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Critical review

Treatment

Improvement of all-cause mortality with high-efficiency post-dilution online haemodiafiltration: Is this standard care for ESRD patients?

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Abstract

Introduction

Renewed interest in convective renal replacement therapy is fuelled by the desire to reduce high mortality of current maintenance dialysis patients. Although encouraging data have been obtained from retrospective analyses or prospective cohort studies, widespread implementation of online haemodiafiltration has been hampered by lack of conclusive evidence of improved survival compared to haemodialysis. This review discusses standard care for end-stage renal disease patients.

Discussion

Recently, three large randomised trials have been published which compared online haemodiafiltration to high- or low-flux haemodialysis. Primary analysis from ESHOL trial and secondary analyses from the Convective Transport Study and the Turkish Online Haemodiafiltration study found that high convective volumes confer a survival benefit to haemodiafiltration patients. However, the evidence from these three studies is not unanimous and each of these trials has been criticised for selection bias or violation of the study protocol. Moreover, it is not clear why some patients who were randomised to high-volume online haemodiafiltration were able to achieve high convection volumes and others were not. Confounding factors for patient selection may have been differences in vascular access or cardiac function determining whether patients could achieve high convection volumes rather than the prescribed protocol. Thus, it is plausible that better survival rates in those with better vascular access simply reflect 'healthier' patients.

A consistent theme that emerges from all three trials is that actual replacement volume seems to matter. Higher volumes were associated with better survival. Mechanisms underlying reduction of all-cause mortality remain obscure, but may involve better removal of uraemic toxins, less systemic inflammation and a lower number of intradialytic hypotensive episodes.

Conclusion

In future, online haemodiafiltration will be frequently used. However, there is an urgent need to define the required minimum/optimal convection volumes (expressed as litres per body weight or per surface) in end-stage renal disease patients who are eligible for online haemodiafiltration by well-designed trials.

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Introduction

Current maintenance dialysis practice patterns (three times per week, single-pool K_t/V_{urea} of 1.2) effectively prevent death of end-stage renal disease (ESRD) patients from uraemia. Numerous advancements in dialysis technology and improvements in patient care have helped ESRD patients to live better with their disease and allowed elderly frail patients to be treated. However, mortality remains an important issue. The expected remaining life span of an incident haemodialysis patient is 18 years for a 25–29-year-old patient on renal replacement therapy (RRT), approximately 8 years for a dialysis patient aged 40–44 years; 4.5 years for those aged 60–64 years, and 3 years for patient population aged 75 years or more. Survival of aged dialysis patients is slightly better when compared to survival in patients with lung cancer or colorectal cancer[1,2].

Conventional haemodialysis procedures do not perfectly reproduce normal excretory renal function. Low-flux haemodialysis membranes clear small water-soluble solutes from the body efficiently by diffusion. Removal of other compounds is, however, limited due to middle or large molecular size, protein binding or sequestration within body compartments. Retention of middle- to large-sized organic solutes, incompletely corrected inorganic ion disturbances and aggravation of low-grade systemic inflammation (so called residual uraemic syndrome) in patients undergoing conventional dialysis (low-flux membrane, commercial dialysis fluid) contribute to high morbidity and mortality of standard dialysis patients. Partial removal of toxic substances by high-flux membranes[3,4] has been shown to improve outcomes, at least in patients with hypoalbuminaemia or diabetes, or patients who have been on haemodialysis for a long period (3.7 years).

The desire to further improve outcomes of dialysis patients by

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enhanced removal of middle- to large-sized uraemic toxins fuelled renewed interest in combining convective and diffusive therapies (haemodiafiltration). The aim of this review is to discuss if high-efficiency post-dilution online haemodiafiltration improves all-cause mortality.

Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Definition of high-efficiency post-dilution OL-HDF

Online haemodiafiltration (OL-HDF) is the currently available most advanced convective technique. It represents a safe and cost-effective mode of RRT. In Europe, 18% of patients receiving extracorporeal RRT in 2011 were treated with OL-HDF. In selected countries such as Switzerland, Slovenia and Slovakia, over 60% of patients were treated with OL-HDF[5]. The growth in the prescription of OL-HDF is attributable to a number of clinical benefits, such as (a) enhanced removal of uraemic toxins; (b) reduced inflammation and oxidative stress, (c) lower incidence of intradialytic hypotensive episodes; and (d) better patient well-being and quality of life[6]. The widespread implementation of this technique, however, has been hampered by lack of conclusive evidence of lower mortality from randomised trials or by lack of approval of online creation of substitution fluid by the US regulatory agency.

