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Development of the New Kibou® Equipment for Continuous Renal Replacement Therapy from Scratch to the Final Configuration

Mauro Neri[a] · Anna Lorenzin[a] · Alessandra Brendolan[a, b] · Francesco Garzotto[a, b] · Fiorenza Ferrari[a, c] · Silvia De Rosa[a, c] · Raffaele Bonato[c] · Gianluca Villa[a] · Simona Bazzano[a] · Fiorella D'Ippoliti[a] · Zaccaria Ricci[d] · Gaetano La Manna[e] · Claudio Ronco[a, b]

[a]International Renal Research Institute of Vicenza (IRRIV), [b]Department of Nephrology, Dialysis and Transplantation, and [c]Department of Intensive Care Unit, San Bortolo Hospital, Vicenza, [d]Department of Cardiology and Cardiac Surgery, Pediatric Cardiac Intensive Care Unit, Bambino Gesù Children's Hospital, IRCCS Rome, Rome, and [e]Department of Experimental, Diagnostic and Specialty Medicine, Nephrology, Dialysis and Transplantation Unit, St. Orsola Hospital, University of Bologna, Bologna, Italy

Abstract

A new technology has recently appeared in the area of extracorporeal therapies for critically ill patients with acute kidney injury. The International Renal Research Institute of Vicenza was involved from the beginning in the development of a new continuous renal replacement therapy (CRRT) equipment with peculiar characteristics. We report the overall experience from design of the new machine to its in vitro and in vivo testing. Kibou® (Asahi Kasei Kuraray Medical Co., Ltd., Tokyo, Japan) is a new multifunctional machine designed for delivering RRT. Kibou® carries out many features of the fourth generation CRRT machines including the possibility of a dynamic prescription and reduction of nursing workload. We describe our first experience with this new device, focusing on several usability and performance parameters. A specific in vitro protocol was designed to analyze the various characteristics and accuracy of performance of the machine. Furthermore, a preliminary in vivo alpha trial with 12 CRRT sessions was performed to test, characterize and evaluate the machine in terms of usability, flexibility and reliability. The in vitro eval-

uation confirmed an adequate design and a good usability of the machine with accurate delivery of prescribed parameters. No adverse events were observed during the in vivo test that confirmed usability and safety together with accuracy of treatment delivery in different modalities. In general, the machine was rated by physicians and nurses involved in the evaluation as practical and easy to use, although a specific training is required to familiarize with the equipment. A large-scale multicenter beta trial is required to confirm the results reported in this preliminary evaluation in terms of safety, accuracy and performance of Kibou®.

Introduction

Acute kidney injury (AKI) is a disease that frequently occurs in intensive care patients, with high mortality rates. This clinical entity has required, over the years, a progressive scientific effort to develop adequate technology for providing safe and reliable treatments.

Continuous renal replacement therapy (CRRT), applied through dedicated machines, is a first-line therapy for the treatment of AKI. The modern history of CRRT is characterized by the development of machines designed specifically for acute renal replacement in intensive care patients. Although in the past these machines were basically derived from hemodialysis blood modules, in the last years they are designed exclusively as self-standing units for CRRT.

The evolution of CRRT machines has seen different eras since the late 1970s [1]. The first CRRT devices appeared in 1977 [2] when continuous arteriovenous hemofiltration (CAVH) was performed. CAVH presented important advantages concerning hemodynamic stability, control of circulating volume and possibility of nutritional support, but the need for arterial cannulation and limited solute clearance represented serious shortcomings. The development of veno-venous CRRT systems in the late 1980s represented a milestone, and formed the basis for modern therapies. At that time, CRRT equipment borrowed some components from chronic hemodialysis machines such as blood pump and ancillary pumps to control volumes of dialysate and/or replacement fluid. Fluid delivery systems and net ultrafiltration control mechanisms were implemented allowing acceptable accuracy. The third generation of machines [3] guaranteed greater blood/fluid flow rate capabilities, additional functionalities and components, and safety features today recommended in every modern equipment. The fourth and latest generation of machines for CRRT, available or to be launched next in the market [4, 5], represents the progressive and continuous evolution of the past forty years of research and development in this field (Fig. 1). The main target of the new generation of machines is an accurate delivery of the prescribed dialysis dose, high safety and easy utilization with a reliable performance of the therapy [6]. In particular, the reduction of

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Fig. 1. CRRT machines from the last 20 years until today [1].

actual dose due to downtime, optimization of alarms management, making the nursing workload lighter and the development of safe protocols for new anticoagulation therapies (e.g., citrate) have been identified as the most critical points.

