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High convection volume in online post-dilution haemodiafiltration: relevance, safety and costs

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Abstract

Increasing evidence suggests that treatment with online post-dilution haemodiafiltration (HDF) improves clinical outcome in patients with end-stage kidney disease, if compared with haemodialysis (HD). Although the primary analyses of three large randomized controlled trials (RCTs) showed inconclusive results, *post hoc* analyses of these and previous observational studies comparing online post-dilution HDF with HD showed that the risk of overall and cardiovascular mortality is lowest in patients who are treated with high-volume HDF. As such, the magnitude of the convection volume seems crucial and can be considered as the 'dose' of HDF. In this narrative review, the relevance of high convection volume in online post-dilution HDF is discussed. In addition, we briefly touch upon some safety and cost issues.

Key words: convection volume, costs, hemodiafiltration, mortality, safety

EuDial objective

The general objective of the European Dialysis (EuDial) Working Group of the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) is to enhance the quality of dialysis therapies in Europe in the broadest possible sense. Given the increasing interest in convective therapies, the Working Group has started by focusing on haemodiafiltration (HDF) therapies. A EuDial consensus conference was held in Paris on 13 October 2011 to discuss definitions, safety standards, clinical outcome and educational issues. Since then, two reports of the EUDIAL group have been published. While the first report revisited the definition, dose quantification and safety of HDF [1], the second report described the relation between HDF and clinical outcome in a systematical review and meta-analysis [2]. This report contains a concise appraisal of the relevance of high-volume HDF as well as some safety and cost aspects.

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Introduction

Despite increasing knowledge of the uraemic syndrome, both morbidity and mortality remain unacceptably high in patients with end-stage kidney disease (ESKD) [3]. Enhancing the removal of middle-molecular weight (MMW) substances may improve prognosis, since their retention has been implicated in this condition. MMW substances are not readily cleared by diffusion, which is the main elimination mechanism in low-flux haemodialysis (HD), but by convection as occurs in haemofiltration (HF). In haemodiafiltration (HDF), diffusion is combined with convection [4]. In modern HDF, fluid balance is maintained by the infusion of 'online' prepared substitution fluid, which can be administered before the dialyser (pre-dilution), midway (mid-dilution) or after the dialyser (post-dilution).

Since the vast majority of publications on HDF and clinical outcome concern online post-dilution HDF, this review is mainly focused on this type of treatment. First, we will describe the available evidence on the relationship between the magnitude of the convection volume and clinical outcome. Subsequently, we will pay attention to some safety and cost issues of HDF treatment. Finally, we will define some of the key questions that still need to be addressed in this field.

Why should we try to increase the convection volume?

Many studies have been performed comparing HDF and HD with respect to effects on biomarkers and surrogate clinical parameters. More relevant, however, are studies that investigated clinical outcomes, such as overall and cardiovascular mortality [2]. In this review, we will pay special attention to those studies that reported not only clinical outcome but also its relation with the magnitude of the convection volume of HDF treatment.

From the results of four observational studies, the Dialysis Outcome Practice and Patterns Study (DOPPS) [5], the RISchio CArdiovascolaare nei pazienti afferenti all'Area Vasta In Dialisi (RISCAVID) study [6], analysis from the European Clinical Database (EUCLID) [7] and a study by Imamovic *et al.* [8], it appeared that treatment with high-volume HDF (DOPPS, substitution fluid >15 L/session; RISCAVID, substitution fluid 23 ± 3 L/session; EUCLID, mean convection volume 22.2 L; Imamovic *et al.*, substitution fluid >20.4 L/session) was associated with a significantly reduced mortality risk in both prevalent and incident ESKD patients, when compared with HD. For prevalent ESKD patients, RR of HDF versus HD was 0.65 ($P = 0.008$) in DOPPS, 0.78 ($P = 0.01$) in RISCAVID and 0.67 ($P = 0.03$) in EUCLID. For incident ESKD patients, treatment with HDF resulted in a RR of 0.24 ($P < 0.001$) in EUCLID and 0.29 ($P = 0.002$) in the study by Imamovic *et al.*, when compared with patients treated with HD. As in DOPPS, RISCAVID and the study from Imamovic *et al.*, net ultrafiltration (UF) during HDF was not taken into account and the convection volumes in these studies were definitively higher. Of note, as in any observational study, causal relations cannot be drawn from these analyses as residual confounding cannot be excluded. Furthermore, allocation or selection bias may be an issue as well.

