
The relevance of convection in clinical practice: A critical review of the literature

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Abstract

Convective treatments (high-flux hemodialysis (HD), hemodiafiltration and hemofiltration) are characterized by enhanced removal of middle and large molecular weight solutes compared with conventional low-flux HD. As these molecules are claimed to play an important role in the genesis of many complications of chronic HD, the availability of these techniques represented an intriguing innovation and a possible means to improve the still poor prognosis of HD patients. Here we will critically review the most important published studies comparing convective treatments with low-flux HD on chronic morbidity, preservation of residual renal function, and long-term survival.

Key words: High-flux hemodialysis, hemodiafiltration, hemofiltration, biocompatibility, dialysis membranes

INTRODUCTION

Despite several technological advances achieved in hemodialysis (HD) over the last decades, along with slight improvements in both short-term and long-term adjusted survival of patients undergoing chronic HD,¹ mortality of HD patients is still significantly higher as compared with non-HD subjects with similar demographics. Cardiovascular diseases are the main causes of mortality and morbidity in HD patients,^{1–3} and they are already often present in the pre-HD period.^{1,4,5} However, survival, morbidity, and quality of life may also be worsened by HD-dependent complications or adverse effects. Therefore, improving the quality of the HD treatment should still represent 1 of the major goals in HD clinical practice. Although low-flux HD, making use of membranes with low-hydraulic permeability, is still the most widely used extra-corporeal treatment for end-stage renal disease, the availability of high-permeability membranes allowed the introduction of the so-called convective treatments in clinical practice (high-flux HD, hemodiafiltration and hemofiltration). These are characterized by enhanced removal of middle and large mo-

lecular weight solutes compared with “conventional” low-flux HD, because of more effective convection ensured by the use of dialyzers with high permeability for water. Given that middle and large molecules are claimed to play an important role in the genesis of many complications of chronic HD, convective treatments are therefore supposed to be clinically favorable over standard HD, at least from a theoretical point of view. However, evidence supporting the clinical superiority of these techniques is still lacking, and the analysis is made difficult by the relatively low number of well-designed randomized clinical trials so far performed. Another important aspect to be pointed out is that convective treatments are performed with highly biocompatible membranes, so that it is often hard to separate the effects of convection from those of biocompatibility. Here we will critically review the most important published studies comparing convective treatments with low-flux HD on chronic morbidity, preservation of residual renal function, and long-term survival.

INTRADIALYTIC CARDIOVASCULAR STABILITY

Hypotension and symptoms such as nausea, vomiting, and headache still complicate 20% to 30% of HD treatments.⁶ Despite the theoretical advantages of convective

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treatments on cardiovascular stability, clinical results have been rather disappointing so far. Besides uncontrolled evidence,⁷ a prospective randomized multicenter trial comparing treatments with different biocompatibility and permeability of membranes (cuprophan HD, low-permeability polysulfone HD, high-permeability polysulfone HD, high-permeability polysulfone hemodiafiltration) found no significant difference in treatment tolerance and cardiovascular stability among the 4 treatment groups over 24-month follow-up period.⁸ However, the lower incidence of hypotensive episodes than expected possibly led to a significantly beneficial effect, if any, being overlooked. Two prospective, nonrandomized, clinical trials^{9,10} compared the effects on patients' treatment tolerance of high-flux HD and online predilution hemofiltration, while using the same membrane (polyamide) and the same purity and electrolyte composition of dialysis fluids in order to minimize possible confounding effects of these factors: both studies showed that patients on hemofiltration rather than on high-flux HD significantly decreased the incidence of intradialytic hypotension. However, as previously reported for postdilution hemofiltration,¹¹ it has been recently demonstrated that even predilution hemofiltration is characterized by reduced sodium removal compared with HD,¹² thus providing at least partial explanation for the lower morbidity rates in predilution hemofiltration. Similar positive results on intradialytic cardiovascular tolerance by hemofiltration have been recently reported in comparison with hemodiafiltration also,¹³ but even in this case the fact that patients treated with hemofiltration underwent a slight but significant increase in predialysis mean arterial pressure levels during the study (98.4 vs. 93.8 mmHg, $p=0.037$) suggests that lower sodium removal might have occurred in these patients. Taken together, the available results therefore do not confirm that convection per se is able to decrease intradialytic cardiovascular stability in HD patients. Further studies, performed in larger populations of patients and taking into account all potential confounding factors, also including sodium removal, are therefore needed.¹⁴

