The second INTEnsive blood pressure Reduction in Acute Cerebral haemorrhage Trial. An international randomised controlled trial to establish the effects of early intensive blood pressure lowering in patients with intracerebral haemorrhage.

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To establish the effects of a management policy of early intensive BP lowering on death and disability inpatients with acute spontaneous, primary, ICH and co-existing elevated BP compared to a moreconservative BP management policy that is based on a…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Central nervous system vascular disorders
Study type	Interventional

Summary

ID

NL-OMON35370

Source
ToetsingOnline

Brief title
Interact 2

Condition

- Central nervous system vascular disorders

Synonym
intracerebral haemorrhage; haemorrhagic stroke; stroke

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: National Health and Medical Research Council of Australia

Intervention

Keyword: Blood pressure, Intracerebral haemorrhage, Management, Randomised trial

Outcome measures

Primary outcome

Primary outcome: the efficacy of the treatment regime will be evaluated on the

combined endpoint of death

and dependency at the end of follow-up.

Secondary outcome

Key secondary outcome: to assess efficacy of the primary outcome in those

patients treated within 4 hours of ICH onset.

Other secondary outcomes: to determine effects of treatment on (a) physical

function, health-related quality of life, recurrent stroke and other vascular

events, days of hospitalisation, and requirement for permanent residential

care, and (b) other serious adverse events.

Study description

Background summary

SUMMARY PROTOCOL

THE SECOND INTENSIVE BLOOD PRESSURE REDUCTION IN ACUTE CEREBRAL HAEMORRHAGE

TRIAL
The main phase of an academic lead and conducted, international, multi-centre, open label, blinded endpoint, randomised controlled trial to establish the balance of benefits and risks of a treatment strategy of early intensive lowering of blood pressure (BP) compared to a conservative BP lowering policy in patients with acute primary intracerebral haemorrhage (ICH) and co-existing elevated BP without any definite indication or contraindication to treatment.

Intracerebral haemorrhage (ICH) is one of the most serious subtypes of stroke, affecting over a million people worldwide each year, most of whom live in Asia. About one third of people with ICH die early after onset and the majority of survivors are left with major long-term disability. Despite the magnitude of the disease burden and cost on healthcare resources, there remains uncertainty about the role of surgery for ICH and no acute medical therapies have been shown to definitely alter outcome in ICH. Although administration of activated recombinant human Factor VII (ie rFVIIa; NovoSeven®) has been shown to limit haematoma expansion, a recent clinical trial failed to show that this effect translated into improved survival and less major disability in ICH. Moreover, future use of this agent will be limited by its short therapeutic time window, contraindication in patients at risk of thromboembolism, and high cost. The management of ICH, therefore, contrasts sharply with that of acute ischaemic stroke, where there is now strong evidence to support the routine use of thrombolysis in carefully selected patients, and aspirin in the majority.
Blood pressure (BP) levels are strongly and positively associated with the incidence of first and recurrent stroke, and there is definitive evidence that BP lowering reduces stroke risk. Although BP levels are commonly elevated early after the onset of stroke, particularly in ICH, the effects of BP lowering treatment in the acute phase of stroke remain unknown. As a consequence, there are wide ranging guideline recommendations for the management of elevated BP in the setting of acute ICH. While these provide an indication of perceived harm associated with *very high* BP levels (>220mmHg), they also highlight persisting clinical uncertainty about what comprises optimal management of BP in this patient group.

The adverse effect of high BP levels on outcome in ICH is likely to involve a number of different
mechanisms: elevated hydrostatic pressure at the site of bleed is likely to result in a larger initial bleed and
early haematoma expansion, while elevated BP increases the likelihood of early re-bleeding, more severe
oedema and early recurrent stroke. The first of these mechanisms is likely to be most relevant in the first
several hours after onset, as haematoma expansion is most frequent in the first several hours after onset.
Reduction of BP may also be important sub-acutely, as peri-haematomal oedema, which appears to be
plasma derived, increases in volume over several days. Against this background of processes is the
increased risk of early stroke recurrence from elevated BP levels.
The INTERACT2 study follows the recently completed initial pilot study (vanguard phase) which established
the feasibility of the protocol, safety of early intensive BP lowering, and effects on haematoma expansion
within 6 hours of onset of ICH. Having established *proof-of-concept* that BP lowering may improve outcome
by reducing haematoma expansion, INTERACT2 aims to establish the effects of the treatment on major
clinical endpoints in patients with ICH recruited from an expanding clinical network around the world.

Study objective

To establish the effects of a management policy of early intensive BP lowering on death and disability in
patients with acute spontaneous, primary, ICH and co-existing elevated BP compared to a more
conservative BP management policy that is based on a commonly used guideline for the management of
high BP in this clinical setting. The study uses a similar design to the pilot study - INTERACT1 - undertaken
in 44 sites in Australia, China and South Korea during 2005-2007. All patients will contribute to assessment
of the mortality/dependency endpoint at 90 days follow-up post-randomisation.

Study design

A multi-centre, prospective, open label, blinded outcome, randomised, controlled, trial involving 2800 patients
with acute ICH recruited from approximately 140 sites in the world.

