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*Technical Note*

# Removal of contrast media by different extracorporeal treatments

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**Abstract**

**Background.** Although the capability of extracorporeal treatments after administration of contrast media to prevent radiocontrast-induced nephropathy is controversial, haemodialysis is performed in many institutions after radiographic procedures. There are conflicting reports on the efficacy of different dialysers and treatment modalities to remove contrast media.

**Methods.** We compared the contrast medium-removing ability of different extracorporeal treatments in a randomized trial. Thirty-nine patients on chronic renal-replacement therapy or with chronic renal failure were randomized to receive low-flux haemodialysis (Low-HD, $n=10$), high-flux haemodialysis (High-HD, $n=10$), online haemodiafiltration (HDF, 10 litre substitution, $n=10$) and online haemofiltration (HF, 18 litre substitution, $n=9$) after administration of contrast medium during routine radiological procedures. Plasma concentrations of contrast medium (iopromide or iomeprol) were measured by energy-dispersive X-ray fluorescence analysis.

**Results.** The extraction ratio for contrast media was $0.64\pm0.1$ for Low HD ($P<0.05$ *vs* High-HD and *vs* HDF), $0.74\pm0.1$ for High-HD ($P<0.05$ *vs* HF), $0.81\pm0.1$ for HDF ($P<0.05$ *vs* HF), and $0.62\pm0.1$ for HF. Mean extracorporeal plasma clearances were $82\pm2$ for Low-HD ($P<0.05$ *vs* High-HD and *vs* HDF), $100\pm2$ for High-HD, $115\pm4$ for HDF ($P<0.05$ *vs* HF), and $86\pm5$ ml/min for HF.

**Conclusions.** We conclude that HDF and High-HD remove contrast media more effectively than Low-HD and HF during the time of each treatment session. However, whether this is also true for the overall elimination of contrast media by these different procedures needs to be addressed in future studies, by a precise assessment of the drug time course after the session.

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## Introduction

Radiocontrast-induced nephropathy (RCN) is a well-recognized complication of radiographic procedures. The incidence of RCN varies between 0 and 100%, depending on the definition of RCN and of the population studied. In non-diabetic patients with normal renal function, the incidence of RCN is 2% [1]. For patients with chronic renal insufficiency, the incidence of RCN rises to about 7%, and for patients with diabetes mellitus and chronic renal failure, it is $>50\%$ [2]. Several strategies have been proposed to prevent RCN including hydration with hypotonic saline [3], administration of calcium-channel blockers [4], atrial natriuretic factor [5] or theophylline [6]. Although the ability of extracorporeal treatments after administration of contrast media to prevent their nephrotoxicity is controversial, haemodialysis is performed in many institutions after radiographic procedures to remove contrast media and to prevent RCN. Lehnert *et al.* [7] demonstrated that haemodialysis eliminates contrast medium, but it does not influence the incidence of RCN. There may be several reasons for the failure of haemodialysis to prevent RCN. Firstly, the time between administration of contrast medium and start of dialysis was too long and nephrotoxicity had occurred before start of dialysis. Secondly, contrast medium was not removed efficiently enough to have a favourable effect on RCN. Indeed, in the cited study using a relatively low blood flow of $139\pm8$ ml/min, only one-third of the contrast-medium dose was removed [7].

Studies investigating whether dialysis prevents RCN should apply the treatment modality that is most efficient for removing contrast media. Therefore the knowledge of contrast-media clearances by different dialysis modalities is essential. There are conflicting reports on the ability of different dialysers and

treatment modalities to remove contrast media. *In vitro* studies demonstrated that with increasing transmembranous pressure, a high-flux dialyser has a higher sieving coefficient than a low-flux dialyser [8]. Another *in vitro* study reported that HDF could remove contrast media more effectively than HF [9]. This finding can be anticipated considering the molecular weight of the tested substance (723 kDa). In contrast, Matzkies *et al*. [10] demonstrated no difference in iopromide clearance between high-flux and low-flux dialysers *in vivo*. There are no studies comparing different extracorporeal treatment modalities for their ability to remove contrast media *in vivo*. We therefore conducted a randomized study comparing low-flux haemodialysis (Low-HD), high-flux haemodialysis (High-HD), haemodiafiltration (HDF), and haemofiltration (HF) for their ability to remove contrast media.

