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New Miniaturized System for Ultrafiltration: Rationale and Design of a Single-Center, Crossover, Randomized, Open-Label, Pilot Study Protocol

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Keywords
Ultrafiltration · Artificial diuresis · Wearable · Portable · Miniaturization · Heart failure · Fluid overload

Abstract

Introduction: Fluid overload and congestion are common features in patients with heart failure and are associated with negative clinical outcomes. Therapies for these conditions are diuretic-centered but frequently fail to achieve patient-adequate hydration status, prompting the use of extracorporeal ultrafiltration. Artificial Diuresis 1 (AD1) is a miniaturized, portable, and wearable system designed to deliver isolated ultrafiltration with the finest degree of simplicity and practicality. ***Methods/Design:*** Single-center, crossover, randomized, open-label pilot study to investigate the safety and the efficacy (concerning ultrafiltration accuracy) of extracorporeal ultrafiltration with the device AD1 in comparison to isolated ultrafiltration with a traditional machine (PrisMaX). Patients with chronic kidney disease stage 5D (on hemodialysis) or intensive care patients presenting acute kidney injury stage 3D (requiring hemodialysis) will carry out a single session of isolated ultrafiltration with each of the machines. The safety primary outcomes will be the occurrence of adverse events. The efficacy primary outcome will be the accuracy of ultrafiltration rate (delivered/prescribed) on each of the devices. ***Conclusion:*** AD1 is a novel miniaturized device for extracorporeal ultrafiltration. This study will be the first-in-human use of AD1 in patients with fluid overload.

Introduction

The prevalence of heart failure in Italy is 1.25% and this percentage is equally distributed in both genders. A rampant increase in prevalence is documented in the elderly population. Specifically, among persons aged 60 to

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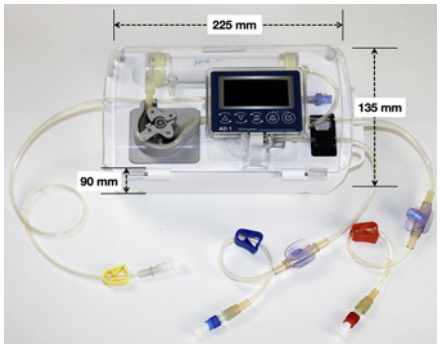

Fig. 1. Artificial Diuresis 1 (AD1). Dimensions of the novel portable, wearable, and miniaturized device for isolated ultrafiltration.

65 years, the prevalence is 1.47%, scaling up to 13% in nonagenarians. Moreover, the incidence of the syndrome is 1.99 per 1,000 person-years [1]. In other middle- or high-income countries, these numbers are similar [2]. Therefore, heart failure is a condition associated with major public health concerns, responsible for relevant financial and social burdens [3].

Acute exacerbations of chronic heart failure are frequent and are a leading cause of overall hospitalization and emergency room visits. Four out of 5 patients who seek hospital care because of acute heart failure present signs and symptoms of congestion [4, 5]. Staggering, the all-cause 1-year mortality for patients with acute heart failure is 23.6%. In contrast, for individuals with chronic heart failure, all-cause 1-year mortality is 6.4%, demonstrating the negative impact of acute exacerbations.

Current guidelines supported by robust evidence from clinical trials recommend a diuretic-centered approach for the management of this condition [6–15]. Nonetheless, frequently, diuretic therapies fail, and mechanical extracorporeal ultrafiltration is required in the treatment of congestion [6, 16, 17]. The safety and efficacy of ultrafiltration have been demonstrated in numerous clinical trials [17].

Present-day machines utilized for extracorporeal ultrafiltration are either capable of performing other extracorporeal blood purification therapies (i.e., continuous renal replacement therapy [CRRT]) or dedicated to isolated ultrafiltration [18, 19]. Despite the evolution of these machines, burdensome personnel training is needed. Moreover, the execution of the therapy is not feasible in hospital wards, preventing its democratization and wide adoption. As a way to overcome these barriers, our group initiated a project of a portable and wearable miniaturized system for isolated ultrafiltration [20]. The innovative project and the device itself were named "Artificial Diuresis 1" (AD1) (shown in Fig. 1). We carried out in silico simulations, in vitro experiments, and in vivo animal experiments. After successfully passing through these necessary phases for hardware development, a pilot and exploratory study in humans could be planned (shown in Fig. 2). Herein, we describe the protocol for the first-in-human use of AD1.

