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Continuous Renal Replacement Therapy for End-Stage Renal Disease

The Wearable Artificial Kidney (WAK)

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Abstract

Daily dialysis offers many benefits but is difficult to implement. CRRT allows dialysis 24/7 but is not suitable for ESRD patients. Thus, the need for a miniaturized ambulatory CRRT device those patients can wear permanently. We report the feasibility, safety and efficiency in uremic pigs, of such a wearable artificial kidney (WAK) that can be worn as a belt, operated with batteries, and weights less than 5 lbs. We used a hollow fiber dialyzer with a surface area of 0.2 sqm. Dialysate was continuously regenerated by a series of cartridges containing several sorbents allowing the use of approximately 375 ml of dialysate. The device includes reservoirs with heparin and electrolytes. Average fluid removal was 100 ml/hr. The Creatinine was 25 ml/min. In 8 hrs the total Creatinine removed was 1 gr, Urea 12 gr, P0.8 gr and K 72 mEq. Weekly st kt/v was extrapolated to approximately 7. There were no side effects. The WAK can be operated safely and continuously 168 hr/week. This would allow for all the advantages of daily dialysis and reduce morbidity and mortality in the ESRD population. It will also reduce cost and manpower utilization.

Introduction

A growing body of literature points out that increased dialysis frequency and prolonged dialysis (preferably daily) are conducive to numerous improvements in quality of life and potentially increased longevity of end-stage renal disease (ESRD) patients. These advantages of daily dialysis are summarized in Table 1.

On the other hand, implementation of daily dialysis encounters several obstacles that make its implementation in a large scale practically impossible. Between these are the inability or unwillingness of most patients to dialyze at

Table 1. The many advantages of daily dialysis

Improved volume control	Improved appetite and nutrition
No hyperphosphatemia	Eliminate phosphate binders
Less hypertension	Reduce hypertension medication
No hypokalemia	No metabolic acidosis
No sodium retention	Improved serum albumin
Reduce bone disease	Improve anemia
Reduce cardiovascular disease	Decrease incidence of stroke
Reduce morbidity	Reduce mortality

home, the lack of manpower both in nurses and technicians to provide more treatments in the dialysis units, and the reluctance of governmental payers to shoulder the expense of additional procedures [1–7].

Even if payers would agree to pay for the additional costs of daily dialysis, it would not only take time, but there would also be major capital investment requirements to build additional capacity in or near the existing dialysis units.

Thus, the need for a technological solution that will allow for increased dialysis time without incurring additional costs or necessitating additional manpower.

Continuous renal replacement therapy (CRRT) in its different versions definitely gives us the possibility of rendering significantly higher doses of dialysis but these modalities are very labor intensive. CRRT machines allow for the delivery of dialysis therapies 24 h a day, 7 days a week. These machines are not suitable to treat ESRD patients because they are heavy, attached to a wall electrical outlet and require many gallons of water, rendering such patients unable to ambulate and perform their activities of daily life. A miniaturized and wearable CRRT machine or wearable artificial kidney (WAK) might solve these problems. In order to build a WAK we had to overcome the following issues:

(1) The device needs to have an ergonomically suitable energy source that though small and light will provide enough energy to power all the necessary systems for a significant period of time and make it independent of a fixed electrical outlet, and all these, however, without creating an excessive weight burden on the patient.
(2) The device has to have enough dialysate with all the necessary additives, and the capability to purify and recirculate such dialysate to avoid requiring many gallons of fluid. However, the volume has to be small enough so that it will not create an intolerable weight burden.
(3) The device must be light and ergonomically adapted to the body contour so that it can be worn continuously without impinging on the patient's ability to ambulate and performs the activities of daily life.

As all these problems were solved and a WAK original model that can be battery operated, worn as a belt and weighing less than 2.27 kg was built and tested on initial bench trials. The purpose of this study was to determine the feasibility, safety and efficiency of the WAK in uremic animals.

Materials and Methods

Twelve pigs underwent ligation of the ureters. Next day, they were anesthetized and dialyzed for 8 h using a double lumen catheter, with a WAK (fig. 1) that can be battery operated, worn as a belt and weighs less than 2.27 kg.