Definition of HDF by the European Dialysis Working Group (EUDIAL) of the European Renal Association – European Dialysis Transplantation Association (ERA-EDTA)

HDF is a blood purification therapy combing diffusive and convective solute transport using high-flux membranes characterised by an ultrafiltration coefficient >20 ml/h/mmHg/m^2 and a sieving coefficient β_2-microglobulin >0.6. Convective transport is achieved by an effective convection volume of at least 20% of the total blood volume processed. Appropriate fluid balance is maintained by external infusion of an ultrapure, non-pyrogenic solution into the patient's blood[7].

Various modes of HDF, which differ by the site of replacement fluid infusion, are used worldwide; they are post-dilution, pre-dilution, mid-dilution and mixed-dilution HDF.

Post-dilution HDF represents the most efficient mode of HDF for clearing middle and large molecular-weight uraemic substances. However, successful post-dilution OL-HDF depends on high extracorporeal blood flow rates (>350 ml/min), reliable vascular access (an arteriovenous fistula with a flow rate of >600 ml/min), the ability to achieve adequate anticoagulation throughout the session and absence of increased blood viscosity (high haematocrit, cryoglobulinaemia and gammopathies)[8].

The EUDIAL group recommends quantification of HDF by using the effective convection volume normalised to a body size-related factor as a surrogate for the convective dose. In post-dilution HDF, the effective convection volume is equal to the total volume that is ultrafiltered, including weight loss. The Dialysis Outcomes and Practice Patterns Study (DOPPS) study defined high-volume or high–efficiency post-dilution OL-HDF as a treatment with substitution volumes over 15 l/session[9]. Today, it may be more appropriate to assume that the threshold of total convective volume should be in the range of 22–24 l/session to reduce mortality of ESRD patients significantly.

Reduction of mortality in ESRD patients with high-efficiency post-dilution OL-HDF: results from recent randomised controlled trials

The collective body of evidence obtained from prospective observational studies or retrospective analyses points towards a survival benefit for ESRD patients undergoing OL-HDF compared to patients maintained either on low-flux or high-flux dialysis. However, early prospective randomised controlled trials (RCTs) were inconclusive. These mostly small studies were either not designed to investigate mortality as an endpoint or did not reach statistical significance. Recently, three large-scale trials—the Convective Transport Study (CONTRAST)[10], the Turkish HDF study[11] and the ESHOL study[12]—analysed the potential impact of high-substitution volume on reduction of mortality of ESRD patients.

The investigators of the CONTRAST trial randomly assigned 714 prevalent (>2 years) haemodialysis patients to online post-dilution HDF or to continued low-flux haemodialysis. The arbitrary planned target volume was 24 l/treatment (6 L/h). The average convection volume, which included weight loss, was only 20.7 L/HDF treatment session. After a mean follow-up of 3 years, the investigators did not detect any beneficial effect of OL-HDF on all-cause mortality (primary outcome) or on fatal or non-fatal cardiovascular events (secondary endpoints). The *post hoc* analysis found that mortality of HDF patients with the highest delivered convection volume (upper tertile >21. 95 L/session) was considerably lower than in patients who were randomised to low-flux haemodialysis[10].

In the Turkish OL-HDF study, 782 prevalent haemodialysis patients

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were randomly assigned to either post-dilution HDF or high-flux haemodialysis. The follow-up period was 2 years, and the mean substitution volume was 17.2 L (13.5–20.0 L)/session. Neither the all-cause mortality rate nor the non-fatal cardiovascular rate was found to be different in the OL-HDF group and in the high-flux group. In a *post hoc* analysis, OL-HDF with substitution volume >17.4 L/session was associated with better cardiovascular and overall survival[11].

The Catalonian investigators assigned 906 chronic haemodialysis patients either to continuous high-flux haemodialysis or to switch to high-efficiency post-dilution OL-HDF. The mean follow-up was 1.9 years. The median replacement volume and the convective volume in OL-HDF patients ranged from 20.8 to 21.8 L/session and 22.9–23.9 L/session, respectively. Compared with patients who continued high-flux haemodialysis, patients assigned to OL-HDF had a 30% lower risk of all-cause mortality, a 33% lower risk of cardiovascular mortality and a 55% lower risk of infection-related mortality. Intradialytic hypotension complicating sessions and all-cause hospitalisations were observed less frequently in patients who had received HDF.

