Pragmatic, prospective, randomized, controlled, double-blind, multicentre, multinational study on the safety and efficacy of a 6% Hydroxyethyl starch (HES) solution versus an electrolyte solution in trauma patients

Published: 04-01-2017
Last updated: 12-04-2024

To investigate the safety of a 6% HES solution (Volulyte 6%) versus an electrolyte solution (Ionolyte) in trauma patients.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Electrolyte and fluid balance conditions
Study type	Interventional

Summary

ID

NL-OMON50632

Source
ToetsingOnline

Brief title
TETHYS

Condition

- Electrolyte and fluid balance conditions

Synonym
'Hypovolaemia' and 'Decreased blood volume'

Research involving
Human

Sponsors and support

Primary sponsor: PRA Belgium BV
Source(s) of monetary or material Support: Fresenius Kabi Deutschland GmbH,Industry

Intervention

Keyword: Hydroxyethyl starch, Hypovolaemia, Trauma

Outcome measures

Primary outcome

Composite endpoint of 90 day mortality and 90 day renal failure (defined as

biomarker increase as defined by AKIN stage 2 or RIFLE injury stage or renal

replacement therapy (RRT) during any time during the first 3 months)

Secondary outcome

Safety:

• Renal function:

o Serum creatinine (SCr)

o SCr-based estimated glomerular filtration rate (eGFR)

o Cystatin-C

o Cystatin-C-based mean eGFR [ml/min] (calculated from the highest cystatin-C

level during day 1-3)

o AKIN & RIFLE score (calculated)

o Highest AKIN stage reached on each day during the first week

o Urine output (if available)

• Coagulation

o Platelet count

o International norm ratio

o Activated partial thromboplastin time

• Inflammation

o C-reactive protein

• Adverse Events

o (Serious) adverse events / reactions

• Outcome

o Length of stay (LOS) in the hospital

o LOS in the intensive care unit (ICU)

o Fit for discharge from ICU/hospital

o Hours on mechanical ventilation

o In-hospital / out of hospital mortality (incl. cause)

o Renal Replacement Therapy (RRT).

Efficacy:

• Fluid administration

o Administration of IP volume

• Fluid balance

o Fluid input and output

• Haemodynamics/ Vital signs

o Heart rate

o Temperature

o Mean arterial pressure

o Systolic arterial blood pressure

o Diastolic arterial blood pressure

o Central venous pressure (if available)

at least one of the following parameters to evaluate volume responsiveness and guide IP administration within the volume algorithm:

o Stroke volume

o Stroke volume variation

o Stroke volume index

o Pulse pressure variation

o Mean arterial pressure

• Laboratory data

o Arterial (preferred) blood gas analysis

Partial pressure of carbon dioxide (pCO2)

- Partial pressure of oxygen (pO2)

- Bicarbonate (HCO3-)

- Arterial oxygen saturation (SaO2)

- Haemoglobin

- Haematocrit

- pH

- Base excess

- Lactate

o Central venous oxygen saturation (ScvO2) (if available)

o Serum electrolytes

- Natrium (Na+)

- Potassium (K+)

- Calcium (Ca2+)

- Magnesium (Mg2+)

- Chloride (Cl-).

Other variables:

• Demographic data & medical history

o Age

o Gender

o Height

o Weight

o Ethnicity

o Anamnesis & concomitant diseases

o Blunt / penetrating trauma

o Injury characteristics (injury severity score, glasgow coma scale)

o Fluid input (colloids, crystalloids) prior to hospital admission (during

emergency situation until hospital admission)

o Surgeries due to trauma (initial and secondary)

• Concomitant medication

o Antibiotic therapy

o Contrast agents

o Vasoactive and inotropic drugs

o Blood products

o Fibrinogen / factor XIII / prothrombin complex concentrate

o Diuretics

o Crystalloids (including basal infusion) / albumin

Study description

Background summary

The purpose of plasma volume substitutes is to compensate for a decrease in intravascular volume, for example to counter during the surgery or after a trauma, and hypovolemia, whereby the hemodynamics and the patient's vital functions remain intact. Plasma volume substitutes are electrolyte solutions or colloidal solutions. Both infusion solutions compensate for the loss of blood. Electrolyte solutions containing various salts (electrolytes) which are dissolved in water. They are administered in the vein, but move partially into the surrounding tissue, where they may give rise to tissue swelling (edema). However, colloid solutions comprise an additional active substance, such as HES, whereby the administered liquid is held in the blood vessels. Therefore, it is assumed that in the use of colloid solutions need to be administered less infusion fluid in order to compensate for the loss of blood and thus there is less formation of harmful tissue swelling. There is evidence that solutions containing HES have a positive effect on the stabilization of the blood circulation and perfusion in the tissue trauma patients.

This clinical study was requested by the European Medicines Agency in order to reassess potential side effects of HES solutions in trauma patients. For this purpose, two different plasma volume substitutes are being compared in this clinical study with respect to safety and efficacy: a HES solution (the investigational test product *Volulyte 6 %*) and an electrolyte solution (the investigational reference product *Ionolyte*).
This clinical trial was imposed by the European Medicines Agency to reassess any side effects of HES solutions in trauma patients. For this purpose in this clinical study two different plasma volume substitutes compared with respect to safety and efficacy: a HES solution (the research test product "Volulyte 6%") and an electrolyte solution (the research reference product "Ionolyte").

HES solutions and electrolyte solutions have been legally approved for years and have been used routinely during operations for decades. In January 2018, the European Medicines Agency EMA found that in clinical routine, HES solutions were often used outside the allowed (approved) indications and as a result recommended to suspend (i.e. put on hold) the use of HES containing solutions in routine clinical practice as a precautionary measure. Use in clinical trials where patient selection is tightly controlled is still allowed. Of note, in this clinical study, the HES containing solution is strictly used in the allowed indication.