A dialyzer weighing less than 100 g made of hollow capillary fibers with a surface area of 0.2 sqm was used. The dialysate utilized was sterile normal saline. It was continuously regenerated by recirculation through a series of cartridges containing activated carbon, urease, zirconium hydroxide and zirconium phosphate [8]. This allowed the use of approximately 375 ml of dialysate. The device includes several reservoirs containing heparin and supplemental electrolytes such as calcium, magnesium, sodium bicarbonate, etc. Volumetric micropumps were used to deliver 0.5–10 cc per hour of these solutions from the reservoirs to the blood or the dialysate circuit. The removal of fluid was controlled using a volumetric micropump at flow rates ranging between 0 and 700 ml per hour with an average rate of fluid removal of 100 ml/h. The animals were divided into 2 groups: Group I: 6 pigs (weight 74.9 ± 1.2 kg) were dialyzed with a blood flow of 44 ml/min and Group II: 6 pigs (weight 47.9 ± 1.7 kg) were dialyzed with a blood flow of 75 ml/min. Creatinine, urea and electrolytes were measured with an i-STAT Portable Clinical Analyzer from Abbott Laboratories. Effective urea and creatinine clearances and standard weekly urea Kt/V were calculated as follows:

Effective clearance = Blood flow × [Δ solute]/[solute in];

Standard weekly Kt/v = Effective clearance × Time/total body water.

Where Δ solute is the difference between urea or creatinine concentrations in and out of the dialyzer. Time was 480 min in the actual tests and 10,080 min for a weekly extrapolation. Total body water was estimated as 60% of body weight.

Results

No adverse events were observed in the animals included in these studies. The average dialysate flow was 73 ml/min in Group I and 85 ml/min in Group II. The results are summarized in table 2.

The measured values of effective creatinine clearance, total creatinine removed, effective urea clearance, total urea removed, standard weekly Kt/V, phosphorus and potassium removed per 8 h are summarized in table 2. The removal of potassium during the treatment was 71.9 ± 13.3 mmol in Group I and 89.1 ± 25.7 mmol in Group II, per 8 h. The removal of phosphorus was 0.8 ± 0.2 g in Group I and 0.84 ± 0.4 g in Group II, per 8 h. The dialysis doses achieved with the WAK were effective creatinine clearance of 25.5 ± 1.4 ml/min in Group I and 24.7 ± 3.2 ml/min in Group II. The average effective urea

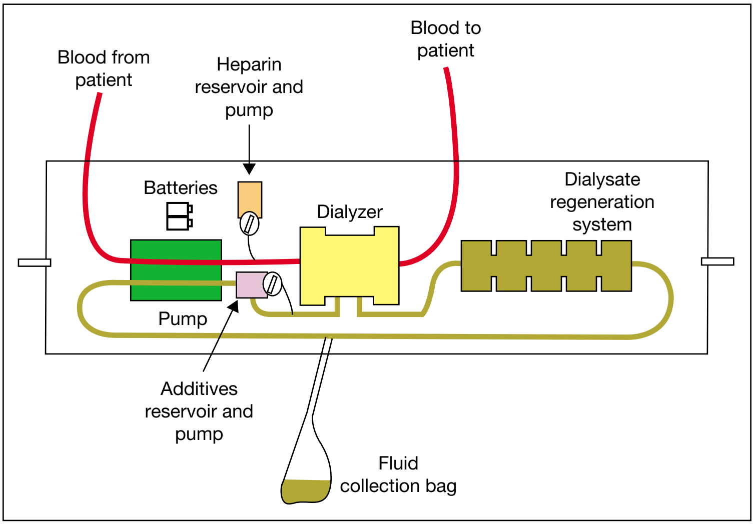

Fig. 1. Schematic draft of the wearable artificial kidney belt.

Table 2. The results of our animal studies (mean ± SD)

Results	Group I	Group II
Effective urea clearance, ml/min	24.3 ± 1.4	23.9 ± 3.5
Effective creatinine clearance, ml/min	25.5 ± 1.4	24.7 ± 3.2
Total urea removal, g	12.7 ± 2.8	12.0 ± 2.9
Total creatinine removal, g	0.9 ± 0.2	1.0 ± 0.1
Total phosphorus removal, g	0.8 ± 0.2	0.84 ± 0.4
Total potassium removal, mmol	71.9 ± 13.3	89.1 ± 25.7
Extrapolated standard Kt/V urea	5.4 ± 2.4	8.4 ± 1.5

clearance was 24.3 ± 1.4 ml/min in Group I and 23.9 ± 3.5 ml/min in Group II. The standard weekly urea Kt/V was 5.4 ± 2 in Group I and 8.4 ± 1.5 in Group II.

