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Quo vadis dialysis?

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It is well known that the prevalence of chronic kidney disease is progressively increasing, with all registries showing continued growth in the number of patients needing renal replacement therapy. The social and economic consequences are very important and morbi-mortality in patients with end-stage renal disease remains unacceptably high[1,2]. There are several reasons for this high mortality, such as a dramatic increase in the age of the patients receiving this treatment, the fact that haemodialysis and peritoneal dialysis only restore 15 to 20 ml/min of renal function, and significant associated comorbidities. The progress that has been made in haemodialysis (including the biocompatibility of membranes, high-flux membranes, increased frequency of sessions, and monitoring of water quality) and peritoneal dialysis (including decreased risk of infections, and introduction of the cycler) has not been followed by a clear improvement in patient outcomes.

So, if after all these years we have improved so little, what does the future hold for the replacement of renal function? This article attempts to depict the future possibilities of facing kidney failure, discussing such techniques such as haemodialysis or peritoneal dialysis.

HAEMODIALYSIS: WEARABLE KIDNEY

As discussed above, the situation faced by haemodialysis patients generally means a great sacrifice for patients and families, mainly stemming from the poor quality of life and the need to travel to dialysis centres three or more times per week. Moreover, the high mortality rate (similar to that of metastatic breast carcinoma, carcinoma of the colon or prostate) forces a move towards different techniques.

The improvement which frequent and prolonged dialysis has made in quality of life, control of anaemia, stress control, hospitalisations, medication reduction (such as anti-hypertensive agents or phosphate binders), improved appetite, improved volume control and reduced morbi-mortality, has influenced current research directed toward these types of techniques in which the treatment is continuous.

It is true that continuous ambulatory peritoneal dialysis (CAPD) could already be accepted as continuous therapy. Although in many centres it is a technique which has been in place for many years, only 10-15% of patients are on CAPD and there has been a tremendous decline over time due to loss of ultrafiltration capacity of the peritoneum or, in many cases, when residual renal function disappears due to dialysis inadequacy.

The requirements of new dialysis technologies are therefore based on the following objectives:

1) Continuous operation
2) Elimination of molecular weight solutes in the same way the kidney does
3) Elimination of water and solutes adapted to the needs of the patient
4) Biocompatibility
5) Portable or better implantable
6) Low cost
7) Safety.

Today four possible models could achieve these objectives in the future: UFH (Human Nephron Filter), microfluidic techniques, WAK (Wearable Artificial Kidney) and RAD (Bioartificial Renal Assist Device).

HNF: HUMAN NEPHRON FILTER

Nisenson *et al.*[3,4] have proposed this model as a breakthrough in the treatment of renal failure. The HNF consists of two membranes operating in series within a container. The first membrane is called the G membrane and is similar to the glomerular membrane of the nephron. Convective transport is used to produce an ultrafiltrate of plasma containing solutes approaching the molecular weight of albumin. The second membrane is called the T membrane and plays the role of the tubule. It is made through molecular engineering and composed of pores of different sizes and angles and each of these pores allows solute-dependent selection, meaning that of solutes with the same molecular weight, some are discarded and others not. Similar pore radiuses are particularly designed to have different selective transport properties. The ultrafiltrate formed once the blood contacts the G membrane contains desirable and undesirable solutes. Moving into the T membrane, this rejects only the unwanted and undesirable solutes, because each pore discriminates by design between what has to stay and what must be eliminated. Blood flows to a flow of 100 ml/min. A dialysate is not used in this system.

There are important differences between the membranes constructed with molecular engineering and normal polymer membranes. The former have a predetermined number of large pores with specific interactions that allow selectivity in transport. By contrast conventional polymer membranes are very thick, producing nonselective transport of solutes, and pore sizes are very different.

The UFH can be portable, including the G and T membrane, and also attached to a belt with a high capacity battery and a discharge bag with a conventional vascular access or using different varieties of percutaneous access.

With provision of significantly greater solute removal than other dialytic approaches and operating continuously, HNF is expected to significantly improve morbi-mortality in CKD patients on haemodialysis.