As a common line, these new devices allow us to perform almost all the available CRRT techniques and are equipped with a groundbreaking touch screen and friendly user interface, like the last generation mobile phones. Clear alarm signals and warnings, together with important treatment parameters like pressure trends, are now clearly displayed on the screen. To provide clinicians with individualized CRRT treatment data, machines have also been implemented and equipped with practical tools to easily download treatment parameters [7].

As in previous occasions, our institute has been recently involved in the development and testing of some of the new generation CRRT machines. Kibou® (Asahi Kasei Kuraray Medical Co., Ltd., Tokyo, Japan) is an example of new technology developed from scratch to a final equipment. "Kibou," a Japanese word meaning "hope," is a CE marked, multifunctional, automatic CRRT machine designed to deliver and monitor continuous blood purification treatments. In this chapter, we will describe the features and characteristics of the

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Fig. 2. Layout of Kibou® machine.

machine according to our initial design specifications, highlighting peculiarities and new aspects. Our in vitro and first in vivo evaluation is reported with specific user ratings including clinical, practical and technical aspects.

Kibou® Design: Features and Characteristics

The Kibou® machine, displayed in Figure 2, is a CRRT platform featuring many characteristics of the fourth generation machines, previously mentioned. Frontally looking, the hardware layout is divided into three panels: the right one is completely dedicated to fresh solutions (dialysate and replacement fluid) necessary to purify blood by convection or diffusion, the central one is dedicate to blood circulation and all safety system sensors and the left part concerns the "dirty" effluent and citrate infusion components (pump and scale).

The machine features a 12-inches, full color touch screen monitor, with function keys required for each phase and process. In total, Kibou® is equipped with 5 peristaltic pumps: blood (range 1–400 mL/min), dialysate/replacement

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Table 1. Modalities and setting parameters performable with Kibou®

CRRT treatment	Adult		Pediatric		Replacement fluid			Dialysate fluid	
	heparin	citrate-calcium	heparin	citrate-calcium	pre	post	pre and post	co-current	counter-current
SCUF	✓	✓	✓	✓	x	x	x	x	x
CVVH	✓	✓	✓	✓	✓	✓	✓	x	x
CVVHD	✓	✓	✓	✓	x	x	x	✓	✓
CVVHDF	✓	✓	✓	✓	x	✓	x	✓	✓
TPE	✓	✓	✓	✓	x	x	x	x	x

CRRT, continuous renal replacement therapy; SCUF, slow continuous ultrafiltration; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration; TPE, therapeutic plasma exchange.

pre-filter (range 10–10,000 mL/h), replacement post-filter (range 10–10,000 mL/h), effluent (range 10–12,000 mL/h) and citrate (10–600 mL/h). One syringe pump is dedicated to heparin or calcium infusion.

Three scales are allocated on the bottom of the machine. Scales for replacement fluid/dialysate and effluent can manage a maximum load of 15 kg. On the citrate one, the maximum load is 2 kg.

CRRT modalities and plasma exchange treatment for both adults and pediatrics are available (Table 1). In continuous veno-venous hemodialysis (CVVHD) and continuous veno-venous hemodiafiltration (CVVHDF), both dialysate counter-current and co-current configurations are possible. Heparin or citrate-calcium anticoagulation therapies can be prescribed and delivered.

The disposable tubing set of the machine is the same for all CRRT treatments: slow continuous ultrafiltration (SCUF), continuous veno-venous hemofiltration (CVVH), CVVHD, CVVHDF. Citrate anticoagulation therapy, pediatric therapy and therapeutic plasma exchange (TPE) are performed with dedicated tubing sets. The machine can be set with the following disposable configurations:

- Adult CRRT kit with heparin as anticoagulation therapy
- Adult CRRT kit with citrate-calcium as anticoagulation therapy
- Pediatric CRRT kit with heparin as anticoagulation therapy
- Pediatric CRRT kit with citrate-calcium as anticoagulation therapy
- Adult TPE kit with heparin as anticoagulation therapy
- Pediatric TPE kit with heparin as anticoagulation therapy.

The pediatric CRRT kit has a priming volume of 80 mL (adult one is 300 mL) and can be applied for patients whose weight is higher than 10 kg.

In case of citrate anticoagulation, several solutions with different concentrations of citrate and calcium can be used:

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- Citrate:
  - Anticoagulant citrate dextrose solution: 112.9 mmol/L
  - Trisodium citrate: 136 mmol/L.
- Calcium:
  - Calcium chloride: 4.56 mmol/10 mL
  - Calcium gluconate: 2.27 mmol/10 mL
  - High concentration solution: 500 mmol/L.