Methods

Trial Design

This is a single-center, crossover, randomized, open-label pilot study to assess the safety and efficacy of AD1 (Medica S.p.A. Medolla, Emilia-Romagna, Italy) in comparison with a standard CRRT machine (PrisMaX, Baxter Healthcare Corporation, Deerfield, IL, US), capable of performing continuous isolated ultrafiltration. The main goal is to analyze safety events during the treatment of isolated ultrafiltration in patients with fluid overload. This trial will not have a pre-defined run-in or washout phases. Each patient will perform only one treatment with either machine. Recruitment will utilize the convenience sampling strategy [21–25]. The trial is registered as CESC Provincia di Vicenza_6.9.22(n.54/22)_1575_29.9.22.

Study Setting

Patients will be recruited from the Department of Nephrology, Dialysis, and Kidney Transplant and from the Department of Critical Care, both at San Bortolo Hospital, Vicenza, Veneto, Italy. Written consent will be obtained from all patients enrolled in the trial.

Eligibility Criteria

Inclusion Criteria

1. Both genders.
2. Established chronic kidney disease G5D patients on maintenance hemodialysis for at least 12 weeks, carrying out in-center sessions, presenting at least 2.5 kg over a pre-defined adequate body weight (dry weight).
3. Established chronic kidney disease G5D patients on maintenance hemodialysis for at least 12 weeks, hospitalized in the intensive care unit, and carrying out sessions in this unit, presenting at least 2.5 kg over a pre-defined adequate body weight (dry weight).
4. Intensive care unit patients presenting acute kidney injury stage 3D (requiring hemodialysis), in whom fluid accumulation is detected, and extracorporeal ultrafiltration is indicated according to the attending physician evaluation. In our unit, fluid accumulation is assessed by physical examination, point-of-care ultrasonography, venous excess Doppler ultrasound, other imaging such as chest radiography, chest computed tomography. Moreover, other variables evaluated for the assessment of congestion are central venous pressure, intra-abdominal pressure, and cumulative positive fluid balance, above 5–10% of presumed dry weight) [26–33].
5. Aged over 18 years.

Exclusion Criteria

1. Planned renal transplant within the study intervention period.

2. Planned conversion to peritoneal dialysis or transfer to another center.
3. Pregnancy or breastfeeding.
4. Indication for hemodialysis, hemodiafiltration, or hemoadsorption according to the attending physician.
5. Patients with current infection by human immunodeficiency virus, hepatitis B, hepatitis C, and SARS-CoV-2.
6. Impossibility of the patient or the next of kin to provide informed consent.

Discontinuation
1. At the discretion of the treating physician.
2. The decision by the patient or family to withdraw at any moment.
3. Partial recovery of kidney function.

Missing Data

Missing data are expected at various time points during the trial. No data imputation techniques will be applied to any of the evaluated variables [34].

Data Monitoring

Data integrity will be enforced by various mechanisms, such as valid values and range checks. Access to the study data will be restricted by personal logging into the system data. All paper forms or electronic devices will be kept in locked cabinets. A complete backup will be regularly provided.

Ethical Considerations

The protocol was reviewed and approved by the Local Independent Ethics Committee (*Comitato Etico per le Sperimentazioni Cliniche della Provincia di Vicenza 6.9.22(n.54/22)_1575_29.9.22*) and submitted to Italian Ministry of Health for the final approval concerning use of devices still not CE-approved (Conformité Européenne). The study will be performed in accordance with the 2013 Fortaleza, Brazil, 7th Revision of the Declaration of Helsinki following good clinical practice standards (D.M. Sanità del July 15, 1997 e s.m.i.) [35]. Personal data will be treated to the General Data Protection Regulation (EU) 2016/679 and "Decreto Legislativo June 30, 2003 n.196 e ss.mm.ii. (Codice in materia dei dati personali)." The trial will be registered at ClinicalTrials.gov website.