DIALYSIS WITHOUT MEMBRANES: MICROFLUIDIC TECHNIQUES

Microfluidic technology is based on the parallel flow of two streams over a single channel two liquids (e.g. blood and a solution of PBS) circulating in a laminar form, side by side, without turbulent mixing and without being separated physically by a membrane. Under these circumstances diffusion occurs, so that small particles (such as ions, small molecules and proteins and many drugs) tend to spread quickly from the side of higher to lower concentration, while large molecules and particles such as cells tend to spread only minimally. Leonard *et al.*[5,6] have suggested that microfluidic technology is a new science of possible application in the field of haemodialysis. Currently there are prototypes of H filters simply allowing gravity to facilitate the diffusion of small molecules from the blood into the dialysis fluid and in the future, the construction of multiple microfluidic chambers may be of clinical application to allow miniaturisation of the artificial kidney and obtain a portable kidney. However, we still need major research to solve problems such as ultrafiltration and retention of albumin.

WAK: WEARABLE ARTIFICIAL KIDNEY

Gura *et al.*[7,8] have developed a portable dialysis machine based on a polysulfone high flux dialyser of 0.6 m^2. It is composed of a blood circuit with the arterial line that sends blood to the dialyser and the venous line back to the patient, a dialysate compartment where the dialysis fluid enters the dialyser and which is not discharged but rather circulates through a series of sorbents where it is regenerated with bicarbonate later added to it. There are a series of miniature pumps that regulate anticoagulation and ultrafiltration.

Davenport *et al.*[9] presented eight patients who were on haemodialysis, and who were treated with the portable kidney for 4-8 hours. Patients received heparin for anticoagulation. There were no significant

cardiovascular changes or adverse effects. The average blood flow was 58 ml/min with a dialysate flow of 47 ml/min with a mean creatinine clearance of 20.7 ml/min. In two cases, a coagulation of the circuit was observed due to a reduction in the heparin dose.

It is clear that the prototype is still in its infancy and that more studies are needed to confirm its long-term safety and efficacy. But it has the potential to become a method to achieve a more comfortable and efficient dialysis in patients with advanced renal insufficiency.

RAD: BIOARTIFICIAL RENAL ASSIST DEVICE

Based on the presence of a number of progenitor cells that regenerate tubular epithelium after tubular necrosis or acute renal failure of any aetiology, Humes *et al.*[10] were able to select this type of cell population growing in collagen gels and form tubule-like elements with programmed growth factors. They introduced an array of fixation within a capillary polysulfone with progenitor cell filling. Culture medium was added to the extracapillary space with growth factors which facilitate the expansion and differentiation of cells to form a layer that filled the capillary inner surface of what fabricated a bioartificial tubule.

Until then renal replacement therapy in acute renal failure had only managed to replace the removal of solutes of small molecular weight and volume but without restoring the metabolic properties and endocrine functions of the kidney, which reside in the same cellular elements.

These researchers developed an apparatus for extracorporeal circulation with a haemofiltration filter that contains 0.5 A1 x 108 human renal tubule cells inside the capillary fibres. Preclinical studies in uraemic animals showed that these cells have transport, metabolic and endocrine properties[11] and, in animal experiments, improved the multiple organ dysfunction seen in septic shock by Gram negative[12,13].

Tumlin *et al.*[14] studied over a period not exceeding 72 hours if the RAD treatment improves survival of patients with acute renal failure compared to continuous replacement therapy in a randomised controlled multimember study in 58 acute renal failure patients requiring dialysis. Forty patients received venovenous haemofiltration associated with RAD and 18 only continuous replacement of renal function. The primary endpoint was mortality at 28 days and other targets were mortality at 90 to 180 days, the recovery time of renal function, length of hospital stay in Intensive Care Units and the total length of hospital stay, and safety. On day 28 the mortality was 33% in the RAD group and 61% in the treatment group receiving continuous renal replacement. They also found better survival at day 180 in the RAD group with a mortality risk of 50% compared to the continuous replacement group. RAD treatment also produced a rapid recovery of renal function and was better tolerated.

Today, this technological advance is in the preparation of phase three multicentre randomised study to evaluate the therapeutic effect in a more consistent way. There are multiple publications in this area[15-19].

Despite all these technological advances the most important problem to solve remains that of vascular access. Focusing on pharmaceutical companies and the dialysis industry has not enabled progress in improving vascular access. The only advances have been in the catheter industry, which does not help to resolve this important issue.