The hardware is designed to be used with any type of dialyzer/filter and dialysate/replacement fluid bag. During the setup phase of the machine, dry or wet dialyzer can be set. Wet filters can be used to improve the air removal process during the priming phase and to prevent type 1 reaction occasionally observed with new dry dialyzers [8]. If diffusive therapy is performed, standard counter- or co-current configuration of dialysate flow can be set. In a practical setting, priming, mounting and use of CRRT circuit are easier in co-current dialysate flow because gas and air bubbles will be removed from the membrane more efficiently [9]. This setting does not reduce significantly the treatment efficiency if blood and dialysate flows are optimized.

The therapy prescription can be set in the machine in 2 ways:

- Setting the flows (or volumes) of purifying fluids
- Setting the dose intended to achieve.

In the second case, the machine will automatically output the flows based on set parameters necessary for the calculation.

In vitro and In vivo Evaluation

Based on the traditional experience of International Renal Research Institute of Vicenza (IRRIV), in vitro and first in vivo evaluation of Kibou® CRRT machine has been conducted with the classic approach of usability and accuracy test.

Staff Involved

Participants for this device evaluation were nephrologists, intensivists, dialysis nurses, intensive care nurses and engineers working in the research center.

In vitro Testing

The in vitro evaluation protocol of the machine has been divided into 5 subsections as:

- General evaluation
- Hardware evaluation
- Software evaluation (bugs, graphical user interface [GUI])

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- Alarm simulation phase
- Fluid balance error.

General Evaluation

The general perception of the machine was quantified through the administration of a survey to each component of the evaluating staff at the end of the in vitro testing. Aspects of functionality, usability, feasibility during all phases of a theoretical CRRT session was judged based on a score between 1 and 5. The purpose was to bring out peculiarities, innovative features, weaker points and issues.

Hardware Evaluation

Not only was the machine in its entirety evaluated, but also each hardware component (display, tubing set, pumps, warmer, scales, pressure transducers, exc.). Evaluation criteria were the same as before.

Software Evaluation (Bugs, GUI)

Functionalities, usability, ease of understanding and accuracy of displayed parameters of GUI were evaluated. In this phase, even software bugs were tracked, highlighted and solved.

Alarm Simulation Phase

In this phase, alarming situations were induced by altering pressures, flows and circuit setup to evaluate the safety of the machine. We checked the type of alarm, intervals of detection and possible alterations of all components. A strict protocol based on the alarms list reported in the user manual was followed.

Fluid Balance Error

During this phase, sessions of 6 and 24 h with physiological saline solution and low fat milk were performed to evaluate the accuracy of fluid balance system of the machine, including scales and software. Measurements after 1, 3, 6 and 24 h were considered. Different modalities and flows were applied. Direct volume measurement of each "compartment" (bag simulating the patient, dialysate bag, replacement bag and effluent bag) was performed using a high-resolution scale. Particular attention was paid on the value of net ultrafiltration volume at specific time points. Comparison between values displayed on the screen and values obtained by weighing bags was considered to estimate the relative fluid balance error.

In vivo Testing

After a deep and long in vitro analysis aiming to technically improve the machine, a preliminary in vivo "alpha test" was performed in our semi-intensive care unit

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of the Department of Nephrology, Dialysis and Transplantation in Vicenza, Italy. The test was performed on nephrology inpatients requiring a short-time session of RRT. We performed 12 RRT treatments in 9 patients. Although Kibou® was already a commercially available CE marked device, we obtained the consent by our internal review board and informed consent from each treated patient.

Staff Training

Nephrologists, intensivists, nurses and engineers involved in the study received a specific training program on the machine.

Prescription

The prescription of CRRT modalities and treatment parameters to be set in the machine was completely left to the discretion of the physician in charge of the patient, based on the specific clinical need.

RRT Disposables and Tubing Set

The tubing set, applied for all treatments, was the adult kit with heparin as an anticoagulant. The dialyzer applied for this preliminary alpha trial was Cureflo 1.3 (Asahi Kasei Kuraray Medical Co., Ltd., Tokyo, Japan). Bags for replacement and dialysate solutions were Duosol™ Bicarb 35 Dialysate K2/Ca3 (B. Braun Medical Inc., Bethlehem, PA, USA).

Collection of Treatment Data and Parameters

Technical data and parameters of the treatment were collected manually and extracted from the device through a USB key. No clinical data were collected since the clinical evaluation of the machine was not included in the aims of the test.