β_2 -MICROGLOBULIN REMOVAL

Convective treatments are believed to more effectively counteract β_2 -microglobulin (β_2 -m) accumulation and subsequent deposition, not only because of higher removal, but also because of increased absorption of β_2 -m to high-permeability membranes and lower membrane-mediated inflammatory stimulation of β_2 -m synthesis. There are indeed several evidences of a more effective

removal of β_2 -m by convective treatments when compared with conventional low-flux HD.^{15,16} Although it is still to be clarified whether higher β_2 -m removal actually translates into some clinical benefit in the long term, several studies found that clinical manifestations of β_2 -m-derived amyloidosis occur less likely with convective treatments than with low-permeability cellulosic membranes.¹⁷⁻²² Some uncertainty however still remains as to whether the higher β_2 -m removal displayed by convective treatments when compared with conventional low-flux HD is the result of different membrane permeability per se or, rather, of other membrane and/or treatment characteristics. Interestingly, a retrospective analysis of patients treated with different membranes showed that both permeability characteristics and membrane biocompatibility were independent determinants of β_2 -m-derived amyloidosis clinical manifestations.²¹ However, in a recent study comparing online hemofiltration and hemodiafiltration, β_2 -m plasma levels significantly decreased during the 6 months run-in phase, when all studied patients underwent low-flux HD with a biocompatible (polyamide) membrane and ultrapure dialysis fluid, whereas they did not further decrease subsequently during the convective therapy.¹³ Although the latter result must be considered with particular caution, as the analysis of β_2 -m plasma levels was not one of the main objectives of the study, nevertheless, it raises the important question, to be addressed in future properly designed clinical trials, whether convective treatments are actually able to provide additional decrease in plasma β_2 -m concentration, once biocompatibility of the overall HD treatment (namely, membrane and dialysis fluids) is optimized to minimize β_2 -m generation.

MALNUTRITION

Convective treatments, because of the enhanced removal of higher molecular weight uremic toxins, are supposed to increase the well-being of the patients and, consequently, their protein and caloric intake; however, their ability to improve the poor nutritional status of HD patients is still a matter of debate. Indeed, it has been suggested that the use of biocompatible high-permeability membranes results in higher dietary protein intake (measured as protein catabolic rate) at every level of Kt/V,^{23,24} but the same finding has not been confirmed in another study,⁸ where no correlation was found between protein catabolic rate and membrane biocompatibility and permeability, although this result could be explained by the high levels of Kt/V delivered in this study. Other studies^{15,16} failed to demonstrate any major influence of

convective treatments on the time evolution of nutritional markers in HD patients, although such studies either were characterized by too short a follow-up period to detect a significant effect¹⁵ or dealt with relatively well-nourished patients,¹⁶ so that further clinical trials, with longer duration and involving sicker patients, should be planned.