The amounts of ultrafiltrate removed are shown in table 2. The volume of fluid removed was changed arbitrarily during the experiment from 0 to 700 ml/h. The limiting factor for the removal of larger amounts of fluid per hour was a progressive decrease in blood flow in the dialyzer with increasing fluid removal rate. The blood flow was reinstated immediately as we diminished the ultrafiltrate removal rate. There were no difficulties, however, in maintaining an average fluid removal of 100 ml/h.

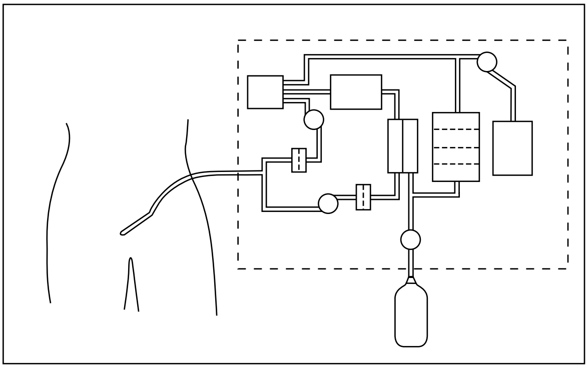

Fig. 2. Wearable peritoneum-based system for continuous renal function replacement [15].

Discussion

The need for increased and more frequent dialysis is well documented. It is abundantly clear by now that this may be the way to improve the currently dismal outcomes in the treatment of ESRD. However, implementing daily dialysis is plagued by several apparently insurmountable limitations, not the least of these being the need for increased funding and nursing manpower. Thus, the nephrology community has to come up with a different technical solution that will answer the need to improve the outcomes in ESRD, without higher costs. The WAK might be the answer.

Several attempts to build a WAK (fig. 2, 3) have been previously described [9–19] but none was ever brought to market.

The lack of suitable light energy sources, the low efficiency of the available membranes, and the inability to miniaturize the components to the extent that the device would perform appropriately with a low-energy budget were main limitations in the past. Similarly, the use of REDY sorbents was incorporated in some of these initial attempts. However, the REDY sorbent cartridge weighs about 2.27 kg and is ergonomically unsuitable for a device that can be worn on a patient's body. The system was never modified or configured to make it light and ergonomically suitable for a WAK. As we addressed those issues one by one, and came up with practical solutions, building a working WAK prototype became feasible.

The use of a sterile dialysate, free of bacterial toxins, would avoid the presumed complications attributed to the current use of water that is not pyrogen free. The relatively small amount of dialysate required by this device, would make the provision of such a dialysate, practical and cost effective.

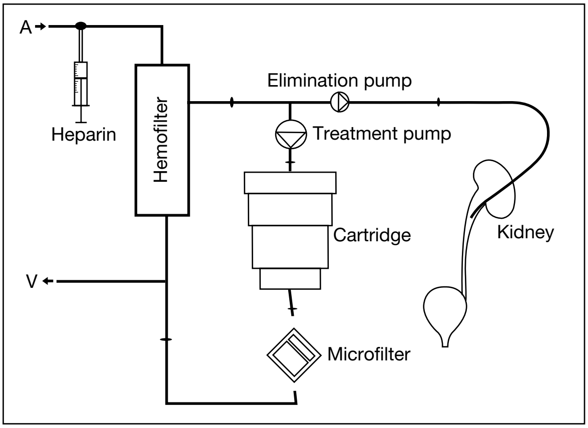

Fig. 3. Continuous arteriovenous hemofiltration in a wearable device to treat end-stage renal disease [17].

The results shown above indicate that the WAK can remove solutes and excess fluids from uremic animals. The amounts removed indicate that if similar results are accomplished in ESRD patients, a major increase in dialysis dose could be provided. The standard weekly Kt/V, about 7 on average, is significantly higher than that commonly administered in the current schedules (fig. 4). The device would provide 168 h per week of dialysis, about 16 times more dialysis hours than that currently used schedules, without interference in the patient's activities of daily life, or increasing the cost of treatment. It seems that the one factor the nephrology community never identified and modified in 6 decades of treatment of ESRD patients, is dialysis time. Yet, the emerging data on daily dialysis seem to indicate that incremental dialysis time is the key for improving the dismal outcomes we obtain today in our ESRD population. The concept that filtering blood with a typical schedule of 12 h a week can accomplish the same task that native kidneys do by filtering the blood 24 h a day, 7 days a week, appears to be erroneous. Molecules of different size, submitted to the same kinetic forces, would travel through membranes at different speeds, according to their molecular weight. Therefore, heavier molecules may not transit in adequate amounts from the blood stream to the dialysate unless they are given enough time to do so. It seems that 168 h a week of blood filtration may be far more physiological than 12 h a week. This may explain, at least partially, the unacceptably high morbidity and mortality of the ESRD population.