Recently, the results of three large RCTs, the CONvective TRAnsport STudy (CONTRAST, $n = 714$), the Turkish HDF Study (THDFS, $n = 782$) and the Estudio de Supervivencia de Haemodiafiltracion On-Line (ESHOL, $n = 906$), were published. All three RCTs compared online post-dilution HDF with HD in terms of overall mortality risks and cardiovascular events [9–11]. In the primary analyses, neither CONTRAST nor THDFS found a difference between HD and HDF. However, in ESHOL, the RCT with the highest mean convection volume achieved a significant decrease in mortality risk for HDF was observed. Importantly, while in CONTRAST, follow-up for the primary endpoint was complete, both the analyses from THDFS and ESHOL suffered from censoring alive [i.e. left the study for other reasons than death or end of the study ($n = 160$ and $n = 355$, respectively)]. *Post hoc* analyses of all three RCTS demonstrated a survival benefit for HDF patients who reached the highest convection volumes per session [THDFS: >19.5 L/treatment (HR 0.54; 95% CI 0.31–01.93) [11]; CONTRAST: >21.95 L/treatment (HR 0.61; 95% CI 0.38–0.98) [10]; ESHOL: 23.1–25.5 L/treatment (HR 0.60; 95% CI 0.39–0.90) and >25.4 L/treatment (HR 0.55; 95% CI 0.34–0.84)], if compared with HD [9]. Naturally, these *post hoc* analyses should be viewed as observational cohort studies, in which residual confounding may remain. In this respect, it should be mentioned, however, that centre policy, such as fixed treatment times and blood flow rates, rather than patient characteristics appears to determine the magnitude of the convection volume [12]. The various relationships between convection volume and mortality risk are summarized in Table 1. As can be seen from the studies included in this table, currently there is no strict lower threshold needed to reduce mortality risk nor an upper limit above which no further benefit can be obtained. Nevertheless, it appears that HDF with a convection volume of >20–22 L/treatment is consistently associated with a beneficial clinical effect over HD [13, 14]. Whether the convection volume should be normalized for body mass index or body surface area remains to be established [1]. In CONTRAST, the influence of body size on the magnitude of the convection volume was only limited, which, however, may well be the result of fixed treatment times in participating centres, irrespective of patient characteristics.

What are the methodological issues of the RCTs that need to be addressed?

Some methodological issues of the three large RCTs need to be discussed. In all three RCTs, at baseline almost similar inclusion and exclusion criteria were used for potential participants with respect to age, dialysis adequacy and use of central venous catheters. However, as patients with a relatively short life expectancy and serious comorbidity were excluded in all three studies, it is possible that participants had a relatively good prognosis when compared with patients who were not admitted to the study. As such, it is debateable whether the results from these RCTs can be extrapolated to subjects who do not meet all inclusion criteria. Since exclusion took place before randomization, however, it is unlikely that upfront selection influenced outcome parameters between HD and HDF patients. Yet, during follow-up, some important issues are to be noted. First, patients randomized to HDF who did not reach a convection volume of ≥18 L/session during the run-in phase were still excluded from participation in ESHOL. Second, both in ESHOL and THDFS, a substantial number of patients was censored alive, mostly due to renal transplantation or moving to a non-participating centre, which may have influenced the results in case of an unequal distribution between the HD and the HDF groups. Third, despite randomization, in ESHOL, the number of HD patients with a catheter was almost twice that of HDF patients (59 versus 34 patients). Fourth, ultrapure dialysis fluid was used in both study arms in CONTRAST and ESHOL, whereas in THDFS, the HD group was treated with standard dialysis fluid. Lastly, as already mentioned, *post hoc* analyses from these studies should be viewed as observational, in which residual confounding may remain, even after extensive correction.

