Effect of High-volume Online hemodiafiLtration on intra-diaLytic hemodynAmic (iN)sTability and cardiac function in chronic hemodialysis patients (the HOLLANT study)

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This study aims at improving the knowledge concerning HV-HDF and thus helps to tailor the optimal ERRT for each individual patient.The following hypotheses will be tested:1. Intra-dialytic hemodynamic stability is better preserved during HV-HDF as...

Ethical review	Approved WMO
Status	Completed
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON50492

Source
ToetsingOnline

Brief title
Effect of dialysis techniques on blood pressure and cardiac function

Condition

- Heart failures
- Renal disorders (excl nephropathies)

Synonym
cardiac function and blood pressure in dialysis paitents

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: B Braun,Niercentrum aan de Amstel (eigendom van VUmc en Elyseklinieken/B.Braun);en B Braun Duitsland

Intervention

Keyword: blood pressure, cardiac function, hemodiafiltration, hemodialysis

Outcome measures

Primary outcome

During dialysis treatment:

nadir in systolic blood pressure (SBP) of 90 mmHg for patient with predialysis

SBP <160mmHg and a nadir of 100 mmHg for patients with predialysis SBP *160

mmHg during treatment

(blood pressure will be measured before and every 15 minutes after the start of

dialysis during the treatment; during 3 consecutive treatments with each

treatment-modality).

Secondary outcome

LV chamber quantification and deformation (longitudinal function withe speckle

tracking) and LV diastolic function during treatment will be obtained before

(t-30), and after 30 minutes (t30) and 3 hours of dialysis (t180).

Other end-points:

* Hemodynamic measurements: diastolic (DBP) and systolic (SBP) blood pressure,

pulse pressure (SBP-DBP), mean arterial pressure (MAP), blood pressure

variability, intra-dialytic hypotensive episodes, number of patients with

nadir SBP <90 mmHg. Changes in blood pressure (beat-to-beat), heart rate, stroke volume, cardiac output and total peripheral resistance during treatment. Blood pressure variability and heart rate variability during treatment.

* Patient tolerance: a modified version of the Dialysis Symptom Index (DSI) will be handed out after each treatment period, and Visual Analogue Scale Thermal Perception (VAS-TP) will be assessed both before and after 1 and 3 hours of treatment.

* Treatment parameters: number of sessions with reached (dry) weight. Relative blood volume (RBV).

* Markers of cardiac damage: biomarker CK-MB (MW 84 kD) will be assessed before and after 4 hours of treatment (at t0 and t240) from the arterial line (tart).

* Markers of endothelial damage: at t0 and t240 extracellular vesicles (EV), sICAM-1 (MW >50 kD) from the arterial line (tart).

* Markers of gut ischemia: at t0 and t240 bacterial DNA in blood and soluble CD14 (MW 20-150 kD, peak around 55 kD) will be assessed in blood samples drawn from the arterial line (tart).

* Markers of inflammation: at t0 and t240 hs-CRP (approximate MW 115kD) and IL6 (MW 23.7 kD) blood samples will be taken from the arterial line (tart).

* Special biomarkers: at t0 and t240 FGF23 (MW 30 kD), blood samples from the arterial line (tart).

* Others: oxygenation during treatment: pO2 from the arterial line and t0 and t240, SaO2 (RBV sensor - patients with central venous catheters and fistulas/grafts will be analyzed separately); tympanic measurement of body temperature at t0 and t240.

