Mobilization of Fluid and Fluid Flows in Hemodialysis

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STUDY PROTOCOL

MVVH
Title
Mobilization of Fluid and Fluid Flows in Hemodialysis

Short title: Fluid Flows in Hemodialysis

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Synopsis

During dialysis, three goals are achieved: 1. Blood is cleansed of waste products. 2. Excess water is removed. 3. Electrolytes are regulated. These processes occur simultaneously but vary from patient to patient depending on their specific needs. Some patients have residual urine production but of poor quality. Others have no residual urine production at all and require removal of fluid from both blood and tissues. Episodes of hypotension may occur during dialysis. These are related to intravascular hypovolemia and inadequate fluid reinfusion, which is common with fluid removal exceeding 400 ml/hour. The rate of fluid removal is influenced by fluid recruitment from the tissues. This mainly occurs in two different ways: either through osmotic recruitment across the capillary membranes from the perivascular space or via lymphatic return. The proportions are not yet clear. When fluid recruitment from the perivascular space occurs, influx of albumin and immunoglobulins is unlikely. This differs from lymph, where albumin and immunoglobins are present. This difference in protein content can be used to calculate the different proportions of fluid recruited from the tissues. This is performed with mass balance calculations based on fluid removal, colloid osmotic pressure, hemoglobin, albumin, and immunoglobulin concentrations.

The rate and proportions of fluid reinfusion into the bloodstream are not yet clarified. Hence the purpose of this study, is to explore these aspects.

Background

In Sweden, approximately 3200 patients are treated annually with hemodialysis[1]. In some cases, the goal is solely blood purification, but for most patients, there is also a need to remove excess fluid accumulated since the last dialysis treatment. The amount of fluid removal is prescribed by the dialysis physician and depends primarily on how much secondary urine the patient produces but also on the patient's fluid intake between dialysis treatments.

The most common complication of hemodialysis is hypotension during treatment, occurring in about 10% of treatment sessions according to previous studies. These hypotensive episodes lead to temporary hypoperfusion, and repeated episodes can result in permanent organ damage[2].

The main cause of these hypotensive episodes is the decrease in circulating volume associated with ultrafiltration, i.e., fluid removal[3]. The excess fluid accumulated by the patient between treatments mostly resides outside the bloodstream. Therefore, during fluid removal in hemodialysis, there is compensatory recruitment of fluid into circulation, which increases the circulating volume and prevents hypotension. How this recruitment occurs and from which fluid compartments fluid is recruited has not been mapped.

To increase understanding of hemodialysis and optimize treatment while minimizing the risk of hypotension, it is of interest to understand how fluid recruitment occurs and from which fluid compartments the recruitment occurs.

With the help of fluid kinetic calculations, it has in connection with albumin infusion been possible to measure whether fluid is recruited perivascularly or from the lymphatic system depending on the concentration of proteins such as IgG and IgM over time[4].

Purpose and Objectives

The aim is to study:

- How much fluid is drawn from the interstitial space during dialysis, depending on whether fluid removal is needed or not.
- The size and rate of fluid reinfusion during ongoing dialysis.
- The composition of the recruited fluid from the interstitium, i.e., the proportion consisting of lymph/lymphatic return and the proportion recruited across capillary membranes/venulae from the pericapillary space.

Hypotheses
The null hypothesis is that we do not find any detectable difference in fluid flows or source of fluid recruitment between patients undergoing extensive dialysis and those patients who do not have significant fluid removal during dialysis.
The alternative hypothesis is that we find a clinically relevant difference in fluid flows from the tissues and the pathway of fluid recruitment to the bloodstream.

Outcome Measures
Primary outcome variables are:
Recruitment of fluid from the interstitium calculated from fluid removal and hemoglobin changes.[5,6].
Proportion of recruited fluid via lymph or via capillary/venular walls based on fluid recruitment and changes in plasma albumin and immunoglobulins G and M.