Study objective

To investigate the safety of a 6% HES solution (Volulyte 6%) versus an electrolyte solution (Ionolyte) in trauma patients.

Study design

Pragmatic, prospective, controlled, randomized, double-blind, parallel-group, multi-centric, multinational study

Intervention

Method of Administration:
The administration of the IPs is performed intravenously.

Dosage:
Dosing of IPs is individualized to the patient*s volume needs and may preferably be guided by a volume algorithm based on either mean arterial pressure or dynamic circulatory parameters.The decision to use a volume algorithm is at the discretion of the treating physcican. The daily dose should not exceed 30 ml/kg. If patients are still hypotensive during administration of IP, they may also receive vasoactive/ inotropic drugs, if regarded necessary due to the patients* clinical condition. HES preparations for volume replacement may rarely cause allergic (anaphylactic/anaphylactoid) reactions of varying degrees of severity. In order to detect the occurrence of an allergic reaction as early as possible, the first 10-20 ml of the solution should be infused slowly and the patient should be under careful observation especially at the beginning of the infusion. In case of an allergic reaction, the infusion must be stopped immediately and appropriate treatment given.

If concomitant blood products are necessary, these should only be given according to the most current version of the ESA guideline on the management of severe perioperative bleeding.

Treatment Duration:
Patients will be treated for maximally 24 hours or until the maximum dose of 30 ml/kg body weight/day is reached whatever occurs first.
If the patient is haemodynamically not yet stabilized after the maximum allowed daily IP dosage of 30 ml/kg had been administered or 24 hours after IP treatment start (whatever occurs first) only crystalloid solutions, or albumin are to be administered. The choice of the solution is at the discretion of the treating physician.

Study burden and risks

If the patient receives the investigational test product Volulyte 6 %, he/she

might possibly require a lower amount of plasma volume substitute to compensate for your blood loss and to stabilise your circulatory system. This might influence and reduce the occurrence of complications following trauma.
If the patient receives the investigational reference product Ionolyte, participation in this clinical trial is not expected to affect the outcome of the medical treatment.
All together, participation in the clinical study will involve more intensive, study-related monitoring and a considerable increase in documentation. This may, taken by itself, result in an immediate benefit during treatment.

The study itself poses no additional risks to the patient. The suspension of clinical routine use does not apply to the use of Volulyte 6% in this clinical trial, where patient selection is tightly controlled and used in the approved indication.
Participation in this clinical study will not impact the risks associated with the condition (i.e. blunt or penetrating trauma).
As in the case of all infusions and blood collection procedures, damage to the blood vessels and/or nerves, bruising, skin reactions and discomfort may occur at the injection site.
Other risks are side effects of the plasma volume substitute that the patient will receive during trauma care.

All IPs have marketing authorizations in most European countries as well as in various countries worldwide. For the investigational test product HES, a second urgent union procedure under Article 107i of Directive 2001/83/EC (EMEA/H/A-107i/1457) had started end of 2017 resulting in the recommendation for a suspension (i. e. recommendation to put the market authorization *on hold*, i. e. not revoked) of the market authorization of HES product in the EU. The recommendation to suspend the market authorization is based on the off-label use in certain patient populations (for example critically ill or severe sepsis/ septic shock patients). This, however, does not affect the use of HES in the present clinical trial in abdominal surgery patients, where patient selection is not only tightly controlled. but also is in line with the registered SmPCs, the annex IV (*Conditions to the Marketing Authorisations Holders*) of the *Recommendation of the Pharmacovigilance Risk Assessment Committee pursuant to Article 107i of Directive 2001/83/EC*, and the *Scientific Advice (EMA/CHMP/SAWP/544745/2014)*.
Furthermore, many of the proposed measures and parameters (laboratory, clinical) are performed/obtained routinely and thus, do not represent major additional burden to the patient.
In conclusion, the risk due to methods and measurements in the present study is considered to be low and a balanced risk-benefit is assessed.

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

• Male or female adult patients >= 18 years of age.
• Women of childbearing potential must test negative on standard pregnancy test (urine or serum) (as soon as possible during emergency care), • Patients with blunt or penetrating trauma suffering from an estimated blood loss of >= 500 ml, • Initial surgery deemed necessary within 24 hours after trauma, • Deferred signed written informed consent form or as locally required, • No signs of intracranial or cerebral haemorrhage, • Administration of less than 15 ml/kg body weight colloid between trauma injury and hospital admission

Exclusion criteria

• Hypersensitivity to the active substances or to any of the other excipients of the IPs, • Body weight >= 140 kg, • Patients expected to die within 24 hours after traumatic injury, • Sepsis, • Burns, • Renal impairment (AKIN stage >= 1 or chronic) or acute and/or chronic RRT, • Critically ill patients (typically admitted to the intensive care unit), • Hyperhydration, • Pulmonary oedema, • Dehydration, • Hyperkalaemia, • Severe hypernatraemia, • Severe hyperchloraemia, • Severely impaired hepatic function, • Congestive heart failure, • Severe coagulopathy, • Organ transplant patients, • Metabolic alkalosis, • Simultaneous participation in another clinical interventional trial (drugs or medical device studies)

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-09-2017
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ionolyte solution for infusion
Generic name:	Isotonic solution of electrolytes
Registration:	Yes - NL intended use
Product type:	Medicine

Brand name:	Volulyte 6% solution for infusion
Generic name:	Hydroxyethyl starch 130/0.4
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	04-01-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-06-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-09-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-01-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-04-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-04-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	16-09-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-10-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-12-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-04-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-05-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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
EudraCT	EUCTR2016-002176-27-NL
ClinicalTrials.gov	NCT03338218
CCMO	NL59903.056.16