The amounts of salt and water removed would make patients free from limitations in the oral intake of water and salt. In addition, this would result in a much-improved control of hypertension and fluid overload and a reduction in

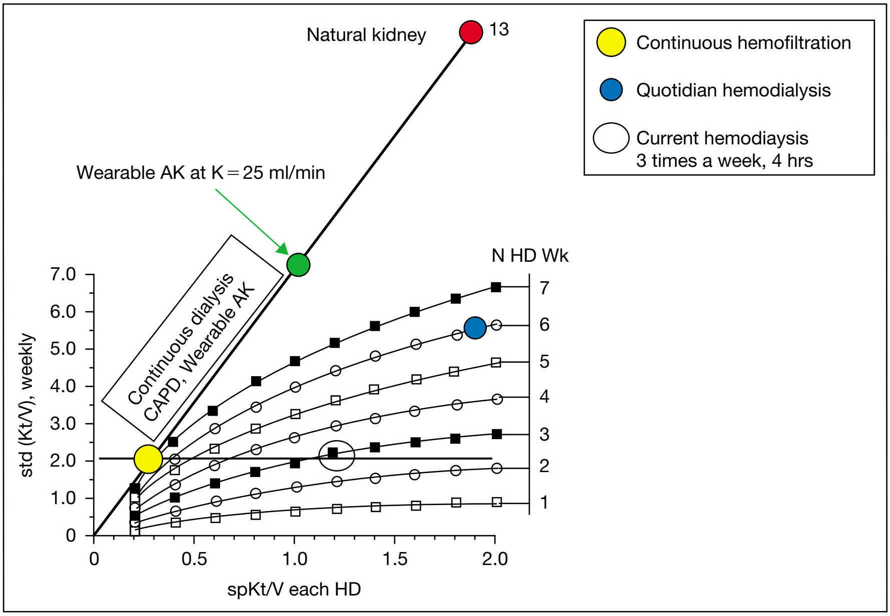

Fig. 4. Standard weekly Kt/V of WAK is higher than those of current schedules [25]. ○ = [26]; ● = [27].

the need for antihypertensive drugs. This notion is further supported by the results obtained with daily [20, 21] or prolonged [22–24] dialysis. Similarly, the amounts of potassium removed in these animals, indicate that if similar results were obtained in ESRD patients, there would be no dietary restriction of potassium, and the risk of hyperkalemia would be greatly reduced.

The amounts of phosphorus we removed with the WAK would eliminate the need for phosphate binders in ESRD. Again, a similar result has been shown in ESRD patients treated with daily dialysis. The beneficial effects of the elimination of hyperphosphatemia on bone disease and arterial calcifications shall be the subject of further studies. In addition, the elimination or reduction of phosphate binders would be an additional, welcome cost reduction in the treatment of ESRD.

Furthermore, the WAK would decrease significantly the amount of capital investments and nursing manpower needed today to provide dialysis to ESRD patients.

Human clinical studies are now needed to corroborate these results in ESRD patients. If successful, the WAK may be the way to provide daily dialysis in an efficient and cost-effective manner.

