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Online hemodiafiltration reduces systemic inflammation compared to low-flux hemodialysis

Claire H. den Hoedt[1,2], Michiel L. Bots[3], Muriel P.C. Grooteman[4,5], Neelke C. van der Weerd[6], Albert H.A. Mazairac[2], E. Lars Penne[4], Renée Levesque[7], Piet M. ter Wee[4,5], Menso J. Nubé[4,5], Peter J. Blankestijn[2] and Marinus A. van den Dorpel[1], for the CONTRAST Investigators[8]

[1]Department of Internal Medicine, Maasstad Hospital, Rotterdam, The Netherlands; [2]Department of Nephrology, University Medical Center Utrecht, Utrecht, The Netherlands; [3]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands; [4]Department of Nephrology, VU Medical Center, Amsterdam, The Netherlands; [5]Institute for Cardiovascular Research VU Medical Center (ICaR-VU), VU Medical Center, Amsterdam, The Netherlands; [6]Department of Nephrology, Academic Medical Center, Amsterdam, The Netherlands and [7]Department of Nephrology, St Luc Hospital, Montréal, Canada

Online hemodiafiltration may diminish inflammatory activity through amelioration of the uremic milieu. However, impurities in water quality might provoke inflammatory responses. We therefore compared the long-term effect of low-flux hemodialysis to hemodiafiltration on the systemic inflammatory activity in a randomized controlled trial. High-sensitivity C-reactive protein and interleukin-6 were measured for up to 3 years in 405 patients of the CONvective TRAnsport STudy, and albumin was measured at baseline and every 3 months in 714 patients during the entire follow-up. Differences in the rate of change over time of C-reactive protein, interleukin-6, and albumin were compared between the two treatment arms. C-reactive protein and interleukin-6 concentrations increased in patients treated with hemodialysis, and remained stable in patients treated with hemodiafiltration. There was a statistically significant difference in rate of change between the groups after adjustments for baseline variables (C-reactive protein difference 20%/year and interleukin-6 difference 16%/year). The difference was more pronounced in anuric patients. Serum albumin decreased significantly in both treatment arms, with no difference between the groups. Thus, long-term hemodiafiltration with ultrapure dialysate seems to reduce inflammatory activity over time compared to hemodialysis, but does not affect the rate of change in albumin.

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Correspondence: *Claire H. den Hoedt, Department of Internal Medicine, Maasstad Hospital, 1 K2 038, PO Box 9119, 3007 AC, Rotterdam, The Netherlands. E-mail: hoedtc@maasstadziekenhuis.nl*

[8]See Appendix for list of CONTRAST investigators.

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Systemic inflammation is commonly observed in patients with chronic kidney disease and has been shown to have a role in the development and progression of cardiovascular disease (CVD) and to predict mortality in end-stage kidney disease.[1–5] Especially in end-stage kidney disease, systemic concentrations of both pro- and anti-inflammatory cytokines are several folds higher, probably because of decreased renal clearance and/or increased production.[6] Several factors, such as microbiological quality of the dialysate, vascular access, membrane bioincompatibility, retention of uremic toxins, infection, poor nutritional status, and comorbidity, have been suggested to contribute to a persistent inflammatory state.[6]

Online hemodiafiltration (HDF) may decrease inflammatory activity through enhanced clearance of middle molecules by convection; on the other hand, the infusion of large amounts of substitution fluid may induce inflammatory activity when water is contaminated. However, the potential risk of contamination is very low as we and others previously showed by analyzing a large amount of samples of dialysis fluids.[7,8] Results from several observational studies have suggested a beneficial effect of HDF on inflammatory parameters such as C-reactive protein (CRP) and interleukin 6 (IL-6).[9–14] Others, however, did not confirm these findings.[15–19] Besides the fact that albumin is a negative acute-phase reactant, loss of albumin in the dialysate has been suggested as a potential drawback of HDF.[20–22] However, thus far, data from observational studies have reported stable predialysis albumin concentrations after long-term HDF.[10,11,15,23]

As observational studies are uncontrolled studies, there is no definite answer on the question of whether HDF has an impact on systemic inflammation. We used data of the CONvective TRAnsport STudy (CONTRAST) to address this question. CONTRAST is a randomized controlled trial that investigated the effects of increased convective transport by online postdilution HDF as compared with low-flux hemodialysis (HD) on all-cause mortality and on cardiovascular morbidity and mortality.[24]

The aim of this study was to compare the effects of HD and HDF on systemic inflammation, measured by predialysis high-sensitivity CRP, IL-6, and albumin.

RESULTS

Effect of HDF on CRP and IL-6

The baseline characteristics of the 405 patients in whom CRP and IL-6 were measured are depicted in Table 1. Figure 1 shows the participant flowchart of this subgroup. Fourteen patients switched from HDF to HD (who were then treated with high-flux HD), and six patients switched from HD to HDF. Supplementary Figures S1–S3 of the Appendix online show the raw data of CRP, IL-6, and albumin during follow-up.

Baseline CRP was 3.9 (1.3 to 10.3) mg/l in the HD group and 4.1 (1.4 to 10.4) mg/l in the HDF group. CRP levels increased significantly in HD patients and remained stable in patients on HDF (Figure 2 and Table 2). The difference in the rate of change in CRP was statistically different between the HDF and the HD group, when adjustments were made for age, sex, residual kidney function (RKF), CRP, and IL-6 at baseline. The annual increase in CRP differed by 20% between the groups. No difference in the rate of change over time was found when only data from baseline to 6-month visit were analyzed (Table 2).

