A pilot study regarding regional anticoagulation by a citrate containing dialysis fluid.

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The study has 3 objectives: 1. Proving that this form of RCA does not increase the risk of bleeding while achieving a degree of anticoagulation of the extracorporeal system that is similar to that when using LMWH. When this study shows that citrate...

Ethical review	Approved WMO
Status	Pending
Health condition type	Coagulopathies and bleeding diatheses (excl thrombocytopenic)
Study type	Interventional

Summary

ID

NL-OMON41845

Source
ToetsingOnline

Brief title
Citradial

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)
- Nephropathies

Synonym
bleeding and clotting, hemodialysis

Research involving
Human

Sponsors and support

Primary sponsor: Albert Schweitzer Ziekenhuis
Source(s) of monetary or material Support: toepassing valt onder normale behandeling

onder DOT 13.21.339

Intervention

Keyword: calcium-free, citrate, dialysis, magnesium-free

Outcome measures

Primary outcome

Primary study objective:

Does RCA prevent the increased anticoagulation in the patient as seen with LMWH?

Primary outcome:

The RCA as proposed prevents a change in TEG in the patient during and after the dialysis session as seen in conventional anticoagulation with LMWH. Due to the small number of observations, hard endpoints like clinical relevant bleeds or the number of blood transfusions will seldom occur. Therefore, these are not used as primary outcome points.

Secondary outcome

Secondary study objectives:

1. Does RCA cause an anticoagulation of the extracorporeal system comparable to LMWH?

2. Are serum Ca- and Mg-values after dialysis comparable to those with a conventional anticoagulation with LMWH and a 1.5 and 0.75 mmil/l containing

dialysis fluid?

The secondary endpoints:

1. During the proposed RCA clotting necessitating termination of the treatment session does not happen more frequently compared to LMWH. The number of signs of clotting in the extracorporeal system is not more frequent in the proposed RCA compared to LMWH.

2. The proposed RCA does not result in a rise in APTT ratio and increase thrombin time in the patient during and after a dialyse session, compared to conservative anticoagulantia with LMWH

3. The serum values of Ca and Mg are similar in both methods.

Study description

Background summary

In hemodialysis, renal replacement is achieved by filtering blood of a hemodialysis patient through an artificial kidney. The patient's blood is led to a blood pump through a needle and subsequently pumped through hundreds hollow fibers forming the artificial kidney. Exchange of waste products is achieved by diffusion to the dialysis fluid which flows on the other side of the hollow fibers. The purified blood is returned to the body. Hemodialysis is typically performed twice or thrice weekly during 3 to 5 hours. If the patient cannot receive a renal transplant, this regimen will remain for the rest of his/her life. As blood is pumped through these very thin fibers, clotting can occur. The clotting can necessitate termination of the dialysis session. To

prevent this, anticoagulation is created during hemodialysis, mostly by administering low molecular weight heparin (LMWH) in a dose varying between 2500 and 10.000 U.

A disadvantage of the anticoagulation with LMWH is the simultaneous anticoagulation of the patient, which poses a tenfold increased risk on a subdural hematoma compared to the normal population. In the Albert Schweitzer Ziekenhuis (ASz), two patients were lost similarly. This strongly increased risk may be due to the simultaneous use of oral anticoagulation or antiplatelet agents for other reasons. It is concluded that ideally only the artificial kidney should be anticoagulated (regionally) and systemic anticoagulation of the patient should be prevented.

This risk of bleeding has led the Nederlandse Federatie voor Nefrologie (NFN) to formulate a guideline on the use of anticoagulants in hemodialysis in 2012. This guideline advises to avoid the use of heparin or LMWH in case of a high risk of bleeding as during active bleeding or dialysis within 2 to 3 days after surgery or trauma. In case of moderate increased risk of bleeding, as during use of other anticoagulants, adaptation of the anticoagulation is advised.

One of the options for achieving regional anticoagulation i.e. exclusively the extracorporeal system is anticoagulated, is the use of citrate. Citrate is an anticoagulant as it binds Factor IV (calcium = Ca) of the coagulation cascade. Continuous veno-venous hemofiltration (CVVH) with citrate (a form of renal replacement in the intensive care unit) is standard practice at the ASz .

Regional citrate anticoagulation (RCA) would be the ideal solution for hemodialysis patient with a moderate increased or high risk of bleeding. Apart from preventing anticoagulation of the patient, RCA results in less clotting of the extracorporeal system than with LMWH (4). Unfortunately, RCA is a technically demanding procedure. Citrate is administered with a syringe pump. The dialysis fluid should be calcium (Ca)- and preferably, magnesium (Mg)-free, while Ca en Mg are infused after the artificial kidney. When the blood pump stops or has to be stopped due to technical problems, as happens frequently, the syringe pump has to be stopped as well. If this is omitted, citrate will accumulate. As soon as the blood pump is restarted, a flush of citrate will reach the patient. This causes a passing hypocalciemia with complaints of cramps and paresthesia, which can be frightening for a patient.

In case of an acute bleeding, the technically demanding RCA is used in several hospitals in the Netherlands; several handbooks call it the first choice in this setting. In cases of a moderate increased risk of bleeding, RCA is not used due to the technically demanding procedure.

Would it be possible to simplify RCA in such a way that patients with a moderate increased risk of bleeding don't have to be exposed to the superimposed risk of bleeding due to LMWH?

Since some years a 0.8 mmol/l citrate containing dialysis fluid is used in the United States (Citrasate®). Also the Swedish firm Gambro produces a similar dialysis fluid. This citrate containing dialysis fluid has not been marketed in order to replace the use of LMWH or heparin. Nevertheless, there is a publication in which it was used as substitution for heparin. Citrasate® reduced clotting but 41% of the dialysis sessions had to be stopped prematurely.