## Subjects and methods

The study was approved by the clinic's ethic committee. The elimination of contrast media was studied in 39 patients. Twenty-six patients were on chronic dialysis treatment without residual renal function, 13 patients had chronic renal insufficiency (serum creatinine $>4$ mg/dl) not yet dialysis-dependent. All patients underwent a radiographic procedure (computed tomography, $n=5$; coronary angiography; $n=20$ or angiography of peripheral arteries, $n=14$) and gave informed consent to the study. Inclusion of patients into the study was decided by two nephrologists (RS or KL) who informed the person (CS) who randomized patients into one of four treatment groups by random procedure. Group 1 ($n=10$) received Low-HD (Hemophan GFS 16 plus, 1.6 $m^2$; Gambro, Hechingen, Germany), group 2 ($n=10$) received High-HD (PF14S, 1.3 $m^2$, polyamide, Gambro). Group 3 ($n=10$) was treated by haemodiafiltration with online preparation of substitution fluid (PF14S, polyamide, Gambro, 10 litre substitution fluid), group 4 ($n=9$) was treated by haemofiltration with online preparation of substitution fluid (HF14, 1.3 $m^2$, polyamide, 18 litre substitution fluid). The blood flow was kept at 200 ml/min for all procedures, the dialysate flow was 500 ml/min for the first three groups. Twenty-one patients had an AV-fistula, five had a PTFE-graft, and 13 were dialysed using a temporary double-lumen catheter. Non-ionic monomeric iopromide (Ultravist, Schering, molecular weight 791) or iomeprol (Imeron, Byk Gulden, molecular weight 777) was used. After the radiographic procedure, patients were transferred immediately to the dialysis ward and dialysed as soon as possible. The time interval between the first injection of contrast media and the start of extracorporeal treatment was recorded and averaged $1.2\pm0.6$ h.

Blood samples were taken at 0.5, 1, 2, 4 and 24 h after start of dialysis. At 1 h, blood samples were taken before and after the dialyser for calculation of extraction rate and extracorporeal clearance. Blood was centrifuged immediately; plasma was obtained and stored at $-20^{\circ}$C until analysis.

Creatinine clearance was estimated using the equation of Cockroft and Gault:

$$Cr_{Cl}: \ (140-\text{age [years]})\times\text{body weight [kg]}/72\times S\text{–Cr [mg/\%]}.$$

Extraction ratio and extracorporeal clearance of contrast media was calculated as follows:

$$\text{Extraction ration (ER)} = (C_{in}-C_{out})/C_{in}$$

where $C_{in}$ is the concentration of contrast medium entering the dialyser and $C_{out}$ the concentration leaving the dialyser.

$$\text{Extracorporeal clearance } (CL_{extra}) = ER^{*}\text{blood flow}^{*}(1-\text{haematocrit}).$$

The elimination half-life ($t_{1/2}$) of contrast medium was calculated as:

$$t_{1/2} = \ln 2/k_d$$

where $k_d$ is the rate constant of elimination of contrast medium, which was calculated from the semilogarithmic concentration-time curve during dialysis.

Plasma concentration of iopromide or iomeprol was measured by energy-dispersive X-ray fluorescence analysis [11]. The test range was between 0.01 and 2 mg iodine/ml. Plasma samples were diluted until their iodine content was in the linear part of the standard curve. Plasma concentrations of creatinine and urea were determined on a Modular® autoanalyser (Roche) in the routine laboratory of the clinic.

### *Statistical analysis*

Data are given as means $\pm$ SEM. Statistical analysis was performed using multivariate analysis of variance (ANOVA) followed by Bonferroni-testing (Instat for Macintosh, Graphpad Software). Significance was defined as $P<0.05$.

## Results

The mean time between the administration of contrast medium and the beginning of dialysis was $1.2\pm0.6$ h. Characteristics of patients are given in Table 1. The distribution of patients in the groups were not different regarding weight, dose of contrast medium administered and number of patients not yet on dialysis (Table 1). Serum creatinine for the patients not yet on chronic dialysis were not significantly different between groups (Table 1).

Data for contrast medium clearance and extraction ratio, elimination $t_{1/2}$ of contrast medium, creatinine- and urea clearance and net ultrafiltration rate are given in Table 2. The highest contrast medium-clearance was observed for HDF, followed by High-HD, Low-HD and HF (Table 2). The same was true for contrast-medium extraction ratios. The values for clearance and extraction ratios were significantly different between Low-HD and High-HD, between Low-HD and HDF and between HDF and HF, but not between HDF and High-HD. HDF decreased the concentration of contrast medium significantly faster than HF. There were no significant differences in elimination $t_{1/2}$ of contrast medium between HDF, High-HD and Low-HD. The lowest creatinine and urea clearance was observed with HF, the highest with HDF (Table 2). Net ultrafiltration rates were highest with Low-HD but not significantly different between groups.

**Table 1.** Weight, dose of contrast medium, number of patients not on chronic dialysis, and the serum-creatinine for these patients

| Group | Weight (kg) | Dose of contrast media administered (g iodine) | Number of patients not on regular dialysis | Serum creatinine of patients not on regular dialysis (mg/dl) | Creatinine clearance of patients not on regular dialysis (ml/min) |
|---|---|---|---|---|---|
| Low-HD | 74±11 | 64±43 | 3/10 | 8.7±3.2 | 8.23±4 |
| High-HD | 70±11 | 63.7±34 | 4/10 | 4.1±0.1 | 11.7±4 |
| HDF | 78±18 | 59.8±15 | 4/10 | 4.7±0.6 | 13±2 |
| HF | 74±10 | 57.3±17 | 2/9 | 5.2±0.25 | 10±1 |

Low-HD, low-flux haemodialysis; High-HD, high-flux haemodialysis; HDF, haemodiafiltration; HF, haemofiltration.