Interventions/Study Procedures

For patients carrying out in-center regimens, isolated ultrafiltration sessions will have a duration from 4 to 6 h and the total fluid removal will range from 500 to 1,500 mL, according to the clinical need. For intensive care unit patients, sessions' duration will vary from 6 to 12 h and total ultrafiltration volume will range from 1,000–1,200 mL, according to the clinical need. Systemic anticoagulation might be provided in the absence of contraindications. For patients already receiving anticoagulants, no anticoagulation will be used. After randomization, patients will be assigned to initiate the first treatment with one of the machines followed by a subsequent therapy with the alternative machine (shown in Fig. 3).

In case of intraprocedural hypotension, ultrafiltration can be momentarily discontinued by clamping the ultrafiltrate line (see Fig. 4). In this situation, the blood pump is not stopped, and the blood still runs through the circuit, minimizing the risk of filter coagulation in case of blood stagnation which occurs when the blood pump is stopped. Moreover, a 1,000-mL saline bag is connected to the venous line of the extracorporeal circuit via a 3-way stopcock if fluid bolus infusion is required to revert an episode of refractory hypotension. The amount of fluid delivered will vary at discretion of the attending physician.

The venous access for patients with acute kidney injury stage 3D will be a temporary venous access with a diameter >11 Fr. For the maintenance hemodialysis patients, the venous access will be a tunneled catheter or a temporary catheter, both with a diameter >11 Fr. Peripheral accesses, arteriovenous fistulas, or arteriovenous grafts will not be utilized. In a previous in vitro study carried out by our group, AD1 was tested in a closed-loop circuit primed with whole blood. The catheters tested were 7 Fr, 10 Fr, and 12 Fr. The experiments with each of the catheters were successful and accurate ultrafiltration was achieved [36].

Primary Objective

Primary safety outcomes will include the incidence of clinical events such as intraprocedural hypotension, bleeding events, hemolysis, hypothermia, electrolyte imbalance, anaphylactoid reactions, and circuit clotting. Primary efficacy outcome will be the percentual variation between prescribed versus delivered total ultrafiltration volume.

Secondary Objective

Secondary safety outcomes will include the incidence of clinical events such as cramps, nausea, vomiting, headache, fever, chills, chest pain, and pruritus and also technical problems such as filter hollow fiber rupture and identification of air in the circuit. Secondary efficacy outcome will be the measurement of user-friendliness and technical complications.

Primary Outcomes (Primary Objective Measurement)

Primary safety outcomes will assess intraprocedural hypotension employing invasive or noninvasive arterial pressure volume, air embolism through clinical evaluation

