Research Article

Elimination of Contrast Agent Gadobutrol with Sustained Low Efficiency Daily Dialysis Compared to Intermittent Hemodialysis

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Keywords

Intermittent hemodialysis · Elimination of contrast agent gadobutrol · Sustained low efficiency daily dialysis

Abstract

Background: In patients with renal failure, gadolinium-based contrast agents (GBCA) can be removed by intermittent hemodialysis (iHD) to prevent possible toxic effects. There is no data on the efficacy of GBCA removal via sustained low efficiency daily dialysis (SLEDD) which is mainly used in intensive care unit (ICU) patients. **Methods:** We compared the elimination of the GBCA gadobutrol in 6 ICU patients treated with SLEDD (6–12 h, 90 L dialysate) with 7 normal ward inpatients treated with iHD (4 h, dialysate flow 500 mL/min). Both groups received 3 dialysis sessions on 3 consecutive days starting after the application of gadobutrol. Blood samples were drawn before and after each session and total dialysate, as well as urine was collected. Gadolinium (Gd) concentrations were measured using mass spectrometry and eliminated Gd was calculated from dialysate and urine. **Results:** The initial mean plasma Gd concentration was $385 \pm 183 \mu\text{M}$ for the iHD and $270 \pm 97 \mu\text{M}$ for the SLEDD group, respectively ($p > 0.05$). The Gd-reduction rate after the first dialysis session was 83 ± 9 and $67 \pm 9\%$ for the iHD and the SLEDD groups, respectively ($p = 0.0083$). The Gd-reduction rate after the second and third dialysis was 94–98 and 89–96% for the iHD and the SLEDD groups ($p > 0.05$). The total eliminated Gd was 89 ± 14 and $91 \pm 4\%$ of the dose in the iHD and the SLEDD groups, respectively ($p > 0.05$). Gd dialyzer clearance was $95 \pm 22 \text{ mL/min}$ and $79 \pm 19 \text{ mL/min}$ for iHD and SLEDD, respectively ($p > 0.05$). **Conclusions:** Gd-elimination with SLEDD is equally effective as iHD and can be safely used to remove GBCA in ICU patients.

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Introduction

Gadolinium (Gd) belongs to the rare earths and although highly toxic to mammals it is used as a contrast agent in magnetic resonance imaging (MRI) due to its paramagnetic properties. To avoid acute toxicity, Gd is given as linear or cyclic chelates that are cleared mostly via glomerular filtration rate [1, 2]. Gd release and its toxicity decreases with the stability of chelation, with higher stability in cyclic than in linear complexes [3, 4], which is explained by the mechanism of transmetalation [5, 6]. Current studies have shown tissue deposition, especially in the brain even in patients with normal renal function [7–9]. These recent findings led to an EMA drug warning and prohibition of linear gadolinium-based contrast agents (GBCAs), however, clinical relevance is still lacking [10].

In contrast, a debilitating condition named nephrogenic systemic fibrosis (NSF) was first described between 2000 and 2001 [11, 12] and related to Gd toxicity due to skin deposition in 2006 [13]. It was predominantly found in patients with severe renal failure including those with end-stage renal disease (ESRD). Up to now, the exact pathophysiology of NSF is unknown. It is suspected that free Gd may be released from the chelate and complexes with phosphate [4, 14]. This hypothesis is supported by the detection of Gd in the tissue of NSF patients [15]. Incidence of NSF varies with the GBCA used, and in patients with chronic kidney disease it ranges from 0.0003 to 0.004%, with higher rates in ESRD patients [16–19]. Among the various GDCA, gadodiamide has one of the lowest thermodynamic stability constants and one of the highest dissociation rates compared with other agents and has been the agent most commonly reported to be associated with the development of NSF [17]. To prevent possible toxicity from free Gd, intermittent hemodialysis (iHD) has been shown to effectively remove Gd, reaching elimination rates of >90% of the applied dose after 3 sessions [20–24]. In the study by Saitoh et al. [20], 74, 92, and 99% of the gadodiamide dose was eliminated by the end of the first, second, and third session, respectively.