Citrasate®, which is commercially available in The Netherlands, has been used in the ASz, Dordrecht, during the dialyses of 3 patients using acenocoumarol. Dialysis had never to be stopped due to clotting in these 3 patients. There were more clotting phenomena in the extracorporeal system than during standard dialyses with LMWH. The explanation for the occurrence of clotting is that Citrasate® contains Ca (1,25 mmol/l) en Mg (0,5 mmol/l). Part of the 0,8 mmol citrate is bound to these cations and not available for anticoagulation (8). Probably, only 0,42 mmol/l citrate is effectively avalable as anticoagulant in Citrasate. Subsequently, in 3 patients using anti platelet agents, some dialyses were performed using a 1,25 mmol/l Ca, 0,5 mmol/l Mg en 1,0 mmol/l citraat (theoretically 0,62 mmol/l available free citraat) containing dialysis fluid. In these sessions, clotting was not more frequent than with LMWH. Serum Ca was lower compared with standard dialyses with LMWH because in LMWH a dialysis fluid containing 1,5 mmol/l Ca is used.

This study envisions to simplify RCA. The current Dutch practice adding the citrate to the arterial blood line by a pump will be replaced by adding the citrate to a Ca- and Mg-free dialysis fluid. The substitution of the Ca and Mg after the artificial kidney to the venous blood line will remain the same. Due to the absence of Ca and Mg, a citrate concentration of 0.83 mmol/l in the dialysis fluid will suffice. The study will be performed in hemodialysis patients using oral anticoagulation or antiplatelet agents.

Study objective

The study has 3 objectives:
1. Proving that this form of RCA does not increase the risk of bleeding while achieving a degree of anticoagulation of the extracorporeal system that is similar to that when using LMWH. When this study shows that citrate does not increase the risk of bleeding and achieves a similar degree of anticoagulation compared to LMWH, this form of RCA will be tested in a larger population of hemodialysis patients to investigate non-inferiority to anticoagulation with LMWH. 2. The simplification of the existing RCA in order to make it available to patients receiving chronic hemodialysis with a moderate increased risk of bleeding i.e. using oral anticoagulation or antiplatelet agents. 3. Investigate whether serum values of Ca and Mg are similar to those during standard anticoagulation with LMWH.

Study design

Dialyses

Each patient will function as its own control and will be treated with both LMWH and citrate. Each patient will be treated with two consecutive citrate dialyses (C1 and C2). These dialyses will be compared to two consecutive standard dialyses with LMWH. (L1 en L2). The citrate- and standard dialyses will be performed on the same day of the week. A possible third dialysis during the week will not be a study session and therefore be a standard dialysis with LMWH.

Intervention

Regional citrate dialysis with calcium- and magnesium-free citrate dialysis fluid.

The dialysis fluid is produced by mixing 9.75 liters of a Ca-, Mg-free, 3,0 mmol/l acetate containing concentrate (Dirinco ACC1208) with 250 ml of a 1500 mmol/l citrate solution (Dirinco Citralock 46.7%, CE 1275).

Ca- and Mg-suppletion with a solution containing Ca 54 mmol/100ml, Mg 14 mmol/100ml and 136 ml Cl/100 ml.

Study burden and risks

The burden will not be different to that of the regular thrice weekly hemodialysis. Time expenditure for the patient will be unaltered. There will be no additional punctures of veins or vascular access. In 2 weeks, an extra amount of 120 ml of blood will be taken from the patient. The possible side effects are known because citrate is often used as anticoagulantia with CVVH at the intensive care departments. It has to be noted that the proposed citrate concentration of 0.83 mmol/l in the dialysis fluid is 30% less than used with CVVH. Excessive administraton (more than 4 times the proposed amount) of citrate kan cause a metabolic alkalosis and symptoms of hypocalciemia. These symptoms are divided according their incidence: seldom paresthesia, extremely seldom muscle contractions, carpopedal spasm, insult, laryngospasm, bronchospasm, increased QT interval, hypotenson, heart failure, arytmhia and papil edema. The chance of these side effects are further diminished by the used concentration of 0.83 mmol/l citrate, the separate administration of calcium and magnesium, and the regular controls of the permanent present dialysis nurse. The risk of clotting is similar to that of Citrasate that has been registered and is used commercially. The expected side effects are less than those seen with Citrasate. If by chance the proposed RCA with citrate does not result in sufficient anticoagulantic effect, clotting may occur. The results of clotting are minimal. At worst, in case of clotting of the

extracorporal system, patient will lose approximately 200 ml of blood.

Contacts

Public
Albert Schweitzer Ziekenhuis

Albert schweitzerplaats 25 Albert Schweitzerplaats 25
Dordrecht 3300 AK
NL
Scientific
Albert Schweitzer Ziekenhuis

Albert schweitzerplaats 25 Albert Schweitzerplaats 25
Dordrecht 3300 AK
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Stable hemodialysis patients older than 18 years using acenocoumarol, fenprocoumon, acetylsalicylzuur, dipyridamol, clopidrogel, prasugrel or combinations of these.

Exclusion criteria

Inability to give informed consent. Hemodialysis patients who have unstable dialysis sessions i.e. hypotensive periods, muscular cramps or patients who have an increased risk of these

afflictions.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2016
Enrollment:	12
Type:	Anticipated

Medical products/devices used

Generic name:	Sodium citrate
Registration:	Yes - CE intended use

Ethics review

Approved WMO

Date:	14-04-2016
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

No registrations found.

In other registers

Register	ID
CCMO	NL50418.078.15