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Convection *versus* diffusion: Is it time to make a change?

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INTRODUCTION

Although the physical and chemical concepts of diffusion and convection have been well known since the beginning, dialysis has been carried out mainly by diffusion during its first four decades. This form of dialysis, haemodialysis (HD), has ensured the survival of millions of patients worldwide with advanced kidney disease and has met the increasing needs generated in the 50 years since dialysis was considered as a chronic renal replacement therapy.

The delay in incorporating convection techniques as routine treatment has technological and economic reasons. Haemofiltration (HF) or haemodiafiltration (HDF) modalities require the use of dialysers of high permeability and, at the same time, monitors with volume control and a dual pump. Replacement fluid is a further cost, and is the main reason for abandoning HF (replacement volumes exceed 20 litres), and was a key constraint on the initial HDF technique with volumes ranging between 3 and 10 litres. Finally, in the 1990s, the introduction of "on-line" HDF techniques using the dialysis fluid itself as a replacement solution has meant a revolution in HD units. It has taken another 10 years to renovate and upgrade water treatment, have specific monitors and incorporate safety filters to ensure the quality of this replacement fluid (ultrapure dialysate).

HD can be considered as a renal replacement therapy that ensures reasonable short-term results. However, long-term clinical results could be improved. Malnutrition and inflammation are common, hyperphosphoraemia control is poor and hypertension and heart failure are common, while rehabilitation and quality of life are less than optimal and rates of hospitalisation and mortality are high. The most common cause of mortality in patients on chronic HD is cardiovascular disease, which is the attributed cause of death in approximately 50% of patients. In other words, the dialysis patient in this condition has the so-called residual syndrome.[1] This includes a greater susceptibility to infections, decreased oxygen consumption during exercise, problems with sleeping or the ability to concentrate, depression, decreased endurance and an increased risk of cardiovascular complications. Residual syndrome has been attributed to incomplete potentially dialysable solute clearance and an accumulation of high molecular weight solutes that are difficult to remove by conventional dialysis. HDF with increased fluid replacement provides an optimal way to remove uraemic substances with a molecular weight range from small solutes to low molecular weight proteins[2,3]

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WHY SHOULD WE INTRODUCE CONVECTION AND SYSTEMATICALLY IMPLEMENT HAEMODIAFILTRATION?

HDF can be indicated for all patients on haemodialysis, as there are no contraindications. High convection volume HDF techniques constitute progress towards renal replacement therapy which is most similar to the native kidney.

These techniques offer a higher clearance of uraemic substances with a greater range of molecular size, they require the use of biocompatible membranes and ultrapure dialysis fluid, which has been associated with additional clinical benefits. Recent large observational studies, adjusted for demographic and comorbidity factors, have shown a lower risk of death is associated with HDF using more than 15 litres of replacement fluid.[4,5]

Possible clinical benefits that convection techniques can provide are: better control of hyperphosphoraemia, malnutrition and inflammation, anaemia, infectious complications, joint pain, amyloidosis associated with dialysis, intradialytic tolerance, insomnia, irritability, restless leg syndrome, polyneuropathy and itching.

Hyperphosphoraemia

HDF improves phosphorus removal and could be considered as an option for the treatment of hyperphosphoraemia.[6] Several authors[7,8] have reported that online HDF achieves greater phosphorus purification than conventional HD. However, we must not forget that it is more important to gain pre-dialysis phosphorus control and, although two studies[9,10] have observed a decrease of 8%, other studies find no changes.[11]

Malnutrition and inflammation

Anorexia in uraemic patients has been associated with the accumulation of uraemic substances. In uraemic rats, Anderstam et al[12] isolated and identified toxins in the range of 1,000-5,000 Da in uraemic plasma that suppressed the appetite in a dose-dependent fashion. The administration of leptin, 16,000 Da in monkeys, decreased food intake and increased energy expenditure, so its accumulation in dialysis patients may have an appetite suppression effect.[13] Convection techniques are better at purifying these much larger toxins. Prospective and cross-sectional studies comparing HD with "on-line" HDF have reported a reduction of markers of inflammation and endothelial injury with convection techniques.[14,15]