PERITONEAL DIALYSIS: VIWAK PD

The Vicenza Wearable Artificial Kidney for Peritoneal Dialysis is an initial prototype that seeks greater comfort for patients receiving peritoneal dialysis, a technique that despite being the most important therapy at home, still has significant barriers such as the time taken daily, which imposes important limitations on maintaining a normal life.

Ronco *et al.*[20] developed a PD ViWAK system aiming to perform CAPD with some procedures in the morning and afternoon only, and freeing the patient during the day and night. The method involves: 1) A double-lumen peritoneal catheter; 2) An output dialysate, 3) A small pump, 4) A circuit for dialysate regeneration with four cartridges in parallel on a mixture of charcoal and resins; 5) A filter for microbiological protection, 6) A line

of input dialysate and 7) A very small computer as a remote control.

The system is designed to be used as follows. The peritoneal cavity is loaded in the morning with two litres of fresh PD solution. After two hours, when dialysate/plasma equilibration at approximately 50% has occurred, recirculation is activated for ten hours at a rate of 20 ml/min. After this period, recirculation stops and glucose is optionally added to the peritoneal cavity to achieve ultrafiltration if needed. After two hours the fluid is drained and a two-litre icodextrin exchange is performed overnight to achieve further ultrafiltration. The clearance provided by the minicycler is further increased by the two-litre exchange and the overnight exchange. Therefore, the system operates 24 hours/day and provides creatinine and β_2-microglobulin clearance in the range of 15-16 litres/day, a weekly clearance of 100-110 litres. The patient has fewer exchanges than in CAPD and uses less fluid than in automated peritoneal dialysis (APD). Furthermore, the handheld computer allows for prescription and assessment of the therapy providing information on cartridge saturation, flow and pressure conditions and offering the possibility of remote wireless control of operations. Some problems still remain to be solved in the present configuration, including the addition of an injection system for glucose and bicarbonate when needed, a system to reduce fibrin delivery to the sorbent and finally a more complex mixture of sorbents to make sure a complete removal of small molecules including urea is achieved.

In short, the techniques outlined above are based on the evolution of technology in recent years that has helped to reduce the size and weight of the instruments. Hopefully in the future miniaturisation will bring better renal replacement treatment with dialysis allowing a more continuous and therefore more physiological treatment.

HUMAN ASPECTS AND REDUCING THE SOCIAL COST OF CHRONIC KIDNEY DISEASE

Technology is one step forward but the future situation of aged patients with numerous comorbidities requires a practical approach. In 2008 about 45,000 people in Spain, i.e. about 1000/per million population, were on renal replacement therapy, a figure that is estimated to nearly double over the next ten years due to the aging population and the increase in the prevalence of other chronic conditions such as diabetes mellitus. The same is true in other parts of the developed world, where even though the incidence is stabilising, the prevalence of patients receiving renal replacement, whether by dialysis or kidney transplantation, also continues to rise dramatically, reaching 2,200/million population in 2008 in Taiwan and 1900 in Japan and 1650 in France[1]. Alarmingly, this increase in prevalence looks set to have a markedly negative impact on the health services of some countries in the future[21].

As in the rest of the developed world, the incident dialysis population in Spain is aging; in the Spanish registry of renal patients in 2007 with a population of 125/million incident, the number of elderly patients over 75 years was 405/million population[22]. Many of these patients aged over 75 have three or more comorbidities and very low life expectancy. The ethical issue must be approached with courage: dialysis for everybody?

In developed countries at present there are no limitations on renal replacement therapy. This situation does not allow us to assess the adequacy of treatment in particular patients, although it is clear that not all patients benefit equally from this treatment. We have to deal with ethical considerations that in Spain are frequently discussed in our nephrology's society's Journal[23-25]. Some retrospective studies analysed the survival of patients over 75 years of age in CKD Stage 5 and the advantage of dialysis is substantially reduced by comorbidity and coronary heart disease in particular[26]. A practical approach to this issue is that conducted by Couchoud *et al.*[27] In this study simple ranking of comorbidities predicts short-term prognosis in patients over 75 years of age starting dialysis. This may help in rational clinical decision-making discussion with patients and families.

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