MRI is also an important imaging modality in intensive care unit (ICU) patients [25], who can be characterized by a high coincidence of acute kidney injury (AKI). From these, approximately 5% need renal replacement therapy (RRT) using either intermittent or continuous hemodialysis modalities. Mortality for those in need of RRT reach 50–60, and 13% of patients with RRT leaving ICU remain dialysis dependent [26–28]. Sustained low efficiency daily dialysis (SLEDD) is a hybrid hemodialysis modality in ICU patients, enabling daily hemodialysis sessions over a prolonged time. Its advantages include reduced nursing time and lower costs compared to CVVH at similar outcomes [29].

Because of significant efforts involved in the transportation of ICU patients, MRI seems to be underutilized and in ICU patients with AKI, application of GBCA might be another obstacle to MRI [30, 31]. Removal via hemodialysis in this population is not well known and it remains unclear if continuous or SLEDD might be equally effective as iHD, which is often poorly tolerated in ICU patients.

In this study, we investigated the elimination of the GBCA gadobutrol using SLEDD in ICU patients and compared the efficacy in ESRD patients using iHD. We demonstrated that Gd-elimination with SLEDD is equally effective as with iHD and can be safely used to remove GBCA in ICU patients.

Materials and Methods

Patients and Dialysis

We enrolled patients in need of a GBCA-enhanced MRI and dialysis at our hospital between 2016 and 2018. Exclusion criteria were age <18 years, residual urine output

>1,000 mL/24 h, and participation in another trial. The study was approved by the Institutional Review Board (IRB) and Ethics Committee (No: 281/2016MPG23). Fully informed and signed consent was obtained from each patient or his caregiver. We enrolled a total of 13 patients: 6 ICU patients with indication for contrast-enhanced MR imaging and dialysis-dependent AKI and 7 ESRD patients. ICU patients received a SLEDD with a FMC Genius 90 dialysis machine (Fresenius Medical Care, Bad Homburg, Germany) and a 1.4 m² high-flux Helixone membrane (F60; Fresenius Medical Care, Bad Homburg, Germany). Dialysis time and blood flow were individually adapted to the patient's hemodynamic status and ranged between 100–200 mL/min and 6–12 h, respectively. During SLEDD, exactly 90 L of dialysate equal to the total tank volume was spent. ESRD patients received an iHD using the FMC 5008 coreDiox dialysis machine (Fresenius Medical Care, Bad Homburg, Germany), a 1.4 m² high-flux Helixone membrane (F60; Fresenius Medical Care, Bad Homburg, Germany) with a fixed time (4 h), a fixed dialysate flow (500 mL/min), and a blood flow between 250 and 300 mL/min (iHD group). Dialysis sessions were performed on 3 consecutive days starting on the day of application of gadobutrol (Gadovist, Bayer, 1 mmol/mL) at a dose of 0.1 mmol/kg body weight. For every patient, the total volume (mL) of injected GBCA was noted.

To measure the Gd concentration, 5 mL blood was stored before and after each dialysis. In the iHD group, spent dialysate was collected in a tank, weighed and one sample was drawn. In the SLEDD group, dialysate samples were drawn from the dialysate tank according to the manufacturer's requirements. If patients had residual renal function, urine was collected, measured and samples were stored.

Measurement of Gd in Serum, Urine and Dialysate

To remove proteins, 1 mL serum was mixed with 1 mL nitric acid (65%). The precipitated serum samples were separated by ultrafiltration to obtain a supernatant. Depending on the expected concentration, the samples were further diluted 1:100–1:5,000 using 1% nitric acid + 0.01% Triton-X 100 + 5 nmol/L terbium as internal standard. Gd concentration was measured by Bayer AG (Berlin) using inductively coupled plasma mass spectrometry (ICP-M, Agilent 7900). The limit of quantification of the MS method was 0.1 nmol/L for the Gd isotope 158. All diluted samples were at least 10-fold above the limit of quantification.

Calculations

The Gd-reduction rate was calculated for each dialysis session using the formula: $(C_{GD \text{ before}} - C_{GD \text{ after}}) / C_{GD \text{ before}} * 100\%$, whereby C_{GD} denotes the Gd concentration. Rebound was calculated from $C_{GD \text{ before next dialysis}} - C_{GD \text{ after previous dialysis}} / C_{GD \text{ after previous dialysis}} * 100\%$.

