Clinical Validation of a Continuous flow Peritoneal Dialysis System with Dialysate Regeneration

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Primary objective:To assess the (short-term) safety of the WEAKID nighttime system in a limited number (n=12) of patients and sessions (6 sessions per patient).Secondary objectives1. To evaluate the incidence of AE*s and DD*s other than SADE*s and...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Renal disorders (excl nephropathies)
Study type	Interventional

Summary

ID

NL-OMON53288

Source
ToetsingOnline

Brief title
CORDIAL

Condition

- Renal disorders (excl nephropathies)

Synonym
End-stage kidney disease, peritoneal dialysis

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Horizon 2020 (Europese Unie);Dutch Kidney Foundation/Health Holland

Intervention

Keyword: Continuous flow peritoneal dialysis, End-stage kidney disease, First-in-human study, Peritoneal dialysis

Outcome measures

Primary outcome

The primary safety objective will be assessed by describing and examining the

incidence of:

• serious adverse device effects (SADE) and device deficiencies (DD) that could

have led to a serious adverse event (SAE)

• critical changes (requiring intervention) in patient*s clinical condition and

vital parameters (blood pressure, heart rate, body temperature and oxygen

saturation) during treatment.

• critical changes (requiring intervention) in hematology and clinical

chemistry (i.a. acid base state, electrolytes) pre- vs post-treatment.

• critical changes (requiring intervention) in intra-abdominal dialysate volume

and intra-abdominal pressure during treatment

Evaluation of the events described above will be used to evaluate the

short-term safety of WEAKID treatment. No formal statistical hypotheses will be

tested.

Secondary outcome

Secondary endpoints are:

1. Assessing incidence of adverse events and DD*s other than SADE*s and DD*s

that could have led to a SAE

2. Session characteristics (number, duration, dialysate flow rates)

3. Evolution of vital signs (blood pressure, heart rate, body temperature and oxygen saturation)

4. Efficacy of UF in relation to glucose concentration in device effluent

• Ultrafiltration volume, peak glucose concentration in the device effluent, amount of glucose that is adsorbed and UF efficiency (volume of osmotic water removal per gram absorbed glucose)

• Peak glucose concentration in device effluent required to achieve appropriate osmotic water removal should be similar or lower than the peak glucose concentrations in the peritoneal dialysate during standard PD in each patient (if WEAKID treatment takes place according to the intended use)

5. Efficacy of solute removal and base release of WEAKID treatment:

• Absolute removal of urea, creatinine, phosphate, potassium, beta-2 microglobulin (B2M)

• MTAC and plasma clearance of urea, creatinine, phosphate, potassium, B2M

• Plasma reduction ratio of protein bound uremic toxins (PBUTs)

• Net release of base to the patient (i.e. bicarbonate plus lactate)

6. Evolution of blood analytes

• Before and after a WEAKID session: uremic toxins (urea, creatinine, uric acid, B2M, PBUTs), phosphate, potassium, hematological parameters, bicarbonate, lactate, sodium, chloride, calcium, magnesium, glucose, LDH, vitamin B12.

• Before and after a series of 3 WEAKID sessions: CRP, liver enzymes and bilirubin*

7. Evolution of dialysate effluent analytes

• Dialysate effluent analytes should be comparable to existing commercially

available peritoneal dialysate formulations and should match the range of PD effluents during standard PD

8. (Technical) device performance

• Number of device deficiencies (DD) and adverse device effects (ADE).

• Evolution of delta intraperitoneal pressure during WEAKID treatment (i.e. intraperitoneal pressure during WEAKID treatment minus intraperitoneal pressure at t=0)

9. Patient tolerance

• Abdominal discomfort (scored using a numeric rating scale (NRS, 0-10) at baseline and during WEAKID treatment)

10. Evolution of uremic symptoms

• Uremic symptoms (scored using the Dialysis Symptom Index (DSI) questionnaire at baseline and after the last WEAKID treatment of each week)

Study description

Background summary

Peritoneal dialysis (PD) is a life sustaining renal replacement therapy for patients with end stage kidney disease (ESKD). With PD, waste solutes and excess water are drawn from the blood across the peritoneal membrane lining the abdominal cavity via diffusion and osmosis, respectively, into dialysis fluid (peritoneal dialysate) that is introduced into the abdominal cavity through a permanent tube (peritoneal catheter). The peritoneal dialysate is replaced 4-6 times/day either manually by the patient or automatically by a machine at night while the patient is asleep. PD is a gentle dialysis technique that provides continuous gradual dialysis while the patient is free to move during the day. However, PD has several disadvantages. Removal of waste solutes is inadequate and technique failure rate is high, contributing to poor quality of life and high (co)morbidity and mortality (10-15% per year). The low solute clearance (~1-7% of that of healthy kidneys (depending on the solute) and lower than that with haemodialysis (HD)) is due to rapid decrease of diffusive transport of

