pressure dropping below the currently advocated minimal acceptable threshold of a MAP of 65 mmHg, and are thus at greater risk of perioperative morbidity and mortality.
The current paradigm of blood pressure management is predominantly reactive: blood pressure is treated when it approaches the minimally acceptable threshold or when it is rapidly dropping. From a risk perspective it makes more sense to shift the paradigm to a proactive approach: keeping the blood pressure at a safe margin above the minimal acceptable blood pressure threshold. Patients at greater risk of severe blood pressure fluctuations need to be kept at a higher target blood pressure to keep them safe. This requires an intervention guideline for the anesthesia team with advise how to keep their patients* blood pressures at the appropriate level.

Study objective

The aim of this adaptive multicentre randomized controlled trial is to maintain patients at a target blood pressure level with a sufficient margin from the minimal acceptable blood pressure threshold of a MAP of 65 mmHg to reduce the incidence of hypotension. This study will investigate whether a proactive blood pressure management approach improves functional disability at six months compared to the reactive blood pressure management approach, i.e. care as usual, in adult patients after elective noncardiac surgery.

Study design

This study is a multicenter adaptive randomized controlled trial. The risk-based intervention strategy will be implemented, further refined and studied for its impact in an adaptive randomized controlled trial, randomizing patients to either the intervention (proactive risk-based intervention strategy) or care-as-usual (predominantly reactive). Patients are either treated at the University Medical Center Utrecht (UMCU) or Amsterdam University Medical Center, location Academic Medical Center (AMC).

Intervention

The hypothesis of this study is that a proactive strategy keeps the blood pressure at a safe margin and avoids dropping below the minimal acceptable threshold of a MAP of 65 mmHg. The proactive strategy consists of two components: 1) a target blood pressure that provides a sufficient safety margin above the minimal acceptable threshold of a MAP of 65 mmHg; 2) a guideline with suggestions how to keep patients at their target blood pressure.
Patients with a high likelihood of IOH require larger safety margins and thus higher target blood pressures compared to those with a low IOH likelihood. In the current literature, no comprehensive list of risk factors is available for this purpose. Hence, using combined historic data from the UMC Utrecht and the Amsterdam AMC, risk factors for the development of intraoperatieve hypotension were identified. Based on their hypotension risk - i.e. their individual predicted risk - patients will be divided into low-, intermediate- and high-risk strata, with resulting blood pressure targets of MAP 70, 80, and 90 mmHg respectively.
The guideline with suggestions how to keep patients at their target blood pressure will have the same core components for all centers, i.e. each center will use the class of drugs that are indicated for the cause of hypotension. The actual drug used may differ between centers and hence the guideline will be adapted to local practices. This way our risk based intervention strategy will have the highest chance of success of widespread implementation in the Netherlands.
The attending anesthesiologist can make patient-specific adjustments to the intervention strategy. The aim of the guidelines is only to reach the target blood pressure, not to make specific treatment decisions. Adjustments that the anesthesiologist can make include adjusting the target blood pressure or use a different vasopressor dosing regimen. Interventions are already documented in the electronic patient record, and the anesthesia team will further be encouraged to document reasons for making patient-specific adjustments.

Study burden and risks

Benefits:
With the proactive risk-based intervention strategy, a possible dangerous low blood pressure may be avoided. Avoiding intraoperative low blood pressure can possible lead to less functional disability after surgery. Besides the positive

effect of this intervention strategy for the patient, it is likely that avoiding hypotension and possibly reducing complications after surgery will reduce the healthcare costs by millions of euros.

Burden:
The burden for participating patients is considered low. All interventions will take place whilst the patient is undergoing surgery. All patients undergoing intermediate/high risk procedures will receive the WHODAS 2.0 and EQ5D-5L questionnaires as part of usual care.

Risks:
It is important to explain that the physiology of patients undergoing elective surgery under general anesthesia is different from patients undergoing an emergency procedure, coming from the intensive care unit or residing at the nursing ward after surgery. Patients undergoing elective surgery are at high risk of developing hypotension as a result of loss of sympathetic tone, vasodilatation and myocardial depression of due to the administration of anesthetics and analgesics. Under elective circumstances, all measures taken by the anesthesia team to maintain adequate blood pressure levels, for example by administrating fluids or vasopressors, serve to counteract the side effects induced by the anesthesia and surgery itself. During urgent procedures or emergency situations, there are either major *mechanical* alterations in a patient*s circulatory system (e.g. hemorrhage or heart failure), or an increased stress response that cause the low blood pressure or even circulatory shock. Specific events during an elective procedure can cause similar mechanical alterations, resulting in an emergency situation that are beyond the scope of the intervention of this study.
The main aim of anesthesia is to attenuate the stress response induced by tissue damage, especially during the surgical procedure. That is why under elective conditions, an elevated stress response that results in atrial fibrillation or circulatory shock do not occur unless a specific event has triggered it (e.g. anaphylaxis). When such a specific event occurs this thus becomes an emergency situation that is beyond the scope of the intervention of this study, and for which other specific clinical guidelines exist are present as emergency checklists in the operating room.

Adverse events can occur both in the intervention group, but also in the care-as-usual group. The intervention is based on treatments options that are widely accepted in standard care, only more uniformilized. Fluid administration and vasopression is not likely to cause atrial fibrillation or decompensation in patient undergoing elective surgery because patients that can not receive a fluid challenge of at least 250-500 ml will not be planned for elective surgery. To improve the safety of the intervention strategy the decision was made to provide guidelines in the form of a medical protocol instead of a fixed protocol that should be followed at all times. The anaesthesia team continuously monitors the patient during the procedure - including the blood pressure - and are at complete liberty to intervene if they believe a different

blood pressure strategy is in the best interest of the patient. In addition, we will closely monitor how the strategy works out on intraoperative blood pressure management during the adaptive phase of the trial and adjust the proactive strategy or the clinical guideline if necessary. In summary, the risk of participating in this study is moderate.

Contacts

Public
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL
Scientific
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Adult patients scheduled for elective non-cardiac surgery under general anesthesia or central neuraxial anesthesia with a scheduled stay at the hospital after surgery of at least one night - i.e. inpatients - will be considered eligible for inclusion

Exclusion criteria

Patients will be excluded when scheduled for low risk surgery, such as ophthalmic surgery, endoscopic gastrointestinal procedures, and (interventional) radiologic procedures. Also all other procedures under 30 minutes and obstetric or organ transplantations will be excluded.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	17-06-2021
Enrollment:	5000
Type:	Actual

Ethics review

Approved WMO Date:	05-03-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	21-12-2021
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO Date:	08-07-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-12-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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
CCMO	NL72175.041.20
Other	NL9391