Statistical Analysis

Descriptive data of in vivo treatments are expressed as mean ± SD. Excel software (Microsoft, Redmond, WA, USA) was used for the analysis.

Evaluation Results

In vitro Testing

In general, Kibou® is considered a small and compact CRRT machine. Based on assigned scores, it allows for easy handling and logistical movement (3.3/5). Visual and acoustic signals for alarms announcement are clear to perceive, especially in a noisy environment like ICU departments (3.9/5). Nevertheless, the steel arm for hanging priming bags could probably be taller and equipped on the

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top with a further LED for an immediate perception of the alarm. The display is quite small (2.7/5), but its dimensions are adequate for an easy rotation on the vertical axis (3.5). The space of the frontal layout is perceived as well organized, especially during the preparation phase (3.6).

Regarding the evaluation of hardware components and disposable, peristaltic pumps (3.3/5), pressure sensors (3.5/5) and all other safety devices allocated in the machine (air bubbles detector, blood leak detector, safety automatic clamp, exc.) received good scores, both in terms of positioning and circuit handling. The installation phase of the disposable part of the tubing set on the heater of the machine was considered a bit cumbersome (1.9/5). The automatic adjustment of the blood level in the air removal chamber in the return line, achieved by 2 ultrasound probes, was considered very useful. However, the shape of the disposable chamber and hemodynamics inside it, may lead to some stagnation of blood and increase risks of clotting.

Dialysate/replacement and effluent scales received a good mark (3.0/5), especially from nurses, because the maximum weight potentially to load (15 kg) was considered practical, potentially reducing the frequency of bags change procedures.

The pediatric blood pump segment has a lower stroke volume than the adult one. A 0.15 m^2 dialyzer was used. Blood flow was accurate for values of 50 mL/min (increments of blood flow rate is 1 mL/min from 1 to 30 mL/min, 5 mL/min from 30 to 400 mL/min). However, blood and effluent pumps work in a discontinuous way for very low flows (1–30 mL/min).

Also, software and graphic user interface were evaluated and considered immediate, comprehensive (3.2/5) and with a good setup and organization on the screen (3.4/5). Figure 3a shows a screenshot of the display during the treatment. A new function of the machine during the prescription phase, the "dose mode" (Fig. 2b), deserves a special mention. By setting the desired prescribed dose (e.g., 30 mL/kg/h [10]) and other parameters, like weight and hematocrit of the patient, the machine automatically calculates replacement (pre- or post-infusion) and/or dialysate flows. Furthermore, the cumulative dose value (Fig. 2a) that takes into account the downtime accumulated during the treatment, is continuously displayed and updated: this value can be compared with the prescribed dose and eventually leads to an adjustment of the clinical prescription, following the new concept of "dynamic prescription" proposed by 2016 ADQI group [11–14].

During alarm simulation phase, no critical issues were detected and an easy troubleshooting was experienced. Based on an internal risks analysis protocol, the time interval from the induction of the alarm to its detection by the machine was considered safe in all cases.

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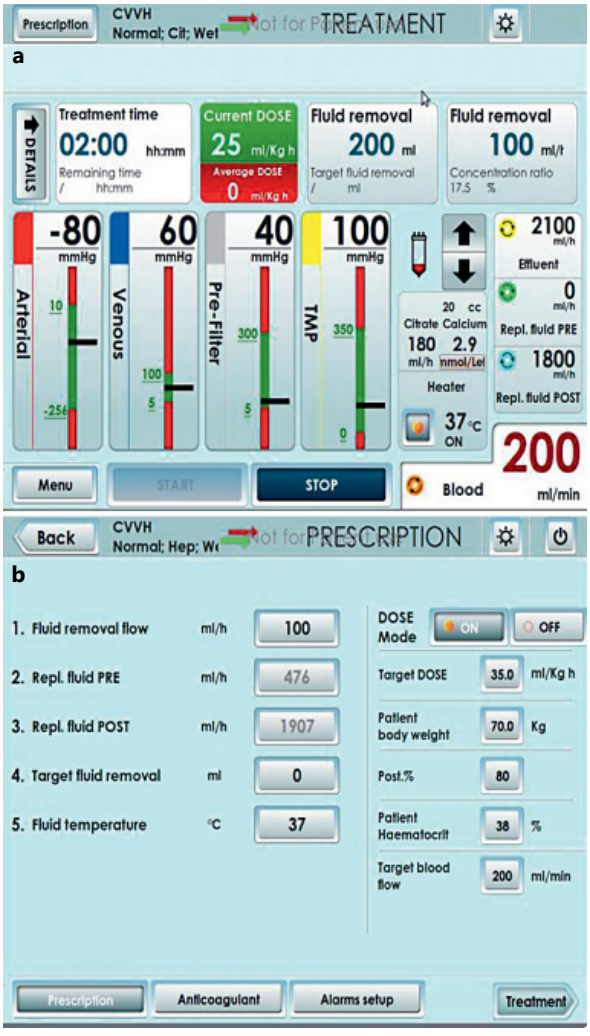

Fig. 3. a Screenshot of the treatment page. **b** Screenshot of the prescription page in "dose mode."