solutes during a dwell due to the disappearance of the plasma-to-dialysate concentration gradient across the peritoneal membrane. The limited technique survival (median 3.7 years) is primarily due to the high incidence of recurrent infection of the peritoneal membrane (peritonitis) and exposure of the peritoneal membrane to very high, harmful glucose concentrations needed for osmotic fluid removal. Both peritonitis and high glucose concentrations cause pathological changes of the peritoneal membrane and eventually ultrafiltration failure necessitating a switch to the more invasive and expensive HD treatment. To reduce the existing shortcomings of conventional PD, a novel continuous flow peritoneal dialysis system with dialysate regeneration (WEAKID) for PD was developed. WEAKID treatment is based on continuous recirculation of peritoneal dialysate via the single lumen peritoneal catheter with regeneration of spent dialysate by means of sorbent technology. The WEAKID nighttime system (weight: ~12 kg) is intended to be used for 8h per day (during the night) on a daily basis. Instead of performing 4-6 exchanges with fresh peritoneal dialysate per day, WEAKID uses one peritoneal dialysate filling which is continuously recirculated and regenerated. The continuous regeneration prevents saturation of the dialysate with toxins and thereby maintains a high plasma to dialysate concentration gradient which enhances diffusive transport of uremic toxins. In addition, the continuous recirculating flow of fluid along the peritoneal membrane is expected to increase the mass transfer area coefficient as observed in previous studies with continuous flow peritoneal dialysis, probably due to reduction of diffusion resistance, renewal of stagnant fluid layers at the tissue surface and an increase of the effective membrane area. Both the high plasma to dialysate concentration gradient and the increase in mass transfer contribute to an enhancement of the clearance. Another advantage of the WEAKID system is that the glucose peak load to peritoneum is lower than with traditional APD and CAPD thanks to the buffering of the sorbents (sorbents adsorb glucose at the start, lowering the initial glucose peak, and release the glucose again at later stage) and the continuous recirculation.

Study objective

Primary objective:
To assess the (short-term) safety of the WEAKID nighttime system in a limited number (n=12) of patients and sessions (6 sessions per patient).

Secondary objectives
1. To evaluate the incidence of AE*s and DD*s other than SADE*s and DD*s that could have led to an SAE
2. To describe the characteristics of WEAKID treatment (i.e. number and duration of sessions, dialysate flow rates),
3. To evaluate the clinical condition and vital signs of the participants during WEAKID treatment
4. To evaluate the effectiveness of ultrafiltration (UF) in relation to glucose concentration during WEAKID treatment
5. To evaluate the efficacy of solute removal and base release of WEAKID

treatment
6. To evaluate the evolution of plasma analytes during WEAKID treatment
7. To evaluate the evolution of dialysate effluent analytes of the WEAKID system
8. To evaluate the (technical) device performance of the WEAKID system by the number of device deficiencies, adverse device effects and changes in intraperitoneal pressure
9. To evaluate patient tolerance during WEAKID treatment
10. To evaluate the evolution of uremic symptoms during WEAKID treatment
11. To evaluate the effectiveness of using sorbents for dialysate regeneration and the effectiveness of continuous recirculating flow in relation to the efficacy of solute removal.

Study design

First-in-human, prospective, open-label, non-randomized, three-center, single-arm study (proof of concept).

Intervention

The WEAKID system will be tested in a clinical setting on 6 days over a period of 2 weeks. During the first week, the subjects will be treated with the nighttime system without sorbents for 4h (first day) or 8h (second and third day) during daytime. The second week, treatment will consist of the nighttime system with sorbents (also 4h (first day) or 8h (second and third day) during daytime). This way, exposure to new components of the system is incremental and the effectiveness of the sorbents can be analyzed separately from the effect of continuous recirculating flow dialysis. A peritoneal equilibration test (PET) will be performed at baseline and follow-up. In addition, patients will collect 24h spent peritoneal dialysate and 24h urine followed by venous puncture for blood sampling 3 times prior to WEAKID treatment during standard PD.

Study burden and risks

Patients might experience discomfort due to the need to come to the hospital on 11 days, regular venous puncture for blood sampling (max. twice daily, total volume of ~100 mL during the study period of 4 weeks), 24h PD fluid collection (3 days at home), 24h urine collection (3 days at home, daily during WEAKID treatment days), and possibly due to (unknown) undesirable effects related to treatment with the WEAKID system (e.g. abdominal discomfort).

WEAKID aims to improve the existing shortcomings of conventional PD by offering enhanced clearance, effective ultrafiltration at lower glucose concentrations, and by reducing the number of (time-consuming) exchanges and number of (dis)connections of the peritoneal catheter and thereby the risk of peritonitis. As a result of the lower risk of peritonitis and reduced glucose exposure, WEAKID may preserve the integrity of the peritoneal membrane and