ANEMIA

Several preliminary studies^{25–27} found that switching HD patients from conventional to highly permeable membranes, while maintaining the same dialysis dose, resulted in increased hematocrit levels and/or improved response to rhEPO, although all of these studies were affected by important methodological limitations. The same hypothesis was tested by Locatelli et al.¹⁵ in a multicenter, controlled, randomized trial: despite an increase in hemoglobin levels in the whole population of the study during the follow-up, no significant differences in this trend were found between the 2 randomization groups (BK-F polymethylmethacrylate vs. cellulose). Several possible explanations may have reduced the power of the study and could account for such deluding results: too short the period of observation, and positively selected patients (well nourished, with relatively not too low-hematocrit levels, without other known factors affecting uremic anemia and receiving adequate dialysis). These results, however, suggest that, when patients are highly selected, adequately dialyzed, and have no iron or vitamin depletion, the effect of high-permeability membranes is much less than could be expected from the results of uncontrolled studies. Online convective treatments have been recently suggested as potentially having a stronger effect on anemia correction compared with more conventional treatments, on the basis of some observational studies showing a significant increase in hemoglobin levels and/or reduction in rhEPO requirements.^{28,29} However, it can be postulated that the main factor accounting for the effect of online treatments on anemia correction is dialysate quality, rather than higher removal of medium and large molecular weight erythroid inhibitors achieved by these techniques. This hypothesis is suggested by the significant and sustained reduction of rh-EPO dose in patients switched from conventional bicarbonate HD (with potentially contaminated dialysate) to a similar treatment modality using online-produced ultrapure dialysate.³⁰ Furthermore, a randomized-controlled clinical trial¹⁶ showed that hematocrit levels and rhEPO dose did not differ between patients treated with low-flux HD and those undergoing online hemodiafiltration, when the

same ultrapure dialysate was used in both groups. In conclusion, the possibility that convective treatments, in particular online hemodiafiltration, may achieve a better control of anemia is intriguing. However, available results suggest that the same objective may be reached by using more conventional treatments, when careful attention is paid to the correction of all known factors possibly affecting anemia control and biocompatibility of the overall HD treatment is optimized.

RESIDUAL RENAL FUNCTION

Preserving residual renal function as long as possible is a major objective in HD patients, as there are several related advantages in terms of patients morbidity and quality of life: the need for lower dietary restriction and shorter dialysis treatment times, better removal of β_2 -microglobulin, and lower decrease in both erythropoietin and calcitriol synthesis by the failing kidney. However, the importance of membrane biocompatibility in preserving residual renal function has not been confirmed in some studies,^{31,32} and the results of studies demonstrating the superiority of high-permeability membranes are weak. Hartmann et al.³³ in a prospective, randomized trial involving 20 normotensive patients found that residual renal function was twice as high in patients treated with high-permeability polysulfone than in those treated with cellulosic membranes after 1 year of follow-up, but the small sample size of the study suggests caution in the interpretation of these results. More recently, in a retrospective analysis of 378 patients beginning dialysis in the same renal unit between 1990 and 1997, HD patients on high-permeability biocompatible membranes and ultrapure dialysate displayed a decline in residual renal function comparable with peritoneal dialysis,³⁴ but it is hard to attribute such positive results to the membrane permeability characteristics or to ultrapure dialysate.

MORTALITY

Several observational, retrospective studies found a significant association between convective treatments and reduced mortality among HD patients^{19,35–38} (Figure 1). Port et al.³⁸ reported a lower relative risk of death for synthetic membranes compared with other membranes and, among synthetic membranes, a lower relative risk of mortality for high- than low-permeability membranes, suggesting that besides biocompatibility the membrane permeability also may have independently contributed to the observed positive results on patient survival. However, results from nonretrospective studies have been

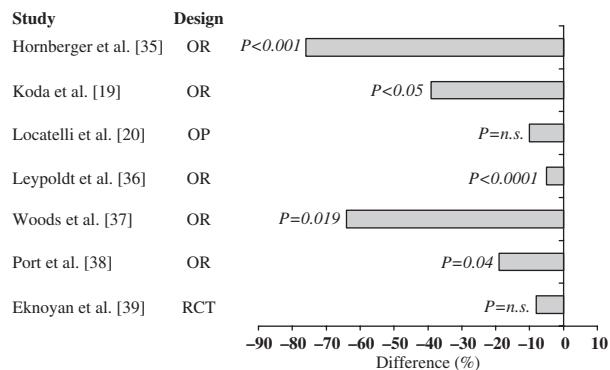


Figure 1 Percent difference in the risk of death in patients treated with convective treatments, as compared with patients treated with low-flux hemodialysis, in different clinical studies. OP = observational prospective; OR = observational retrospective; RCT = randomized clinical trial.