References

1 Lockridge RS Jr: The direction of end-stage renal disease reimbursement in the United States. Semin Dial 2004;17:125–130.
2 Lockridge RS Jr, McKinney JK: Is HCFA's reimbursement policy controlling quality of care for end-stage renal disease patients? ASAIO J 2001;47:466–468.
3 Manns BJ, Johnson JA, Taub K, Mortis G, Ghali WA, Donaldson C: Dialysis adequacy and health related quality of life in hemodialysis patients. ASAIO J 2002;48:565–569.
4 Mapes DL, Lopes AA, Satayathum S, McCullough KP, Goodkin DA, Locatelli F, Fukuhara S, Young EW, Kurokawa K, Saito A, Bommer J, Wolfe RA, Held PJ, Port FK: Health-related quality of life as a predictor of mortality and hospitalization: The Dialysis Outcomes and Practice Patterns Study (DOPPS). Kidney Int 2003;64:339–349.
5 McFarlane PA, Bayoumi AM, Pierratos A, Redelmeier DA: The quality of life and cost utility of home nocturnal and conventional in-center hemodialysis. Kidney Int 2003;64:1004–1011.
6 Mohr PE, Neumann PJ, Franco SJ, Marainen J, Lockridge R, Ting G: The case for daily dialysis: Its impact on costs and quality of life. Am J Kidney Dis 2001;37:777–789.
7 Patel SS, Shah VS, Peterson RA, Kimmel PL: Psychosocial variables, quality of life, and religious beliefs in ESRD patients treated with hemodialysis. Am J Kidney Dis 2002;40:1013–1022.
8 Marantz LB, Giorgianni MG, inventors: Urease in insoluble form for converting urea present in liquid. US patent 3989622, 11/2/1976.
9 Beltz AD, inventor: Wearable, portable, light-weight artificial kidney. US patent 5284470, 2/8/1994.
10 Bonomini V, Roggeri G, inventors: Hemodialysis and/or ultrafiltration apparatus. US patent 4269708, 5/26/1981.
11 Henne W, inventor: Artificial kidney. US patent 4212738, 7/15/1980.
12 Horiuchi T: [Wearable artificial kidney, portable artificial kidney and implantable artificial kidney]. Nippon Rinsho 2004;62(suppl 5):182–188.
13 Kolff WJ, Jacobsen S, Stephen RL, Rose D: Towards a wearable artificial kidney. Kidney Int 1976;(suppl 7):S300–S304.
14 Mineshima M: [Artificial kidney therapy in next generation]. Nippon Rinsho 2004; 62(suppl 6): 606–609.
15 Roberts M, Lee DB-N, inventors: Wearable peritoneum-based system for continuous renal function replacement and other biomedical applications. US patent 5944684, 8/31/1999.
16 Scott RD, inventor: Wearable, continuously internally operable and externally regenerable dialysis device. US patent 4765907, 8/23/1988.
17 Murisasco A, Reynier JP, Ragon A, Boobes Y, Baz M, Durand C, Bertocchio P, Agenet C, el Mehdi M: Continuous arterio-venous hemofiltration in a wearable device to treat end-stage renal disease. Trans Am Soc Artif Intern Organs 1986;32:567–571.
18 Senoo S, Otsubo O, Watanabe T, Yamauchi J, Yamada Y, Inou T, Takai N, Takahashi H, Fukui H, Kawata Y: [The wearable artificial kidney: Development of a small blood pump]. Jinkou Zouki 1982;11:48.
19 Tada Y, Horiuchi T, Ohta Y, Dohi T: A new approach for the filtrate regeneration system in the wearable artificial kidney. Artif Organs 1990;14:405–409.
20 Lockridge RS Jr: Daily dialysis and long-term outcomes – The Lynchburg Nephrology NHHD experience. Nephrol News Issues 1999;13:16, 19, 23–26.
21 Lockridge RS Jr, Spencer M, Craft V, Pipkin M, Campbell D, McPhatter L, Albert J, Anderson H, Jennings F, Barger T: Nocturnal home hemodialysis in North America. Adv Ren Replace Ther 2001;8:250–256.
22 Charra B, Chazot C, Jean G, Hurot JM, Vanel T, Terrat JC, Vovan C: Long 3×8 hr dialysis: A three-decade summary. J Nephrol 2003;16(suppl 7):S64–S69.
23 Charra B, Chazot C, Jean G, Laurent G: Long, slow dialysis. Miner Electrolyte Metab 1999;25: 391–396.
24 Charra B, Terrat JC, Vanel T, Chazot C, Jean G, Hurot JM, Lorriaux C: Long thrice weekly hemodialysis: The Tassin experience. Int J Artif Organs 2004;27:265–283.
25 Gotch FA: The current place of area kinetic modelling with respect to different dialysis modalities. Nephrol Dial Transplant 1998;13:10–14.

26 Murisasco A, Baz M, Boobes Y, Bertocchio P, el Mehdi M, Durand C, Reynier JP, Ragon A: A continuous hemofiltration system using sorbents for hemofiltrate regeneration. Clin Nephrol 1986;26(suppl 1):S53–S57.
27 Suri R, Depner TA, Blake PG, Heidenheim AP, Lindsay RM: Adequacy of quotidian hemodialysis. Am J Kidney Dis 2003;42(supp 1):S42–S48.

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