Anaemia

Online HDF may improve the response to erythropoietin as a result of purifying large and medium-sized molecules that may inhibit erythropoiesis. Bonforte et al[16] demonstrated an improvement in the anaemia of 32 patients with high convection volumes. Osawa et al[17] were able to decrease the dose of erythropoietin in patients with push/pull HDF. Maduell et al[11] noted a correction of anaemia in 37 patients with lower doses of erythropoietin when they changed from conventional HDF (4L) to online haemodiafiltration (24L). Ward et al[18] and Wizemann et al[19] were not able to confirm these observations in 24 and 23 patients, respectively, treated with online HDF compared with 21 patients treated with high-flow HD and 21 patients treated with low flow HD.

Infectious complications

Uraemic patients are at significant risk of infectious complications. In fact, these complications are the leading cause of hospitalisation and the second leading cause of death in HD patients. Several granulocyte-inhibiting proteins are present in uraemic patients and may contribute to the high incidence of infectious complications. Degranulation inhibiting proteins I (DIP I) and granulocyte inhibiting proteins (GIP II) inhibit in vitro glucose uptake and chemotaxis of polymorphonuclear leukocytes. Complement factor D decreases the clearance of immune complexes and inhibits degranulation of granulocytes. All these uraemic toxins are removed better with high-volume convection HDF.[18,20]

Joint pain

Maeda et al[21] observed a significant increase in the range of arm movement and improvement in pain in the shoulder joint in 30 patients after renal replacement therapy was changed from HD to push/pull HDF (30l convection volume). Clinical observations from Kim et al[22] support the hypothesis that substances related to joint pain have a molecular size larger than the beta-2-microglobulin. They investigated the relationship between joint pain improvement and the purification pattern of lower molecular weight proteins, and found higher rates of clearance for alpha-1-microglobulin and alpha-1-acid glycoprotein with on-line HDF than with high flow HD. Sato et al[23] also observed a decrease in joint pain and significant improvements in the range of adduction and abduction movements in upper limbs when they changed 6 patients receiving haemodialysis to online HDF.

Amyloidosis related with dialysis

Patients treated with dialysis for more than 5 years develop a progressive form of amyloidosis, mainly osteoarticular, due to the deposition of beta-2-microglobulin fibrils. Using data from the Japanese registry of dialysis patients, Nakai et al[24] investigated which mode of renal replacement therapy was more effective in the treatment of dialysis-related amyloidosis in 1,196 patients. Taking low-flow HD as a baseline, the risk of carpal tunnel syndrome was reduced by 51% for patients using high-flux HD, while it was 99% with on-line haemodiafiltration.

Intradialytic tolerance

Convective treatments are characterised by providing better cardiovascular stability, reducing intradialytic hypotension even in patients at high cardiovascular risk.[25] Donauer et al[26] described a reduction of hypotension side effects during treatment with online HDF and HD at low temperature. In some patients with severe hypotension, we have observed improvements in predialysis blood pressure with highly convective treatments (data unpublished).

Neurological complications

Insomnia, irritability, restless leg syndrome, polyneuropathy or itching may be due to the accumulation of medium-sized or large molecules. High-volume HDF replacement improves these symptoms due to improved clearance.[27,28]

DOES HAEMODIAFILTRATION IMPROVE SURVIVAL?

En 2005, Rabindranath et al[29] conducted a meta-analysis of HD, HDF and Acetate-Free Biofiltration (AFB) and found no significant differences between them. However, even if it is a systematic review, this work does not confront the reality of the problem, as in the end they only included 19 studies with a total of 588 patients. Of these patients, 205 (35%) were from the Locatelli study published in 1996 with a short follow-up that compared low-flux HD with high-flux HD (whether or not HDF techniques were used). If the patients who received HDF with more than 15 litres of replacement volume are included, the number drops to below 50. Comparing 588 patients who received a mixture of low-flux HD, high-flux HD, HDF with less than 15 litres of replacement fluid (some with AFB) and HDF with more than 15 litres, without differentiating the infusion mode (dilutional or post-dilutional), does not seem appropriate from a methodological point of view. Also, the follow-up period, ranging from one session to a year in 84% of the studies, does not seem adequate.