Study description

Background summary

Worldwide, over 2 million patients are treated with extracorporeal renal replacement therapy (ERRT).
Despite the use of high permeable dialyzers, which combine diffusive with convective clearance, the clinical outcome of hemodialysis (HD) patients remains poor. In post-dilution online hemodiafiltration (denoted further on as HDF) diffusive clearance is similar to HD, while the amount of convective transport is considerable increased. Recently, 4 randomized controlled trails have been published which compared HD with HDF. Although the results of the individual studies were inconclusive, a recent meta-analysis, using individual patient data of these studies, showed a superior outcome for patients treated with HDF (mortality reduction of 14% [95% CI 1-25]). The largest mortality reduction was obtained in patients receiving the highest convection volume (high-volume HDF [HV-HDF] >23 L/1.73 m2/session): all-cause mortality [22% (95 % CI 2-38)], cardiovascular mortality [31% (95 % CI 0-53)].
It is far from clear, however, why (HV)HDF is associated with an improved survival. Both long term and short term effects may be involved. With respect to the latter, the intra-dialytical removal of middle molecular weight (MMW) uremic retention products and a superior bio-incompatibility (BI) profile may play a role. In addition, treatment with HDF may induce less intra-dialytic hypotension (IDH) and less tissue injury. Enhanced removal of the MMW substance FGF23 may reduce the intra-dialytical acute phase reaction (APR), which is regarded a chief element of HD-induced BI. Other key components which may contribute to IDH and are supposed to be alleviated by HDF, include dialysis-induced hypoxia and release of extracellular vesicles.
Pathophysiologically, IDH depends both on a decline in the circulating blood volume and an impaired response to hypovolaemia. As a result, venous return,

cardiac output and peripheral vascular resistance are impaired.
Microcirculatory dysfunction is a prominent feature of HD patients. Since IDH occurs in 20-30% of the sessions, any interference with an already abnormal perfusion may further deteriorate the structure and function of vital organs, such as the brain, gut and heart. HD-associated cardiomyopathy, which is considered a model of repetitive organ ischemia-reperfusion injury, is superimposed on the cardiac changes resulting from the various inflammatory and metabolic derangements of pre-dialysis kidney disease. As measured by imaging techniques and biomarkers, HD induces a fall in cardiac perfusion and elicits tissue injury. While cardiac MRI is considered the reference method for LV quantification, intra-dialytical measurements can only be obtained in stable patients who can be safely transferred to the radiology department. Echocardiography, though, can be performed in all individuals at the bed-side, including hypotension-prone patients. Because of its superiority over standard echocardiography, especially with respect to diastolic (dys)function, speckle tracking echocardiography is preferred.
Since IDH is reduced by HD with cool dialysate (C-HD), thermal factors seem to play an important role in the preservation of intra-dialytical hemodynamic stability during C-HD. Hence, patients may not only benefit from a reduction in IDH and related symptoms, but also encounter an increase in cold sensations. Considering patient-reported outcomes, it is currently unclear whether and to what extent the beneficial effect of C-HD and LV-HDF on IDH is counterbalanced by concurrent patient discomfort. Interestingly, in a recently published French study it appeared that patient tolerance was significantly better during treatment with HV-HDF, as compared to S-HD.
As mentioned above, the effect on long term survival is especially prominent when HV-HDF is applied. Theoretically, HV-HDF is also the preferred treatment to circumvent dialysis-induced IDH, and hence, to alleviate the repetitive intra-dialytical tissue damage.

Study objective

This study aims at improving the knowledge concerning HV-HDF and thus helps to tailor the optimal ERRT for each individual patient.
The following hypotheses will be tested:
1. Intra-dialytic hemodynamic stability is better preserved during HV-HDF as compared to S-HD, C-HD and LV-HDF.
2. Left ventricular diastolic function is better preserved during HV-DF as compared to S-HD, C-HD and LV-HDF. As a result of superior hemodynamic stability, HV-HDF induces less intra-dialytic injury to the heart, blood vessels and gut as compared to S-HD, C-HD and LV-HDF.
3. The mechanism of a better preserved intra-dialytic hemodynamic stability during HV-HDF depends on its superior thermal balance and/or bio-incompatibility, clearance of MMW substances, or a combination of these items.
4. The above-mentioned beneficial effects of HV-HD are accompanied by a reduction in IDH-related symptoms and not by an increase in thermal sensations,

such as shivering and the quest for blankets.

Study design

This study is designed as an open, prospective cross-over, randomized controlled intervention trial.

Intervention

Patients will be subjected to different types of ERRT. In all modalities high-flux dialyzers are used.