Intervention

Patients will be randomised via a 24-hour central internet-based randomisation system (or IVRS system, currently in development) to either (a) intensive or (b) conservative management of BP. Treatment is to start as soon as possible after randomisation (eg in the emergency department) and will be continued in a monitored facility (ie intensive care unit, high dependency unit, or stroke unit) for all randomised patients.
Intensive BP lowering - patients allocated to the intensive BP lowering group will be started on a standardised treatment regime commencing with intravenous and then changed when feasible to oral (or via a nasogastric tube) agent(s). The treatment goal is to achieve a systolic BP goal (<140 mmHg) within one hour of commencing the randomised treatment. The second goal will be to maintain the systolic BP to 140 mmHg or less or at least 7 days in hospital, and subsequently on discharge and for 90 days postrandomisation.
Specific treatment protocols are developed for each participating region/centre based on the availability of BP lowering agents for routine use.
Conservative BP lowering - patients allocated to this group will receive BP management that is based on American Heart Association (AHA) guidelines. In this group, the threshold to be considered for the initiation of treatment will be a systolic BP -180 mmHg.
For both groups, patients must be on an oral anti-hypertensive agent by day 7 or discharge from acute care hospital, with a long-term target systolic BP of 140 mmHg, as per secondary stroke prevention guidelines.

Study burden and risks

Data collection and follow-up:
Key baseline information will be collected at the time of randomisation.
Follow-up data will be collected on four occasions: 24 hours and 7 days (or at the time of death or hospital discharge, if this should occur before day 7), and 28 days and 90 days, with the latter two assessments able to be carried out either in-person or over the telephone.
Most of the baseline and follow up assessments are part of the routine procedures for any patient admitted with an intracerebral haemorrhage.
The following examinations will be performed specifically for study puposes:
On day 1: NIHSS (standard on admission, but not standard at day 1);
On day 7: NIHSS, modfied Rankin Scale;

On day 28: modified Rankin Scale, Euroqol 5D.
On day 90: modified Rankin Scale, Euroqol 5D.
The duration of the contact at day 28 and 90 will be around 30 minutes.

Risks:
The blood pressure lowering drugs may cause side effects. These are generally mild and infrequent, and may be resolved immediately by reducing or stopping the treatment, but can include hypotension (low blood pressure), dizziness, headache, vomiting and other drug-specific side effects.
A theoretical severe and irreversible side effect is ischaemic stroke due to the rapid lowering of blood pressure and circulation in the brain.
As with any medication, an allergic reaction to blood pressure lowering drugs is possible, but is quite rare.
In INTERACT 1, the pilot study including 404 patients with an intracerebral haemorhage and high blood pressure, early, intensive treatment of high blood pressure was feasible and safe (Lancet Neurology, mei 2008).
The CT-scan <24 hours (+/- 3 hours) after randomisation entails a very small additional exposure to radiation.

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

a. 18 years or older.
b. Acute stroke due to sponataneous ICH, confirmed by clinical history and CT scan.
c. At least 2 separate blood pressure measurements of systolic blood pressure >=150 mmHg, and <=220 mmHg.
d. Able to commence assigned blood pressure treatment within 6 hours of stroke onset.
e. Able to be actively treated (not moribund).
(zie pagina 17 van het protocol)

Exclusion criteria

a. Known definite contraindication to an intensive BP lowering regimen (eg severe carotid, vertebral or cerebral arterial stenosis, known Moya Moya disease or Takayasu*s arteritis, high-grade stenotic valvular heart disease, or severe renal failure).
b. Known definite indication for an intensive BP lowering regimen that is similar or more intensive than the active treatment arm of this study (eg very high systolic BP >220 mmHg, hypertensive encephalopathy, or aortic dissection).
c. Definite evidence that the ICH is secondary to a structural abnormality in the brain (eg an AVM, intracranial aneurysm, tumour, trauma, or previous cerebral infarction) or previous thrombolysis.
d. Previous ischaemic stroke within 30 days.
e. A very high likelihood that the patient will die within the next 24 hours on the basis of clinical and/or radiological criteria (eg massive haematoma with mid-line shift of hemisphere or deep coma on presentation, defined by Glasgow Coma Scale Score of 3-5), (NB seizures occur commonly after the onset of ICH, so a reduction in the level of consciousness that isdisproportionate to the size of the haematoma may be secondary to epilepsy rather than mass effect from the ICH).
f. Known advanced dementia or significant pre-stroke disability (eg modified Rankin Score [mRS] of 3 or more).
g. Concomitant medical illness that would interfere with outcome assessments and follow-up (eg advanced cancer or respiratory disease).
h. Already booked for surgical evacuation of haematoma.
i. Previous participation in this trial or current participation in an investigational drug trial.
j. A high likelihood that the patient will not adhere to the study treatment and follow-up regimen.

Study design

Design

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

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-08-2011
Enrollment:	60
Type:	Actual

Ethics review

Approved WMO

Date:	28-09-2010
Application type:	First submission
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
ISRCTN	ISRCTN73916115(Europe);NCT00716079(US);ACTRN12608000362392(Australia)
CCMO	NL29972.041.10