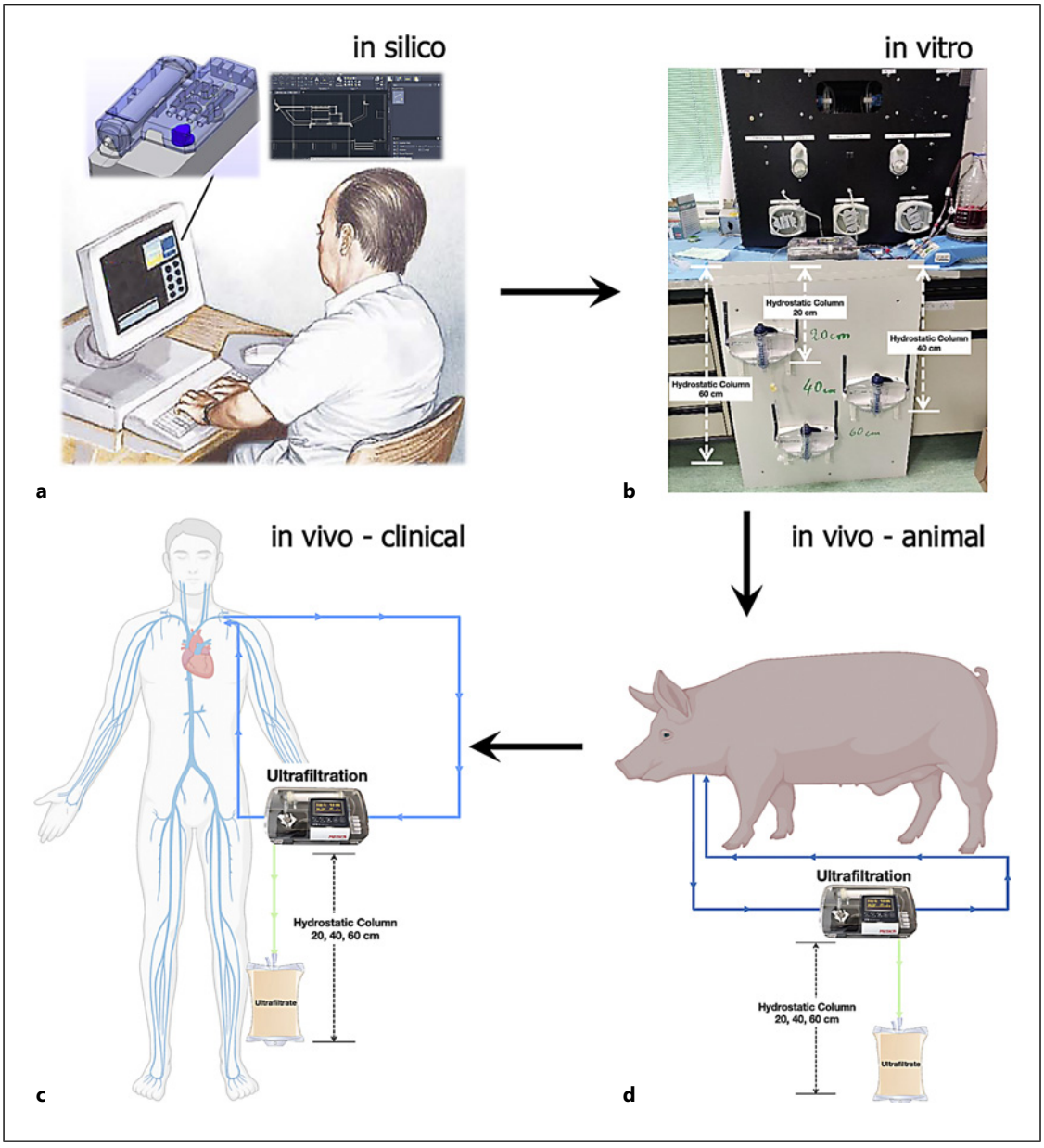

Fig. 2. Phases of the development of a miniaturized portable device for extracorporeal ultrafiltration. **a** In silico 3D project drawing and performance simulations. **b** In vitro testing with the GALILEO machine. Ultrafiltration and circuit pressures were determined in different conditions such as access type and diameter, blood flow, and height of the collection bag (hydrostatic column). **c** In vivo experimental pig model. Three pigs carried out a single session each. Vital signs remained stable during the therapy; ultrafiltration was precise without technical problems. **d** In vivo, clinical safety and efficacy pilot trial.

and peripheral oxygen saturation monitoring, hemolysis by a change in the effluent color, hypothermia via intermittent or continuous temperature monitoring, electrolyte imbalances by biochemical blood sampling, circuit clotting by visual inspection, and anaphylactoid reactions by physicians' judgment. Primary efficacy outcomes will be measured by collecting the effluent volume of the AD1 or PrisMaX.

Secondary Outcomes (Secondary Objective Measurement)

Secondary safety outcomes will be presented as percentual of the occurrence of events during all the therapies. Secondary efficacy outcomes will be assessed by the completion of a user satisfaction questionnaire and the measurement of technical issues that required