Secondary outcome variables are:
Weight, blood pressure and changes in bioimpedance variables.

Study Design
Open-label, prospective clinical observational study, where patients are divided into two groups. One group patients with sufficient urine production and dialysis performed solely to "purify" the blood, and another group without or with minimal urine production, who, in addition to blood purification, are in need of a significant fluid removal.

Number of Patients
The study population consists of 15 patients with minimal fluid removal during dialysis and 15 patients in need of fluid removal exceeding 2000 ml.
According to earlier experience, 15 patients in each group should be sufficient to clearly observe a pattern in fluid recruitment from the tissues (lymph or pericapillary fluid). For 80% power at 25% difference in fluid recruitment balance between the groups and a standard deviation of 20%, at least 11 patients should be recruited to each group to achieve a significance level below 0.05 with a T-test or Wilcoxon (if the material is not normally distributed).

Recruitment and Consent
Patients receiving hemodialysis regularly at the dialysis department at Vrinnevi Hospital in Norrköping are screened if they are expected to meet the inclusion criteria for the study. Those who meet the inclusion criteria and have no exclusion criteria to participate are asked for participation and consent. Consent is obtained by one of the investigators verbally and in writing, during a hemodialysis session prior to the actual study procedure.

Inclusion Criteria:
Patients receiving hemodialysis (<500 ml or >2000 ml ultrafiltration):
Signed informed consent that the patient accepts participation in the study after oral and written information.

Exclusion Criteria:
Patients who may be affected by blood sampling, i.e., have low hemoglobin concentration, independent of dilution before dialysis (Hemoglobine 85 g/L).

Patients who drink large amounts of water during regular dialysis (> 2 glasses, approximately 0.4 L).
The study is discontinued in case of a severe reaction (even if not related to the study), such as the need to interrupt dialysis. The patient or participant may also choose to discontinue participation in the study at any time.

Intervention and Procedures

Patients in need of dialysis and who regularly undergo dialysis at the dialysis unit at Vrinnevi Hospital in Norrköping are asked to participate in the study. Patients who are eligible are those who have fluid removal of either <500 ml or >2000 ml. These patients are approached during a routine dialysis visit to the dialysis unit. If the response is positive, a trial session is planned for a later date.

Before dialysis begins, the patient is weighed. Then, the regular dialysis procedure starts, with the dialysis machine being connected. At the same time, Bioimpedance is also connected to the patient, and values for lean body mass (LBM), fat mass (FM), ECV, and ICV are recorded. Pulse and blood pressure are also recorded. Once the dialysis machine is connected with an intravenous access, the first blood samples, i.e., "zero samples," are taken. Dialysis then commences.

The selected dialysate is recorded, as well as the continuous fluid removal and blood pressure. Blood samples are taken every 30 minutes for 150 minutes (Hb, hematocrit, albumin, Immunoglobulins G and M, and colloid osmotic pressure (COP)), bioimpedance values are recorded, and pulse and blood pressure are registered. This continues until the end of dialysis. At the end of dialysis, the final samples and measurements are taken. The patient is weighed once again.

Fluid intake if it occurs is also recorded. When the patient leaves the dialysis unit, the study concludes.

In case of pressure drops, these are treated in the usual manner, i.e., the patient is placed in the Trendelenburg position or supplemented with Albumin 20%. Measures are recorded.

In total, blood sampling amounts to approximately 50 ml, at most 75 ml, equivalent to 3 to 5 tablespoons.

Measurements

Weight is taken before and after dialysis.

Bioimpedance is connected and values for body composition, i.e., lean body mass (LBM), fat mass (FM), ECV, and ICV are recorded before and after dialysis, as well as during blood sampling.

Hb, albumin, Ig G + M, and COP are measured and analysed before, at 1, 30, 60, 90, 120, and possibly at 150 minutes after the initiation of hemodialysis, as well as at the end of dialysis. These samples are taken from the access (cannula) used during dialysis. Therefore, no additional punctures are needed.