Limitations of recently published trials

Although the CONTRAST, the Turkish OL-HDF and the ESHOL studies were RCTs, all three studies present some significant pitfalls that reduce the strength of evidence of the conclusions.

The important concern is whether high-convection volumes can be achieved in the majority of patients in everyday clinical practice.

In ESHOL study, in order to consider the general applicability, it would be interesting to know the number of patients screened in order to select the 939 participants. Astonishingly, more than 90% of the participating OL-HDF patients achieved the targeted convection volume. However, almost 30% of the participating patients terminated the study prematurely. Fifty patients who were on OL-HDF, but no patients on high-flux HD dropped out because of vascular access problems. In the Turkish HDF study, 40 patients of the OL-HDF group terminated the study early due to vascular access problems, mainly the insufficient blood flow rate. In the CONTRAST study, ultrafiltration volumes of 20–24 L/session were achieved only in one-third of the patients. There were large variations of ultrafiltration volumes from centre to centre underscoring the gap between HDF prescription and delivery (13–22 L/session). In theory, both patient-related and technique-associated factors may reduce the prescribed ultrafiltration rate. For a fixed treatment duration time, ultrafiltration volumes rely on poor blood flow, high albumin and high hematocrit. In the Turkish study, the substitution volume ranged from 13.5 to 20 L, but 96.7% of the patients were treated with more than 15 litres of replacement volume per session (target volume). There is no doubt that inadequate achievement of target ultrafiltration volume represents a severe protocol violation that may invalidate primary objectives of the CONTRAST study. It is not clear why some patients who were randomised to high-volume post-dilution OL-HDF were able to achieve target convection volumes, but others were not. Confounding factors for patient selection may have been differences in vascular access or cardiac function determining whether patients could achieve high convection volumes rather than the prescribed protocol. Thus, it is plausible that better survival rates in those with better vascular access simply reflect "healthier" patients.

Unfortunately, in ESHOL study, patients who were randomised to OL-HDF were younger, more often men, very few patients had diabetes mellitus, a higher percentage of patients were using a fistula and a few were using catheters, and they had a lower comorbidity index than patients who were assigned randomly to high-flux HD. Of clinical relevance, more patients in the OL-HDF group underwent renal transplantation. They were censored at transplantation and by definition they were survivors until transplantation. Blood flow and dialysate flow rates were significantly lower in the high-flux group of the ESHOL trial, and these patients had significantly lower K_t/V_{urea} values. These differences in baseline characteristics may have influenced group differences with respect to survival.

High-efficiency post-dilution HDF improves survival: putative mechanisms

Recent RCTs suggest that high-convection volumes confer a survival benefit for HDF patients over haemodialysis patients. A trial reached this conclusion based on the primary analysis of the endpoints and two trials concluded based on *post hoc* analyses. They reinforced the concept of a convective dose–survival relationship as proposed by the DOPPS investigators. The threshold total convective volume remains unknown to bring a significant survival effect to ESRD patients, but it should be at least 22–24 L/session. It is not clear whether the convective volume dose should be tailored to individual patients needs and expressed as litres per kg or per body surface area.

The mechanisms through which high convection volumes reduce mortality from cardiovascular or infectious disorders remain elusive. It is not clearly understood whether the benefits of high-efficiency HDF on patient survival partly depend on higher clearance of toxic uraemic molecules, less systemic

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inflammation and/or lower episodes of intradialytic hypotension. β_2-microglobulin seems to be one of the most representative and clinically relevant uraemic toxins and it is strongly implicated in morbidity and mortality of ESRD patients. Our prospective randomised crossover investigations have clearly shown that high-efficiency OL-HDF is associated with lower time averaged concentrations of β_2-microglobulin[13]. In the ESHOL study, the plasma levels of β_2-microglobulin increased significantly, probably due to the loss of residual renal function[12]. In comparison, the β_2-microglobulin levels in the Turkish OL-HDF were unchanged in both the treatment groups[11]; whereas in the CONTRAST study, β_2-microglobulin level decreased through HDF as expected because prior dialysis treatment in this study was performed with impermeable low-flux membranes[10]. Threshold concentration of β_2-microglobulin cannot be established as a risk reference indicator without measuring residual renal function during HDF for ESRD patients receiving renal replacement therapy.

Conclusion

Current renal replacement therapies of ESRD should not be considered as competing therapeutic options, rather as complementary methods of dealing with uraemia. Each modality has its own unique advantages and disadvantages; and at the same time, all modalities share problems. Neither one is the best suited for all patients.