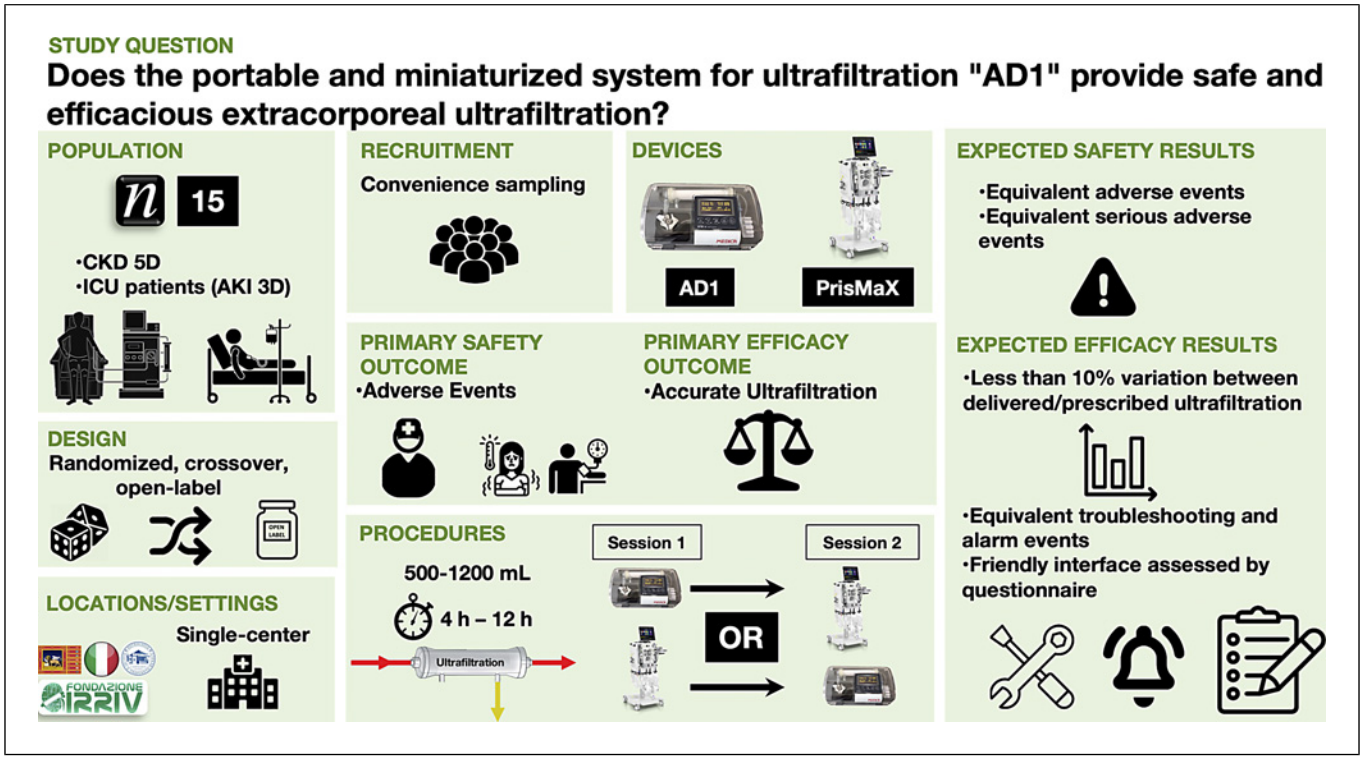

Fig. 3. Graphical abstract summarizing the protocol. The study question is at the top. Each square displays a section of the protocol. The upper box in the left column, population, shows the planned sample size of 15 patients, including in-center CKD 5D and ICU patients presenting AKI 3D. Downward in the same column, the second box, design, demonstrates a randomized, crossover, and open-label study. In the same column, the last box, locations/settings, shows that the study will occur in San Bortolo Hospital, in which the IRRIV is also located. The upper two boxes of the middle column indicate recruitment strategy and devices (AD1 and PrisMaX) that will be utilized. In the middle box of the middle column, primary safety outcomes (adverse events) and primary efficacy outcome (ultrafiltration accuracy) are depicted. In the bottom box of the middle column, the procedures are demonstrated. In brief, the ultrafiltration range and the possible duration of the therapies are shown. This box also illustrates that the first session can be carried out with AD1 or with PrisMaX, followed by the alternative hardware in the subsequent session. Finally, the right column, the expected results are demonstrated. AD1, Artificial Diuresis 1; AKI 3D, acute kidney injury stage 3D (requiring dialysis); CKD 5D, chronic kidney disease stage 5D (requiring dialysis); IRRIV, International Renal Research Institute of Vicenza.

nurses' intervention (troubleshooting) summarize in Table 1.

Sample Size Calculation

The sample size was calculated based on the primary outcome. We did not find evidence from medical literature concerning trials about ultrafiltration with a similar design. Based on previous studies about human device testing carried over along more than 40 years [18] in our hospital and expert input from the manufacturer, we estimated that 15 patients would be required. This sample size was considered adequate to increase the probability of occurrence and detection of the safety outcomes already specified. Moreover, concerning the primary efficacy endpoints, we considered that 15 treatments on each machine could demonstrate the accuracy of AD1 with a variation of less than 10% between delivered versus prescribed ultrafiltration total ultrafiltration volume.

Randomization

Fifteen opaque sealed envelopes will be provided; in eight of them, the designated treatment will be ultrafiltration with AD1 and in the remaining seven, ultrafiltration with the CRRT machine.