Fluid removal and any spontaneous diuresis are recorded. Patients with spontaneous diuresis are asked to urinate before and after dialysis.

Oral fluids consumed during dialysis are recorded.

Risk- Benefit assessment

Disadvantage for patients is a loss of approximately 50 to 75 ml of blood, which corresponds to half a decilitre of blood (3 to 5 tablespoons) (about 1% of the total blood volume). In connection with the study, there is enhanced monitoring, and the closer pressure and pulse controls can detect an impending drop in blood pressure slightly earlier.

The advantage of the study is more long-term. The study contributes to mapping how the recruitment of fluid/oedema from the interstitium occurs. Consequently, one should be able to more easily predict potential drops in blood pressure by taking take preventive measures such as adjusting composition of dialysate and rate at which the hemodialysis is performed.

Treatment and administration of other medications

Hemodialysis is performed according to standard procedures. No restrictions on the administration of medications or treatments will be made, except for a selection of patients who do not drink more than 2 glasses, approximately 0.4 litres of water, during regular dialysis sessions.

The study does not affect the patient's ongoing care or management.

Studied data/Registration of effects

Changes in Hemoglobine, albumin, and COP during hemodialysis

Changes in plasma volume are calculated partly using changes in Hemoglobin and partly using Mass Balance calculations.

Once all samples are analyzed, any remaining blood/plasma is destroyed.

Mass balance

Plasma volume. Initial blood volume calculated with the Nadler formula [7].

BV_0, based on height h, (meters), weight w (kg) and gender.

$$\textit{Men: } BV_0 = 0.3669\ h^3 + 0.03219\ w + 0.6041$$
$$\textit{Female: } BV_0 = 0.3561\ h^3 + 0.03308\ w + 0.1833$$

How mass balance calculations will be performed is described in a work on 5% albumin solution. [5,6]. Total mass hemoglobin at study start is calculated from BV_0 and hemoglobin at start of hemodialysis, Hb_0; [7]

$$MHb_0 = BV_0\ x\ Hb_0$$

Blood volume (BV) at a later occasion, t, is calculated in a similar manor;

$$BV_t = \frac{MHb_t}{Hb_t}$$

Plasma volume (PV) is calculated;

$$BV_t\ (1 - Hct_t) = PV_t$$

The percentage increase/decrease in plasma volume will then be (ΔPV%);

$$\frac{PV_t - PV_0}{PV_0} \times\ 100 = \Delta PV\%$$

Recruited fluid (RE) from the tissue is based on the change in plasma volume and total diuresis/fluid removal. However, this volume must be corrected for diuresis and ingested fluid.

$$RE\ extravascular = Ultrafiltrate + Diuresis - Ingested + (PV_t - PV_0)$$

Statistics and Data Processing

The study aims to follow a fluid kinetic process. In previous studies, we routinely used 10 healthy subjects to study similar processes. This has been sufficient to describe clear trends and differences in how the body responds to fluid infusions. However, in this study, we increase the number of participants to fifteen in each group to even more clearly establish the processes.

As there are only two groups to be compared, a t-test will primarily be used for the primary variable, i.e., the effect on plasma volume. For secondary variables, chi-square tests will be used. In the case of non-normally distributed data, Wilcoxon's test will be used instead.

Safety Regulation
The study will be conducted according to the protocol and applicable regulations, LVFS 2011:19, ICH GCP, and the latest version of the Helsinki Declaration. Patients will be monitored in the usual manner in the dialysis department.

Quality Assurance

- relevant health status data from medical records or health declaration
- signed consent
- The study is conducted in accordance with the protocol

Study Director Joachim Zdolsek participated in a GCP course at Linköping University Hospital on April 25 - 26, 2007, and subsequently conducted several studies approved by the Medical Products Agency.

Ethics
Patients are approached for participation in a calm stage when they are receptive to information. If there is potential interest from the patient to participate, the study investigator informs the patient about the study. The responsible physician obtains the patient's written consent, and a copy of the signed consent form is provided to the patient.