prolong technique survival. Although WEAKID was found safe in preclinical testing and the risk-evaluation concluded that all risks were reduced to an acceptable level, treatment with the WEAKID system may theoretically have undesirable effects/risks including abdominal discomfort or even (mechanical) irritation of the peritoneum due to the rapid cycling of peritoneal dialysate into- and out of the peritoneal cavity, peritonitis due to bacterial contamination, disturbance of acid-base balance, and disturbance of fluid and electrolyte balance. WEAKID may also include risks which are unknown, i.e. which were not identified on a theoretical ground or during the risk evaluation. These risks include infrequent events which can only be identified during prolonged exposure of a sufficiently large population and effects which only manifest after prolonged treatment with the WEAKID system.
Risks have been minimized to the greatest extent feasible by taking appropriate measures. Accordingly, the structured risk analysis showed that all risks, after appropriate measures, were minimized to an acceptable level. The preclinical biological evaluation showed no evidence of cytotoxicity in vitro or acute and subchronic systemic toxicity in vivo (see IB). The following measures are taken to minimize risk to patients during the study:
(1) the study is designed to minimize risk to patients (e.g. the small sample size minimizes the number of patients at risk, the eligibility criteria reduce risks to patients, the consecutive treatment of at least the first two patients at each site allows for a thorough safety evaluation by the study team before the next patients receive WEAKID treatment, patients* clinical condition and biochemistry and haematology will be closely monitored in a clinical setting).
(2) All AE's and DD's that might have led to an (S)AE will be documented and assessed by the (local) investigational study team, and all reportable events (SADE's and DD's that might have led to an SAE if appropriate action had not been taken) will be reported to the sponsor within 3 calendar days after awareness. In case of a reportable event which indicates imminent risk of death, serious injury, or serious illness and that requires prompt remedial action, any next WEAKID treatment will be postponed. WEAKID treatments will be resumed once the sponsor 1) has discussed the event with the Medical Monitor and DSMB, 2) decided that it is safe to continue, and 3) decided whether the concerning subject must be withdrawn from the study or not. In case the sponsor decides that a (temporary) halt of the study is required, the MREC and the NCA shall be informed as applicable, and restart of the study (after appropriate measures have been taken to prevent such an event from happening again) shall only occur after the MREC approved the restart.
(3) Dialysate flow rate will be reduced if necessary to prevent abdominal discomfort or pain.
(4) To prevent peritonitis, all disconnections of the peritoneal catheter and sampling procedures will be performed under strict hygienic operating procedures by trained personnel.
(5) In case of hypervolemia due to insufficient ultrafiltration it can be decided to (temporary) discontinue WEAKID treatment and resume conventional PD to remove excess fluid.
(6) Study personnel will receive appropriate training on use of the WEAKID

system and study procedures.
(7) The WEAKID system is equipped with sensors and alarms to detect device deficiencies.
(8) Pregnancy testing will be performed in all female patients <55 years and reliable contraception will be recommended to prevent the possibility of fetal exposure to unknown teratogenic effects of WEAKID treatment.

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

• >=18 years of age.
• Treated with peritoneal dialysis for at least 3 months prior to enrolment
• Well-functioning peritoneal catheter and no peritoneal catheter replacement for at least a month prior to enrolment.

• No PD-related infection (exit-site infection, tunnel infection or peritonitis) less than 8 weeks
prior to enrolment (counting from the day that the treatment has been finished).
• Previous or current use of Extraneal® with no contra-indications
• Capable of understanding the patient information sheet and informed consent form (ICF) and give informed consent.
• Willing and able to comply with all study procedures and attend all study visits.

Exclusion criteria

• Patients who are unable to provide informed consent.
• Patients who are unable to comply with study procedures.
• Patients who received renal replacement therapy other than conventional PD less than 8 weeks prior to enrolment.
• Patients who participated in an intervention trial less than 8 weeks prior to enrolment or are currently participating in an intervention trial. Patients in an observational study without any interventions or in post-market surveillance do not need to be excluded.
• Patients with PD related infection (exit-site infection, tunnel infection or peritonitis) less than 8 weeks prior to enrolment.
• Patients with peritoneal catheter dysfunction or mechanical issues less than one month prior to enrolment.
• Patients who have never used Extraneal® dialysis fluid or have a contra-indication for Extraneal®:
• Patients with an incompatible PD connection to the device (e.g. Fresenius PD system)
• Patients with haemoglobin concentrations < 6.2 mmol/L (< 10 g/dL) less than 8 weeks prior to enrolment.
• Patients with hyperkalemia (> 6.0 mmol/L) or hyponatremia (< 130 mmol/L) in the 8 weeks prior to enrolment.
• Patients with hypocalcemia (plasma total calcium concentration corrected for albumin <2.20 mmol/L or ionized calcium <1.15 mmol/L) or hypomagnesemia (plasma magnesium concentration <0.70 mmol/L) in the 8 weeks prior to enrolment.
• Patients with any serious medical condition which in the opinion of the investigator, may adversely affect the safety of the participant and/or effectiveness of the study.
• Female patients who are either (planning to become) pregnant within the study period or breast feeding.
• Patients with a life expectancy <3 months.
• Anticipated living donor kidney transplantation <3 months.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-01-2024
Enrollment:	4
Type:	Actual

Medical products/devices used

Generic name:	WEAKID
Registration:	No

Ethics review

Approved WMO Date:	27-09-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	12-12-2024
Application type:	Amendment
Review commission:	METC NedMec

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	NCT06314503
CCMO	NL83843.000.23