definitely more disappointing (Figure 1). The clinical trial by Locatelli et al.⁸ did not reveal any difference in survival related to membrane biocompatibility or permeability, although this study was not primarily designed to analyze survival. The Lombardy Registry Study,²⁰ which prospectively followed more than 6,000 patients starting an extracorporeal renal replacement treatment between 1983 and 1995, found that patients treated with hemodiafiltration or hemofiltration had a 10% lower adjusted relative risk of death compared with those treated with conventional HD, but this result was not statistically significant. Two large-scale randomized-controlled clinical trials have been designed to assess the effect of high-permeability membranes on patient survival: the Hemodialysis (HEMO) study in the United States, and the Membrane Permeability and ESRD Patient Outcome (MPO) study in Europe. The HEMO study, which enrolled 1,846 patients randomized to different membranes and different dialysis doses in a 2 × 2 factorial design, failed to demonstrate a significant benefit of high-permeability membranes, compared with low-permeability but similarly biocompatible membranes, on all-cause mortality.³⁹ Only when the analysis was limited to cardiac death or to patients who had been on dialysis for more than 3.7 years at the time of enrollment did it reveal significantly better survival in the high-permeability group.³⁹ Although clearly disappointing, the results of the HEMO study must be interpreted with caution, in light of some drawbacks. First of all, it excluded patients with low plasma albumin and higher body weight, i.e., those patients at highest risk for morbidity and mortality, who might have possibly benefited from high-permeability HD. Second, the mean age at inclusion was relatively

low (58 ± 14 years) and patients had already been on dialysis for an average of 3.7 years, further suggesting that positive selection occurred, and therefore rendering the study sample not representative of the entire HD population. Third, a carry-over effect could not be ruled out, as 60% of the patients were treated with high-permeability HD before enrollment; thus, at least some patients were shifted to low-permeability HD after a long treatment on high-permeability HD. Fourth, the reuse practice allowed by the protocol may have confounded the final results of the study, as the reprocessing procedure might have influenced the performance characteristics of the membranes. For all these reasons, doubts on the general applicability of these results are emerging, and the results of the MPO study are therefore awaited with much interest, in order to draw definitive conclusions. This prospective, randomized, clinical trial, which enrolled 744 patients between 1998 and 2003, and whose results will be available by 2006, has been specifically designed to evaluate the long-term effects of membrane permeability on clinical outcome and, unlike the HEMO study, enrolled only incident patients, without excluding high-risk patients, and not allowing reuse of dialyzers.⁴⁰

CONCLUSIONS

It is likely that the concept of HD adequacy, so far evaluated only in terms of urea removal, should be widened to also include medium and high molecules removal, as well as biocompatibility. In this context, the availability of the so-called convective treatments (high-permeability HD, hemodiafiltration, and hemofiltration), providing increased clearances of larger molecular weight solutes, represents an intriguing innovation in the field of HD and a possible means to improve the still poor prognosis of HD patients. In the past years, several observational studies showed that convective treatments indeed seem to reduce both morbidity and mortality of HD patients, but the results of prospective randomized-controlled trials, first of all the HEMO study, have been more conflicting and in many cases rather disappointing. Furthermore, many studies to date have not been able to separate the beneficial effects of convection from those of biocompatibility, so that a basic question still persists, namely whether convective treatments are superior to conventional low-permeability HD when the latter is performed optimizing the biocompatibility of the entire treatment through the use of low-permeability biocompatible synthetic membranes and ultrapure dialysis fluids. For these reasons, results of large-scale, well-designed clinical trials, such as the MPO study, are needed to draw definitive

conclusions about the ability of convective treatments to improve the clinical outcome of HD patients.

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