**Table 2.** Net ultrafiltration rates, extracorporeal clearances for contrast media, creatinine and urea and half-life of contrast media

| Group | Extracorporeal clearance of contrast media | Contrast media extraction ratio | Half-life of contrast media (min) | Extracorporeal creatinine clearance (ml/min) | Extracorporeal urea clearance (ml/min) | Net ultrafiltration rate (ml/h) |
|---|---|---|---|---|---|---|
| Low-HD | 82±2.3§ | 0.64±01§ | 115±26 | 101±13 | 115±17 | 482±108 |
| High-HD | 100±2.2 | 0.74±0.03 | 100±18 | 100±14 | 119±12 | 355±81 |
| HDF | 114±4 | 0.82±0.01 | 95±25 | 115±13 | 133±11 | 299±63 |
| HF | 86±5§ | 0.62±0.03§ | 130±32§ | 75±14* | 69±16* | 417±105 |

* $P<0.05$ *vs* all other treatments, § $P<0.05$ *vs* HDF.
Low-HD, low-flux haemodialysis; High-HD, high-flux haemodialysis; HDF, haemodiafiltration; HF, haemofiltration.

## Discussion

This is the first randomized study comparing the ability of different dialysis modalities to remove contrast media *in vivo*. The observation that HDF is superior to HF and Low-HD for elimination of contrast media is in accordance with *in vitro* studies: Gouge *et al.* [8] reported higher clearances for a high-flux dialyser compared to a low-flux dialyser, especially at higher ultrafiltration rates. Okahisa *et al.* [9] employed a bovine blood tank model and reported that HDF removes contrast media more effectively than HF. In contrast, Matzkies *et al.* [10] demonstrated no difference in iopromide clearance between high-flux and low-flux dialysers *in vivo*. The authors claimed that elimination of iopromide is not dependent on the pore size of the membrane during haemodialysis. The reason for this discrepancy is unclear. The only difference between their study and ours is the higher blood flow rates in the investigation by Matzkies *et al.* [10] (250 *vs* 200 ml/min). It is possible that higher net ultrafiltration rates in the low-flux group contributed to higher elimination rates for contrast media, but no data for net ultrafiltration rates are given in the cited study [10].

We included both patients on chronic dialysis treatment and those with chronic renal failure not yet on renal replacement therapy. Although the number of patients with residual renal function were similar in all groups, the degree of residual renal function was different (Table 1). Patients not on chronic dialysis in the Low-HD group had a higher serum-creatinine than in the other groups. Besides the fact that this difference was not statistically significant, an unequal distribution of residual renal function between groups does not affect dialyser clearance or extraction ratio. Residual renal function may influence the total elimination of contrast media and therefore the elimination $t_{1/2}$, but not the extracorporeal clearance of contrast media calculated 1 h after start of treatment from pre- and post-dialyser contrast-medium concentrations, blood flow, and haematocrit.

'Prophylactic haemodialysis' has been proposed to prevent RCN based on observations that contrast media can be removed by haemodialysis. Moon *et al.* [12] dialysed patients with chronic renal failure immediately after angiographic procedures and reported no increase in serum creatinine in these patients. The authors claimed that haemodialysis prevented RCN but this study did not provide an undialysed control group. Lehnert *et al.* [7] randomized patients to haemodialysis or conservative treatment after administration of contrast medium and failed to demonstrate a beneficial effect of haemodialysis on RCN. However, in order to have a clinical impact on RCN, the employed treatment must remove contrast medium rapidly and efficiently. Our data suggest that HDF or High-HD with high blood flow rates should be used in future studies investigating the usefulness of extracorporeal treatments to prevent RCN.

From the present data, we cannot recommend or reject the usefulness of 'prophylactic haemodialysis' to prevent RCN. Even the most effective method to remove RCN may have no beneficial effect on RCN when employed too late. In our study, the mean interval between administration of contrast media and

extracorporeal treatment was $1.2 \pm 0.6$ h. A shorter interval is clinically not feasible unless haemodialysis is performed during the radiological procedure. Contrast media cause a rapid increase followed by a sustained decrease in renal blood flow [13,14]. The ischaemia caused by renal vasoconstriction is one of the pathophysiological mechanisms leading to RCN. On the other hand, direct cellular toxicity may be another factor, and if toxicity on tubular cells occurs after filtration of contrast media, there might be a substantial delay between administration of contrast media and onset of RCN. To date it is difficult to determine which factor is the more important for causing RCN [2]. If toxicity on tubular cells after glomerular filtration of contrast media is the major pathogenetic mechanism for RCN, even a delayed removal of contrast media may be clinically beneficial. It must be noted that even with the most efficient method employed (HDF), the elimination $t_{1/2}$ for contrast media was still $95 \pm 25$ min. Since we did not assess possible redistribution of contrast media after treatment, it remains uncertain whether HDF is able to contribute significantly to total body clearance in addition to endogenous clearance. Randomized studies employing effective methods to remove contrast media have to be performed to clarify the clinical impact of 'prophylactic haemodialysis' to prevent RCN.

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