Table 1. Mortality rates in randomized controlled trials and observational studies stratified and arranged by convection volumes, on-treatment analyses

Reference	CV# (L/treatment)[a]	SV## (L/treatment)[b]	IDWL (L/treatment)	HR	95% CI of HR
ESHOL[c]	<23.1			0.90	0.61–1.31
2013 [9]	23.1–25.4			0.60	0.39–0.90
	>25.4			0.55	0.34–0.84
Turkish HDF study[d]	18.8	16.2	2.6	1.10	0.68–1.76
2013 [11]	20.3	18.1	2.2	0.54	0.31–0.93
CONTRAST[c]	<18.18			0.80	0.52–1.24
2012 [10]	18.18–21.95			0.84	0.54–1.29
	>21.95			0.61	0.38–0.98
RISCAVID[e]		14		0.69	
2008 [6]		23		0.46	
DOPPS		5.0–14.9		0.93	
2006 [5]		15.0–24.9		0.65	
EUCLID 2015 [7]	22.2	19.9		0.62	0.42–0.93
Imamovic *et al.*[d]		<20.4		0.84	0.46–1.53
2014		>20.4		0.29	0.13–0.68

[a]Sum of the intradialytic weight loss and the amount of substitution fluid.
[b]The amount of fluid infused into the bloodstream to compensate for water and solute movement from the blood to the dialysate.
[c]In ESHOL and CONTRAST, survival risks were reported by tertiles of convection volume (CV).
[d]In the Turkish HDF study and Imamovic *et al.*, survival risks were reported for patients above and below the median SV (17.6 L).
[e]In RISCAVID, 'Relative Risks' (and not HRs) are reported for offline HDF treatment (mean SV 14 L) and online HDF (mean SV 23 L).
CI, confidence interval; CONTRAST, CONvective TRAnsport STudy; CV, convection volume (SV + net ultrafiltration); DOPPS, Dialysis Outcomes and Practice Patterns Study; ESHOL, Estudio de Supervivencia de Haemodiafiltration On-Line; HDF, Haemodiafiltration; HR, hazard ratio; IDWL, interdialytic weight loss; RISCAVID, RISchio CArdiovascolare nei pazienti afferenti all' Area Vasta In Dialisi; EUCLID, European CLInical Database; SV, substitution volume.

Table 2. Summary of intervention and comparator arms in recent meta-analyses that compared convective therapies with diffusive therapies

Meta-analysis	Intervention arm	Comparator arm
Susantitaphong *et al.* [15]	- Haemodiafiltration - Haemofiltration - High-flux haemodialysis	- Low-flux haemodialysis
Wang *et al.* [16]	- Post-dilution haemodiafiltration - Pre-dilution haemodiafiltration - Paired online haemodiafiltration - Haemofiltration - Acetate-free biofiltration	- Low-flux haemodialysis - High-flux haemodialysis
Nistor *et al.* [17]	- Online haemodiafiltration - Offline haemodiafiltration - Haemofiltration - Acetate-free biofiltration	- Low-flux haemodialysis - High-flux haemodialysis
Mostovaya *et al.* [2]	- Online post-dilution haemodiafiltration - Offline post-dilution haemodiafiltration - Pre-dilution haemodiafiltration	- Low-flux haemodialysis - High-flux haemodialysis

What did meta-analyses on convective therapies tell us?

To further elucidate the question whether convective therapies have a beneficial effect over diffusive therapies with regard to clinical outcomes, in the last 2 years, four meta-analyses have been performed which showed inconclusive results [15]. However, both the intervention groups and the comparator therapy included in these meta-analyses were highly different, as is shown in Table 2. Actually, three out of these four meta-analyses included low-volume convective therapies (i.e. generally <10 L/session), such as high-flux HD, *offline* HDF or acetate-free biofiltration in the intervention arm [15–17]. Consequently, these investigations compared a mixture of low- and higher volume convective therapies with HD. As described earlier, the magnitude of the convection volume appears crucial for the effect of HDF on clinical outcome. Therefore, in our opinion, only high-volume online post-dilution HDF should be regarded as a modern clinically effective convective therapy [18]. The fourth meta-analysis included six RCTs comparing HDF with HD, out of which five reported the magnitude of the convection volume. This meta-analysis clearly showed a beneficial effect of HDF on both all-cause and cardiovascular mortality [HR 0.84 (95% CI 0.73–0.96) and 0.73 (95% CI 0.57–0.92), respectively] [2]. Taken together, the available evidence suggests a favourable effect of online post-dilution HDF on clinical outcome, if the convection volume achieved amounts to 20 L/session or more.

Is haemodiafiltration a safe treatment?