We have already commented that there are two large multicentre observational studies, adjusted for confounding demographic and comorbidity factors, which show a 35% reduction in mortality for patients receiving haemodiafiltration with more than 15 litres of replacement fluid.[4,5] Being retrospective and non-randomised studies, they may not provide the degree of evidence required to be sure that this treatment is superior to HD. More recently, the prospective observational study RISCAVID[30] also showed a reduction in mortality for patients receiving on-line HDF compared with patients receiving HDF with replacement bags, which was even more significant when compared with those receiving HD.

Santoro et al[31] recently published a randomised study which concluded that patients who received HDF had improved survival over the HD group. The main limitations of this study were the total number of patients (n = 64) and the fact that it was held in a single centre.

There are currently several multicentre, prospective randomised studies in progress which may help us to analyse whether the convective techniques are superior to HD or not. However, it should be borne in mind that each has a different design. They are discussed below:

Italian multicentre study.[32] The aim was to include 246 patients, 50% with low-flux HD, 25% with on-line HDF with dilutional infusion and 25% with dilutional HF. A follow-up period of over 2 years has been proposed.

The Dutch Convective Transport Study (CONTRAST).[33] Published in 2005, it aims to include 800 patients, 50% on low-flow HD, and 50% with on-line HDF with post-dilutional infusion. The monitoring period is 3 years and the primary objective is survival.

French multicentre study.[34] The aim was to include 600 patients over 65 years of age, 50% with high-flux HD and 50% with on-line HDF with post-dilutional infusion. The monitoring period is 2 years and the primary purpose is intradialytic tolerance.

A Catalan multicentre study of survival using on-line HDF (ESHOL). This is as yet unpublished and includes more than 900 patients, 50% with high-flux HD and 50% with on-line HDF with post-dilutional infusion. With a follow-up period of 3 years, the primary objective is survival.

IS IT TIME TO CHANGE FROM DIFFUSION TECHNIQUES ONLY TO CONVECTION?

For all the reasons given in this review, we conclude that now is the time to change to convective techniques. Firstly, because technological development in water treatment and advances in monitors, as well as the widespread use of synthetic high-flux dialysers make this a feasible proposition. In fact, the latest generation monitors, known as therapeutic systems, are designed to work under convective conditions at all times using the dialysis fluid itself as replacement solution. And secondly, because we have listed the possible clinical benefits these treatments can provide and have found no published literature showing any undesirable effects. However, we are awaiting the results from the multicentre studies to provide increased scientific evidence.

KEY CONCEPTS

1. **Convective techniques with high fluid replacement provide an optimum method of removing uraemic toxins and currently represent the renal replacement therapy most similar to the native kidney.**
2. **The delay in using convective techniques as a routine treatment is due to technological and economic developmental reasons.**
3. **The introduction of on-line HDF techniques has led to a revolution in haemodialysis units. More than 10 years has been required to improve water treatment methods and to have the required monitors available.**
4. **Clinical benefits that convective techniques can provide are control of the following: phosphorus, malnutrition, inflammation, anaemia, joint pain, amyloidosis associated with dialysis, intradialytic tolerance, insomnia, irritability, restless leg syndrome, polyneuropathy and itching.**
5. **Large multicentre observational studies, adjusted for confounding demographic and comorbidity factors, have shown a 35% reduction in mortality for patients receiving haemodiafiltration with more than 15 litres of fluid replacement.**
6. **Four multicentre prospective randomised studies are ongoing, with differences in the design, which could provide enough scientific evidence to show the superiority of convective techniques.**
7. **We conclude that the time is right to change to convective techniques. Technological developments achieved in water treatment and monitors, along with the widespread use of high-flux dialysers and potential clinical benefits mean such a change is highly recommended.**

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