Ideally, patients treated with high-volume convective modalities, such as high-efficiency OL-HDF, require a vascular access capable of delivering a blood flow rate between 350 and 400 ml/min or higher consistently. Vascular access flow rate plays a fundamental role in removing middle molecules and the advantages of higher convective volumes are strongly limited by inadequate vascular access. As the number of older patients and patients with diabetes mellitus or hypertensive nephrosclerosis is increasing both in the incident or prevalent dialysis populations, it is anticipated that not all ESRD patients may have an ideal vascular access for high-efficiency OL-HDF.

Recently conducted RCTs provided encouraging data that high-efficiency post-dilution OL-HDF results in higher survival, less morbidity and better quality of life in ESRD patients. These results may vary in clinical practice. High-efficiency OL-HDF will be used more often.

The volume of ultrafiltration seems to be the key performance factor of the best clinical HDF practice. To confirm and add more details to the results of published RCTs, properly designed trials relating various levels of convective volumes to clinical endpoints seem to be the only appropriate way to define the minimal and/or optimal convective dose of OL-HDF.

Abbreviations list

CONTRAST, Convective Transport Study; ESRD, end-stage renal disease; EUDIAL, European Dialysis Working Group; OL-HDF, online haemodiafiltration; RCT, randomised controlled trials.

References

1. Collins AJ, Foley RN, Herzog C, Chavers BM, Gilbertson D, Ishani A, et al. Excerpts from the US Renal Data System 2009 Annual Data Report. Am J Kidney Dis. 2010 Jan;55(Suppl 1):S1–420, A6–7.
2. Steenkamp R, Shaw C, Feest T. UK Renal Registry 15th Annual Report: Chapter 5 Survival and Causes of Death of UK Adult Patients on Renal Replacement Therapy in 2011: National and Centre-Specific Analyses. Nephron Clin Pract. 2013 Jun;123(Suppl 1):93–123.
3. Locatelli F, Martin-Malo A, Hannedouche T, Loureiro A, Papadimitriou M, Wizemann V, et al. Effect of membrane permeability on survival of haemodialysis patients. J Am Soc Nephrol. 2009 Mar;20(3):645–54.
4. Delmez JA, Yan G, Bailey J, Beck GJ, Beddhu S, Cheung AK, et al. Cerebrovascular disease in maintenance haemodialysis patients: results of the HEMO Study. Am J Kidney Dis. 2006 Jan;47(1):131–8.
5. Bowry SK, Canaud B. Achieving high convective volumes in on-line hemodiafiltration. Blood Purif. 2013 Feb;35(Suppl 1):23–8.
6. Schmid H, Schiffl H. Hemodiafiltration and survival of end-stage renal disease patients: the long journey goes on. Int Urol Nephrol. 2012 Oct;44(5):1435–40.
7. Tattersall JE, Ward RA; EUDIAL group. Online haemodiafiltration: definition, dose quantification and safety revisited. Nephrol Dial Transplant. 2013 Mar;28(3):542–50.
8. Penne EL, van der Weerd NC, Bots ML, van den Dorpel MA, Grooteman MP, Levesque R, et al. Patient- and treatment-related determinants of convective volume in post-dilution haemodiafiltration in clinical practice. Nephrol Dial Transplant. 2009 Nov;24(11):3493–9.
9. Canaud B, Bragg-Gresham JL, Marshall MR, Desmeules S, Gillespie BW, Depner T, et al. Mortality risk for patients receiving hemodiafiltration versus haemodialysis: European results from the DOPPS. Kidney Int. 2006 Jun;69(11):2087–93.
10. Grooteman MP, van den Dorpel MA, Bots ML, Penne EL, van der Weerd NC, Mazairac AH, et al. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. J Am Soc Nephrol. 2012 Jun;23(6):1087–96.
11. Ok E, Asci G, Toz H, Ok ES, Kircelli F, Yilmaz M, et al. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. Nephrol Dial Transplant. 2013 Jan;28(1):192–202.
12. Maduell F, Moreso F, Pons M, Ramos R, Mora-Macià J, Carreras J, et al. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in haemodialysis patients. J Am Soc Nephrol. 2013 Feb;24(3):487–97.
13. Schiffl H. Prospective randomized cross-over long-term comparison of online haemodiafiltration and ultrapure high-flux haemodialysis. Eur J Med Res. 2007 Jan;12(1):26–33.

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