Finally, the precision of fluid balance system was analyzed. The absolute value of observed mass balance error at every time-sampling points varied less than 0.3% with respect to theoretical value of net ultrafiltration, as declared in the user manual of the machine.

In vivo Testing

Twelve CRRT daily treatments were performed in nine patients. Modalities and parameters are summarized in Table 2. Kibou® was utilized in CVVH (2), CVVHD (4), CVVHDF (3) and SCUF (3). On an average, a downtime of 5.30% of total treatment time (3.20% in CVVH, 5.39% in CVVHD, 9.70% in CVVHDF,

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Table 2. Treatments and parameters performed with Kibou®

Treatment	Modality	Treatment time (min)	Blood flow (mL/min)	Pre replacement flow (mL/h)	Post replacement flow (mL/h)	Dialysate flow (mL/h)	NET UF flow (mL/h)	Anti-coagulation therapy	Anti-coagulation flow (UL/h)
1	CVVH	240	182	2,000	1,000	–	293	Heparin	667
2	CVVHD	240	200	–	–	3,000	400	NO	–
3	SCUF	190	200	–	–	–	600	Heparin	667
4	SCUF	240	220	–	–	–	700	NO	–
5	SCUF	165	190	–	–	–	400	NO	–
6	CVVHDF	270	200	–	2,000	2,000	500	Heparin	667
7	CVVHDF	180	190	–	1,000	7,000	10	Clexane	667
8	CVVH	180	200	2,000	1,000	–	600	NO	–
9	CVVHD	260	180	–	–	9,000	700	NO	–
10	CVVHDF	180	190	–	1,000	2,000	500	Heparin	667
11	CVVHD	240	225	–	–	7,000	200	NO	–
12	CVVHD	210	200	–	–	5,000	10	Heparin	667

NET UF, net ultrafiltration; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; SCUF, slow continuous ultrafiltration; CVVHDF, continuous veno-venous hemodiafiltration.

3.22% in SCUF) was observed due to alarms detection, change bags procedure and other clinical interventions to the patient.

Fluid balance error at the end of the treatment, performed comparing the NET UF volume displayed real-time by the machine and values of bed scales, was lower than 0.3%, confirming the in vitro findings. During these CRRT sessions, no issues related to clotting of circuit and dialyzers were detected.

During the in vivo evaluation, users were able to better understand the usability of different phases of the treatment. They appreciated the low priming phase duration (13 min), the guided assistance of the machine during the preparation phase and the main screen during treatment, that was considered practical and immediate (3.7/5). Some difficulties were occasionally encountered during the disposable circuit placement on the machine (2.6/5).

Conclusions

A fourth generation machine for CRRT has been created and further developments are planned for the years to come. The new generation of machines is modifying the scenario of technology applied to critically ill patients. Some of these new technologies have not reached their full clinical potential yet. Nevertheless, they represent the future of this field. Our experience allows us to imagine how CRRT will evolve from today to the next ten years [15]. In addition to safety features of the therapy, other aspects have become important in further

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developments including smooth treatment performance, easy usability and consequent efficient use of resources, application of a standardized nomenclature to various parameters and possibly, a biofeedback-controlled treatment using signals from patients and machines to drive treatment parameters [16, 17].

Kibou® is a new multifunctional CRRT machine that meets most of the features required in a fourth generation CRRT equipment. Peculiarities and different aspects have been evaluated and described in this paper.

This represents a preliminary yet complete in vitro and short-time in vivo evaluation that should be soon completed by a comprehensive evaluation of the machine in a larger study. A larger-scale multicenter beta trial considering several CRRT sessions and modalities is scheduled to evaluate performance, safety and efficiency of the machine.

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Mauro Neri
International Renal Research Institute of Vicenza (IRRIV)
San Bortolo Hospital, Viale Rodolfi, 37
IT–36100 Vicenza (Italy)
E-Mail neri.mauro@gmail.com

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