Allocation Concealment

A box containing the envelopes will be secured in an office staff room. None of the staff members will be aware of the trial's progress. Contact will be made by phone call. The opened envelopes will progressively be discarded.

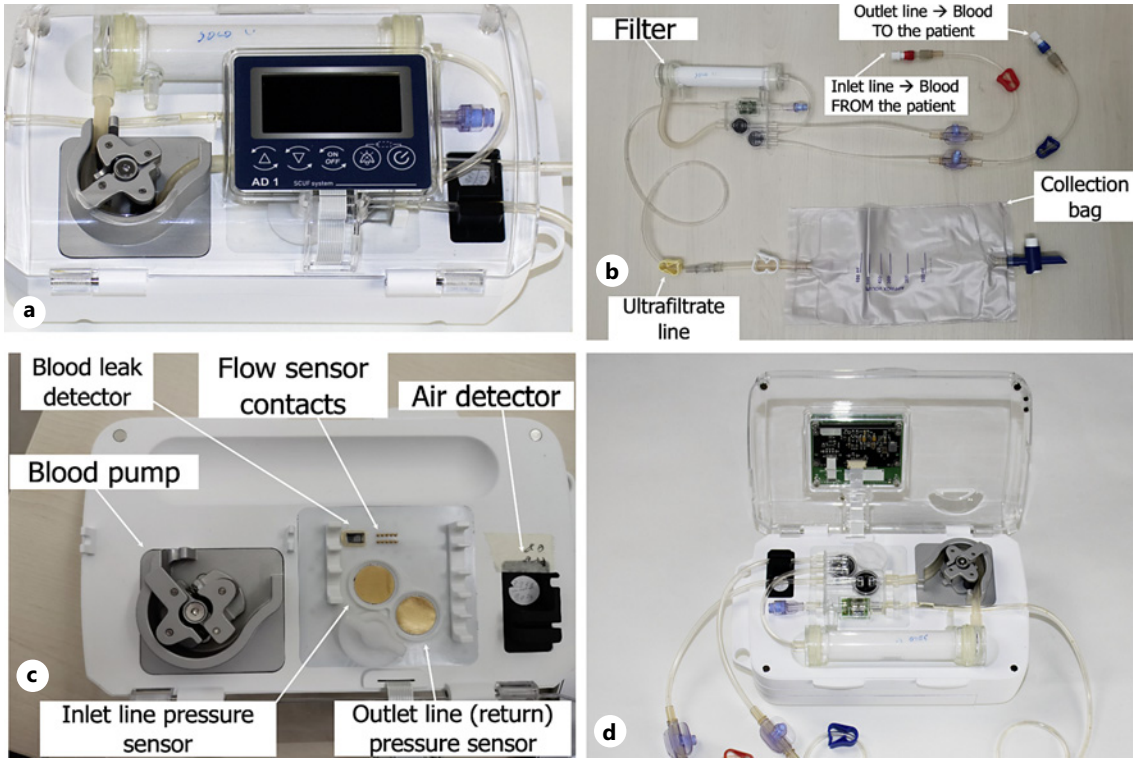

Fig. 4. Components of the Artificial Diuresis 1 (AD1) hardware. **a** External case with a membrane keyboard placed on a polycarbonate cover. **b** Disposable circuit displaying inlet and outlet lines, hollow fiber filter, ultrafiltrate line (effluent line), and the collection bag. **c** Opened device without the circuit cassette. The main components are the peristaltic blood pump, blood leak detector, flow sensors, air detector, inlet and outlet line pressure detector. **d** Opened device with the disposable circuit in place.

Table 1. User questionnaire

Items	Score: 1: unaccomplished despite using operator's manual 2: accomplished under operator's manual guidance 3: accomplished without operator's manual support
Getting started	a) Check battery charge; b) battery installation; c) power on; d) home screen
Connecting set	a) Set visual inspection (filter, lines, bags); b) load disposables; c) blood line self-loaded to blood pump
Priming and connecting the patient	a) Blood line connections; b) running the treatment; c) blood flow adjustment; d) battery replacement; e) treatment start; f) stopping the treatment; g) treatment conclusion
Blood returning and disconnecting the patient	a) Arterial line disconnection; b) blood return; c) venous line disconnection
Disconnecting and discarding the set	a) Remove disposable set; b) return to home screen; c) power off; c) remove battery; d) recharge battery

Statistical Analysis

Continuous variables will be described according to central tendency measures (mean and median) and dispersion measures (standard variation, confidence interval, interquartile range). Data will be presented as means ± standard deviation for continuous variables with normal distribution and median and interquartile range for non-normally distributed variables. Normality will be assessed a priori by visual inspection of histograms and by performing statistical tests such as the Kolmogorov-Smirnov or Shapiro-Wilk. Categorical variables will be presented as percentages and absolute numbers.