As the infusion of large amounts of online-produced substitution fluid is necessary to compensate for the convection volume that is removed during HDF, microbiological and chemical purity is of utmost importance and should be sufficiently guaranteed. On the one hand, it is conceivable that episodic contamination may induce an inflammatory reaction in these individuals. On the other hand, however, removal of MMW acute-phase proteins, such as interleukin-6 (IL-6) and tumour-necrosis-factor α (TNFα), by convection may reduce the chronic micro-inflammatory state that is commonly observed in ESKD patients [19]. Although the three recently published RCTs were not specifically designed to evaluate safety, no indication whatsoever was obtained that HDF is an unsafe treatment modality. In an analysis of >11 000 treatment sessions, CONTRAST investigators reported that it is possible to produce high-quality substitution fluid over a prolonged period of time [20]. Moreover, although both treatment arms showed an increase in both C-reactive protein and IL-6 values during follow-up, the rise was least pronounced in HDF patients [21]. Altogether, there seems to be no indication that by infusing large amounts of fluid, a chronic inflammatory state is induced. If anything, it is the contrary. Finally, in ESHOL, the study with the highest mean convection volume, mortality risk due to infectious complications was considerably lower in the HDF group than that in HD patients [HR 0.45 (95% CI 0.21–0.96)] [9].

As HDF is an unselective process, the question arises as to whether the combination of a large pore high-flux dialyser and high trans-membrane pressure, needed to produce large convection volumes, leads to undesirable losses of albumin and other nutrients [22, 23]. Indeed, in THDFS, albumin levels were lower in HDF than those in HD patients [11]. However, neither CONTRAST [21, 24], nor ESHOL [9], nor a large recent observational study [25], could confirm these findings. Of note, in ESHOL, the RCT with the largest convection volume, albumin levels decreased equally over time in both study arms. Obviously, other factors, such as progressive wasting and inflammation in long-term dialysis patients, may play an important role in this respect [26]. With respect to the (micro)nutrients vitamin B12, folate, zinc and selenium, no differences were found in a small follow-up study between HD and HDF, although the average concentrations of both zinc and selenium were low in both modalities [27]. Others found a significant loss of ascorbic acid during treatment with HDF, in which diffusive transport was responsible for two-thirds and convective transport for one-third of the loss [28].

Is high-volume HDF a costly therapy?

Dialysis is a costly treatment, with annual costs in the range of €45 000–€85 000 across international settings [29]. Recently, several studies have been performed which evaluated the (extra) costs of HDF. Based on data that were collected before 2012, Mazairac *et al.* analysed the CONTRAST study and found that HDF was ∼3.6% more expensive than low-flux HD (respectively, €88 622 ± 19 272 versus €86 086 ± 15 945/year, P = ns), which could be attributed mainly to higher procedural costs, such as expenses for disposables and control of water purification. Quarterly costs for hospitalizations and medication were similar. When cost utility was approached from a societal perspective, which includes productivity loss, HDF was as cost-effective as HD [30]. Moreover, as today's prices of high-flux dialysers are almost similar to low-flux dialysers and guidelines have markedly decreased the frequency of dialysate purity control, the costs of HDF treatment will currently approach those of other dialysis modalities. Lebourg *et al.* calculated the additional cost of HDF in >28000 treatments performed in a single dialysis facility. From this analysis, it appeared that the extra cost for HDF over high-flux HD varied from −€1.29 to +€4.58 per session, depending on the monitor used and the HDF modality applied (post-dilution being cheaper than mid- and pre-dilution) [31]. Comparable findings were published by Oates *et al.* who found that online post-dilution HDF was more expensive than HD when a blood line with a cuvette was used, but cheaper if the standard blood line was purchased together with the reinfusion line [32]. As high-flux dialysers were used in both arms in this study, the frequency of microbiological testing was similar in both modalities. Furthermore, a modest saving in phosphate binders was observed as well. Lastly, from a small short-term Japanese study by Takura *et al.*, it was concluded that HDF could potentially be cost-saving compared with HD due to a lower incremental cost-utility ratio [33].

What information do we still need?

Although the currently available data suggest that treatment with online post-dilution HDF is safe and has a favourable effect on survival, especially when high convection volumes are applied, many issues are still unclear.

First, if one accepts the idea that online post-dilution HDF is beneficial to the patients, the question arises why this should be. As the magnitude of the convection volume appears crucial in this respect, the most rational explanation is superior removal of uraemic toxins. So far, however, changes in the blood levels of accumulated retention products could not explicitly be related to a better clinical outcome. None of the large RCTS comparing online post-dilution HDF with HD reported on a relation between ß2-microglobulin levels (the best-established marker of MMW substance clearance) and outcome [9–11]. An alternative explanation is a better haemodynamic stability, with fewer episodes of intradialytical hypotension and consequently less cardiac stunning and gut ischaemia [34, 35], especially in patients with widespread cardiovascular disease. However, as similar results have been obtained by cooling the dialysate in conventional HD [36], it is doubtful whether this is a HDF-specific phenomenon.