Standard treatment: HD with a dialysate temperature of 36.5 °C. (S-HD)

Comparators:
- HD with a (cool) dialysate temperature of 35.5 °C (C-HD)
- HDF with a convection volume of 15 L/session and a dialysate temperature of 36.5 °C (LV-HDF)
- HDF with a convection volume of >23L/session and a dialysate temperature of 36.5 °C (HV-HDF)

HDF will be performed in the post-dilution mode with a target convection volume (substitution volume + net UF volume) of 15L (LV-HDF) or >23L (HV-HDF). Extracorporeal blood flow rate will be targeted at 350-400 ml/min, and filtration fraction (blood flow rate/ convection flow rate) at 25-32%.

Run-in phase during 2 weeks followed by randomisation to treatment with C-HD, S-HD, LV-HDF and HV-HDF during 2 weeks.

Total study duration is 2 weeks (run-in phase) + 8 weeks(study phase) = 10 weeks per patient.

Study burden and risks

As none of the study treatments is experimental, no specific adverse events are to be expected.

Possible inconveniences for the patient:
During the study, patients will be dialyzed with several modalities.Treatment time and all the other procedures are however similar in all modalities and will therefore cause no extra risks or put extra mental pressure on the patients.

Application of C-HD may induce shivering, which is uncommon in LV-HDF despite a similar energy transfer. In theory, HV-HDF may induce an even greater loss of heat and hence provoke cold sensations in participants.

Since the measurement of intradialytical hemodynamics is an essential part of this study, extra BP recordings, which will be taken every 15 minutes during the last week of every dialysis modality, may cause some discomfort.

The beat-to-beat nonivasive bloodpressure measurements will be perfomed during a total of 4 dialysis treatments with a fingercuff and may cause some discomfort.

The speckle tracking echocardiography assessment will be performed during 4 dialysis treatments.

In the entire study, during 4 dialysis treatments blood samples will be taken before and after the dialysis from the ECC. Therefore no extra punctures are needed.

The total amount of blood sampled during the study is 203 ml. If the Hemoglobin level decreases below 6.8 mmol/L, the dosage of Erythropoietin Receptor Agonists will be increased (according to routine clinical practice).

A modified version of the Dialysis Symptom Index (DSI) will be handed out after each treatment period (totally 4 times) and Visual Analogue Scale Thermal Perception (VAS-TP) will be assessed both before and after 1 and 3 hours of every dialysis treatment. Filling in the forms will take a maximum of 1 (VAS-TP) and 5 minutes (DSI) every time.

Possible advantages for the patient:
As far as we know, however, shivering has not been reported in HV-HDF, nor are we aware of this discomfort in clinical practice. In theory, HV-HDF may enhance both the efficacy and the quality of dialysis treatment by lowering the incidence of dialysis-induced IDH and thus:
* avoid the subjective symptoms of intra-dialytical low blood pressure
* alleviate the repetitive intra-dialytical organ injury of chronic ERRT [and hence, to contribute in part to the superior survival of HV-HDF (evidence level A1)]
* diminish or even prevent the cold sensations of C-HD
* achieve these goals within 12 hours of dialysis/week, in contrast to schedules of extended dialysis, up to 24-48 hours/week, with similar objectives
* gain knowledge about patient perceptions during dialysis with these 4 different modalities

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

Inclusion criteria:
- treatment with hemodialysis or hemodiafiltration 3 x per week during at least 4 hours for at least 2 months
- ability to understand study procedures
- willingness to provide informed consent
- spKt/Vurea * 1.2
- achievement of blood flow of *360 ml/min and/or convection volume of >23 Liter per treatment during the run-in phase
- access recirculation <10%

Exclusion criteria

- current age < 18 years
- severe incompliance to dialysis procedure and accompanying prescriptions, especially frequency and duration of dialysis treatment
- life expectancy < 3 months

- participation in another clinical intervention trial

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	29-05-2018
Enrollment:	40
Type:	Actual

Medical products/devices used

Generic name:	hemodialysis techniques
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	24-04-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	12-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NCT03249532
CCMO	NL61210.029.17

Study results

Date completed:	15-02-2021
Results posted:	26-11-2021
Actual enrolment:	45

First publication
26-11-2021