The care for the individual patient is minimally affected. Patients will not be impacted in any other way except for undergoing additional tests. However, it may be necessary to retrieve information from the medical record, which could potentially be seen as an intrusion into personal privacy.

Participation in the study is noted in the medical record.

The longer-term benefit of the study would be that through a better understanding of fluid dynamics, hemodialysis for dialysis-dependent patients could be tailored in a physiologically better way.

Source Data/Original Data and Archiving
Laboratory analyses (e.g., B-Hb, P-albumin...) conducted by the laboratory medicine department will be requested in printed form, so that they can be sorted into binders and used as reliable primary data when needed. Analyses conducted by the study group themselves (e.g., colloid osmotic pressure) will be immediately entered into the patient's Case Report Form (CRF) at the time of analysis. All study-related data (CRF and laboratory results) will be recorded in "CRF binders," with all collected information divided by individual patients. All CRF binders will be kept locked and only accessible to the trial team.

As the data are entered into Excel spreadsheets (i.e., computerized), they will be de-identified. However, a source data verification list will be established. This list will only be accessible to the investigators. The Patient ID list, which is only accessible to the trial team, and other study-related documents will be archived and stored for at least 15 years after the end of the study.

Insurance
Region Östergötlands insurances apply.

Publications/Timeframe
Joachim Zdolsek is primarily responsible for data collection and report writing. All investigators will have access to trial data and are expected to contribute to data analysis and report writing. Approximately one and a half years after study begin, we expect that all patients will have completed the study. Results, evaluation, and initial drafting are expected to take an additional 6 months to a year after the practical experiments have concluded. Subsequently, the time required for final reporting in the form of a published article is estimated to be at least another one and a half years. In total, the estimated time from the start of the study to its completion is expected to be approximately 3 to 4 years. The objective is to present the study results at an international congress and publish them in an international journal.

Other collaborators
Responsible for the practical part of the study in Norrköping are Erik Golsäter, Jonatan Bodare, Robert Svensson, and Fredrik Sundelin. Support functions and patient care will be handled by regular staff (nurses and nurse assistants). They will be thoroughly informed about the study. Joachim Zdolsek will write the project description and the ethics application. He will also assist with evaluation and writing, along with Professor Robert Hahn.

Information and responsibility
Joachim Zdolsek is responsible for study planning and design.
Erik Golsäter and Jonatan Bodare are responsible for the practical management at the Dialysis Department in Norrköping.
Relevant personnel in Norrköping will be informed by Erik Golsäter and Jonatan Bodare.

References:

1) Njurförbundet, Annual report 2021.

2) Davenport A. Why is intradialytic hypotension the commonest complication of outpatient dialysis treatments? Kidney Int Rep. 2023;((3):405-418

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4) Zdolsek JH., Zdolsek M., Hahn RG. Recruitment of efferent lymph during infusion of 20% albumin. Microvascular Research 2023;148:104539

5) Zdolsek M, Hahn RG, Zdolsek JH. Recruitment of extravascular fluid by hyperoncotic albumin.
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6) Zdolsek M, Hahn RH, Sjöberg F, Zdolsek JH. Plasma volume expansion and capillary leakage of 20% albumin in burned patients and volunteers.
Crit Care. 2020 May 5;24(1):191. doi: 10.1186/s13054-020-02855-0

7) Nadler SB, Hidalgo JH, Bloch T. Prediction of blood volume in normal human adults. Surgery 1962 Feb;51(2):224-32.

Signed agreement

I agree to the terms of this study protocol. The study will be performed according to the protocol and according to the principles of LVFS 2011:19, ICH GCP and the latest version of the Helsinki agreement.
Jag accepterar villkoren I detta studieprotokoll. Studien kommer att genomföras enligt protokollet och gällande regelverket, LVFS 2011:19, ICH GCP och senaste versionen av Helsingforsdeklarationen.

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Date Principal investigator/sponsor