Second, insufficient data are available to suggest that certain subgroups, such as diabetics and patients with a low albumin level [5, 6], profit especially from HDF. Yet, In ESHOL, a high Charlson comorbidity index at baseline appeared to be an independent predictor for the beneficial effect of HDF on all-cause mortality [9]. Furthermore, while the THDFS included only patients without residual kidney function (RKF) and RKF was not monitored in ESHOL, patients without RKF (diuresis <100 mL/24 h) did not especially benefit from HDF in CONTRAST [9–11]. As the number of patients in CONTRAST was too small in the highest tertile of convection volume to analyse the effect of HDF in patients without RKF separately, it remains unclear whether patients without RKF benefit especially from high-volume HDF.

Third, all RCTs comparing HDF with HD in terms of mortality and cardiovascular events were based on dialysis regimes three times per week. The role of HDF in more intensified dialysis programmes, such as daily and nocturnal dialysis, is unclear, despite promising results in phosphate and blood pressure control [37].

Fourth, as the currently available studies only enrolled adults requiring long-term dialysis, no evidence is provided for children.

In this category of patients, HDF may reverse the delay in growth, which is commonly observed during treatment with HD [38].

Fifth, limited information is available on the various patient- and treatment-related factors that determine the magnitude of convection volume. More information is needed as to whether these factors are consistent in different patient populations. It is important to keep in mind that the relation between convection volume and a determinant is not necessarily causal. For example, treatment time may be shortened in sicker patients and increased in patients with a high interdialytic weight gain. In these cases, dose-targeting bias may play a role [39]. Data from CONTRAST have shown that treatment time and blood flow rate, both potentially modifiable dialysis-prescription characteristics, are important determinants of the convection volume achieved [12]. In this respect, it is interesting to note that in ESHOL, the RCT with the highest mean convection volume, the dialysis staff was specifically trained how to achieve high convection volumes [9]. In this study, mean blood flow was 389 mL/min, as compared with 332 mL/min in CONTRAST and 318 mL/min in the THDFS. When CONTRAST was designed a decade ago, there were no data on the relation between dosage of HDF and outcome. Hence, in retrospect, it may not be surprising that considerable differences in convection volumes were noted between participating centres [12]. The latter findings support the hypothesis that awareness and motivation of doctors and nursing staff play an important role in achieving high convection volumes.

A next step is the combination of individual patient data from recent RCTs into one data set to address some of these and other questions. At present, such an approach is in progress under the umbrella of EuDial. To find out whether, and if so to what extent, the convection volume can be safely manipulated in everyday clinical practice, a feasibility study has started recently (NCT01877499). According to the protocol, treatment time, blood flow rate and filtration fraction are consecutively increased in a step-wise fashion. If indeed high convection volumes can be achieved in the vast majority of ESKD patients, a new RCT, comparing high-volume HDF with HD, could give a definitive answer to the question whether high-volume HDF leads to a better clinical outcome than HD treatment.

Summary and conclusions

Retention of MMW uraemic toxins has been related to both mortality and morbidity in patients with ESKD. Therefore, interest has shifted from diffusive dialysis treatments, such as low-flux HD, towards convective therapies, such as HDF. Controversy exists, however, as to whether the positive effect of HDF on the clearance of MMW substances translates into a clinical benefit. In two observational studies and three recent large RCTs, comparing online post-dilution HDF with HD, an inverse relationship was found between the amount of convection volume and mortality risk. Therefore, the magnitude of the convection volume appears the most practical and easiest quantification of the 'dose' of HDF. Studies evaluating the microbiological purity of the dialysis fluid and blood levels of inflammatory markers indicate that online HDF is a safe long-term treatment. So far, insufficient data are available that provide information regarding losses of albumin and/or (micro)nutrients, such as zinc or selenium. Vitamin C levels should be monitored and replenished when needed. Future research should be directed towards the identification of subgroups especially likely to benefit. Whether high convection volumes (>22 L/treatment) can be safely achieved in the majority of patients is currently under investigation. If so, a new RCT may definitively answer the question whether high-volume HDF has a beneficial survival effect over standard HD.

Conflict of interest statement

None declared.

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