The comparison of independent categorical variables and dependent continuous variables with normal distribution will apply a *t* test. If the distribution of the dependent continuous variable is non-normal, the Mann-Whitney Wilcoxon test will be used. In the comparison between independent categorical variables and dependent categorical variables, the χ^2 or Fisher's exact test will be applied. Data will be processed in IBM SPSS for Windows (IBM Corp., Armonk, NY, US).

Discussion

In the proposed single-center, crossover, randomized, open-label pilot study, we plan to pragmatically assess the safety and efficacy of a new miniaturized ultrafiltration device in comparison with a traditional machine. The defined sample size will likely be reached because the eligibility criteria are broad and our hospital has a large intensive care unit and a large hemodialysis center. In both settings, condition of fluid overload is prevalent. The physicians and nurses have the needed technical expertise and other first-in-human uses of machines were carried out in our center. Thus, we expect that staff training will occur at a fast pace.

If safety and efficacy outcomes are achieved, researchers in the field of cardiorenal medicine and intensive care will certainly be encouraged to carry out randomized controlled trials. We believe this is a groundbreaking and innovative investigation, justifying the application of human and financial resources to this project. The long-term goal will be to assess the beneficial adjuvant effects of a miniaturized portable device associated with diuretics to improve the management of fluid overloaded patients in acute settings. In addition, we suppose that the exploration of extracorporeal ultrafiltration in the elective management of cardiorenal patients, in whom fluid accumulation is highly prevalent, is highly needed. Therefore, there is a strong rationale to investigate the efficacy of the device as an elective therapy.

Statement of Ethics

The protocol was reviewed and approved by the Local Independent Ethics Committee (*Comitato E. per le Sperimentazioni Cliniche della Provincia di Vicenza 6.9.22 (n.54/22) 1575_29.9.22*). Informed signed consent will be obtained from all the participants. The informed consent form will be accessible online in the supplementary material section (for all online suppl. material, see https://doi.org/10.1159/000530943). The study will be performed in accordance with the 2013 Fortaleza, Brazil, 7th Revision of the Declaration of Helsinki following good clinical practice standards.

Conflict of Interest Satement

Alessandra Brendolan, Anna Lorenzin, Luca Sgarabotto, Valentina Corradi, Nicola Marchionna, and Monica Zanella do not have any potential conflicts of interest. Claudio Ronco has received research grants, funding for lectures, been consultant or advisory board member for Asahi, Astute, B. Braun, Baxter, bioMérieux, Bioporto, CytoSorbents, Estor, Fresenius Medical Care, General Electric (GE), Jafron, Medtronic, and Toray. Thiago Reis has received funding for lectures, been consultant or advisory board member for AstraZeneca, B. Braun, Baxter, bioMérieux, Boehringer Ingelheim, Contatti Medical (CytoSorbents), Eurofarma, Jafron, Lifepharma, Medtronic, and Nova Biomedical.

Funding Sources

No funding was received.

Author Contributions

Thiago Reis: methodology (equal); writing – original draft (lead); and writing – review and editing (lead). Luca Sgarabotto, Anna Lorenzin, Valentina Corradi, Nicola Marchionna: methodology (equal); writing – original draft (supporting); and writing – review and editing (equal). Alessandra Brendolan: methodology (lead); writing – original draft (lead); and writing – review and editing (equal). Monica Zanella: methodology (equal); writing – original draft (equal); and writing – review and editing (equal). Claudio Ronco: conceptualization (lead); funding acquisition (lead); investigation (equal); methodology (equal); project administration (lead); resources (lead); writing – original draft (equal); writing – review and editing (equal); and supervision. All authors were responsible for critical revision of the manuscript and approved the final version before submission.

Data Availability Statement

Data are available on request due to privacy or other restrictions.

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