Baseline IL-6 was 2.0 (1.2 to 3.4) pg/ml in the HD group and 2.1 (1.3 to 4.1) pg/ml in the HDF group. IL-6 levels increased in HD patients, and remained stable in patients on HDF (Figure 3 and Table 2). After adjustments for age, sex, RKF, CRP, and IL-6 at baseline, the difference in the rate of change was significantly different between the HDF and the HD groups. The annual increase in IL-6 differed by 16% between the groups. No difference in the rate of change over time was found when only data from baseline to 6-month visit were analyzed (Table 2). These data did not change after adjustment for the number of dialysis sessions per week.

No support was found for different effects of HDF compared with those of HD on CRP and IL-6 in different subgroups of age (interaction term CRP: $P=0.49$, IL-6: $P=0.10$), sex (CRP: $P=0.44$, IL-6: $P=0.91$), diabetes mellitus (DM) (CRP: $P=0.59$, IL-6 $P=0.36$), previous CVD (CRP: $P=0.19$, IL-6: $P=0.11$), or dialysis vintage ($P=0.52$, $P=0.09$). We found a trend toward a different effect on CRP between HDF and HD in patients who had RKF as compared with anuric patients (P interaction $=0.06$). In those with RKF, we found no difference in the rate of change of CRP between HD ($+5.9\%$ per year) and HDF ($+5.9\%$ per year). The rate of change in CRP in the anuric patients was $+31.1\%$ per year in the HD group and -0.80% per year in the HDF group. A significant interaction was found for IL-6 and the presence or absence of RKF ($P=0.03$). In those with RKF, we found no difference in the rate of change of IL-6 between HD ($+7.9\%$ per year) and HDF ($+8.0\%$ per year). In the anuric patients, the rate of change was different between HD ($+21.6\%$ per year) and HDF (-2.8% per year).

In patients with RKF at baseline, the estimated glomerular filtration rate decreased to a similar extent in patients treated with HD (-0.80 ml/min per 1.73 m^2 per year (-1.14 to -0.46)) or HDF (-0.69 ml/min per 1.73 m^2 per year (-0.99 to -0.38)).

Table 3 shows the changes of CRP and IL-6 across baseline tertiles. We found no statistically significant differences in effect between HDF and HD in the three baseline tertiles. Patients with CRP or IL-6 levels in the lowest tertile tended to have the largest increases over time.

Table 1 | Characteristics of the CRP and IL-6 cohort of CONTRAST at baseline

Variable	HDF ($N=201$)	Low-flux HD ($N=204$)
Age (year)	64 ± 14.2	63 ± 13.6
Male sex, no. (%)	121 (60)	130 (64)
Region		
The Netherlands, no. (%)	194 (97)	197 (96)
Norway, no. (%)	7 (3)	8 (4)
History of cardiovascular disease, no. (%)	91 (45)	87 (42)
Diabetes mellitus, no. (%)	46 (23)	39 (19)
Dialysis vintage (year)	2.4 ± 2.3	2.7 ± 2.6
Median (interquartile range)	1.7 (0.9–3.1)	2.0 (0.9–3.7)
Systolic blood pressure, mm Hg[a]	147 ± 22	149 ± 21
Diastolic blood pressure, mm Hg[a]	75 ± 12	76 ± 12
Vascular access		
AV fistula, no. (%)	164 (82)	176 (86)
Graft, no. (%)	31 (15)	22 (11)
Central catheter, no. (%)	5 (2)	5 (2)
Number of treatments/week		
3, no. (%)	182 (91)	193 (95)
2, no. (%)	19 (9)	11 (5)
Duration of a dialysis session, min	228 ± 23	227 ± 23
Blood flow, ml/min	305 ± 37	308 ± 35
Dialysis single-pool Kt/V_{urea}	1.41 ± 0.23	1.36 ± 0.17
Delivered convection volume (l/session)	18.7 (16.4–20.9)	NA
Residual kidney function, no. (%)[b]	120 (60)	111 (54)
Glomerular filtration rate (ml/min per 1.73 m^2)	0.67 (0–3.59)	0.53 (0–2.99)
Hemoglobin, mmol/l	7.4 ± 0.6	7.3 ± 0.5
Phosphorus, mmol/l	1.69 ± 0.56	1.65 ± 0.47
β2-Microglobulin, mg/l	28.6 ± 11.5	31.6 ± 11.9
Body mass index after dialysis, kg/m^2	24.7 ± 4.9	25.3 ± 4.7
Albumin, g/l [c]	40.0 ± 3.9	40.1 ± 4.3
Creatinine (μmol/l), predialysis	837 ± 242	896 ± 255
Hs CRP, mg/l	4.1 (1.4–10.7)	3.9 (1.3–10.3)
IL-6, pg/ml	2.2 (1.3–4.0)	2.0 (1.2–3.4)

Abbreviations: AV, arteriovenous; CONTRAST, CONvective TRAnsport STudy; HD, hemodialysis; HDF, hemodiafiltration; Hs CRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; NA, not applicable.
Values are means ± s.d., median (interquartile range), or number (percentage).
Hemoglobin in mmol/l to g/dl, divide by 0.62; to convert phosphorus in mmol/l to mg/dl, divide by 0.3229; to convert albumin in g/l to g/dl, divide by 10; to convert creatinine in μmol/l to mg/dl, divide by 88.4.
[a]Predialysis.
[b]Residual kidney function if diuresis >100 ml per 24 h.
[c]Albumin concentrations measured with the bromcresol purple method were converted to bromcresol green concentrations.