The percentage of eliminated Gd was calculated as: $n_{GD \text{ collected}} / n_{GD \text{ injected}} * 100\%$, whereby n_{GD} denotes the amount of Gd.

The estimation of Gd dialyzer clearance was calculated as follows: $CL_{GD} = N_{GD \text{ collected}} / AUC_{GD \text{-concentration before and after HD}}$. AUC was calculated using the triangle formula: $(C_{GD \text{ before HD}} + C_{GD \text{ after HD}}) / 2 * t_{\text{dialysis}}$ (μmol*min/mL).

In addition, we normalized the post-dialysis Gd concentration to the change of volume status (VS) of the patient by changes in serum-albumin concentrations. The amount of albumin is not affected by dialysis ($n_{\text{pre}} = n_{\text{post}}$). Pre-dialysis VS was defined as 1 ($V_{\text{pre}} = 1$). The VS post-dialysis is affected by fluid intake or ultrafiltration during dialysis. The formula $n_{\text{pre}} = n_{\text{post}}$ equals $c_{\text{pre}} * V_{\text{pre}} = c_{\text{post}} * V_{\text{post}}$. Therefore, the relative change in VS is defined as $V_{\text{post}} = c_{\text{pre}} / c_{\text{post}}$.

We corrected the $c_{GD \text{ after}}$ by multiplying with V_{post} and calculated GdRR and CL_{GD} also with these corrected values. The amount of serum of subject 3 was too small, resulting in a total number of $n = 12$ (6 iHD; 6 SLEDD) for the calculations with corrected VS.

Table 1. Characteristics of patients

	iHD	SLEDD
Age, years	58±17	60±13
Height, m	1.71±0.09	1.75±0.14
Weight, kg	73.2±15.1	85±29.8
BMI, kg/m ²	25±3.2	27.2±6.1
Female/male, %	43/57	17/83
Urea distribution volume (Watson formula), L	38±8	43.3±12.8
Hypertension, <i>n</i> (%)	6/7 (86)	2/6 (33)
Atrial fibrillation, <i>n</i> (%)	1/7 (14)	2/6 (33)
Renal disease, <i>n</i> (%)		
AKI	1/7 (14)	5/6 (83)
SLE	2/7 (28)	0/6 (0)
HRS	1/7 (14)	1/6 (17)
Ntx failure	1/7 (14)	0/6 (0)
Nephrectomy	1/7 (14)	0/6 (0)
Toxic	1/7 (14)	0/6 (0)

Baseline characteristics of the iHD group and the SLEDD group. BMI, body mass index; AKI, acute kidney injury; SLE, systemic lupus erythematosus; HRS, hepatorenal syndrome; Ntx, kidney transplantation; iHD, intermittent hemodialysis; SLEDD, sustained low-efficiency daily dialysis.

Statistics

Statistical analysis was performed using the SAS JMP program (SAS Institute, Cary, NC, USA). We calculated descriptive statistics using sample sizes, arithmetic means for gadobutrol concentrations, SD 95% CI of the mean where appropriate. Groups were compared using the *t* test. A *p* value <0.05 was considered statistically significant.

Results

The subject characteristics of the patients in both groups are shown in Table 1. The cause of acute renal failure from acute tubular necrosis with consecutive dialysis was found in 5 out of 6 patients in the SLEDD group. One patient was diagnosed with hepatorenal syndrome. In the iHD group, chronic dialysis dependent kidney disease was due to systemic lupus (2/7; 28%), bilateral nephrectomy (1/7; 14%), transplant failure (1/7; 14%), ifosfamide toxicity (1/7; 14%), hepatorenal syndrome (1/7; 14%), and 1 case of status post-AKI (1/7; 14%). The median residual urine output was 266 mL/24 h (533; 0 mL/24 h) and 216 mL/24 h (2,300; 0 mL/24 h) for iHD and SLEDD groups (*p* > 0.05; Table 2).

The initial mean serum Gd concentration was 385 ± 183 μmol Gd/L and 271 ± 97 μmol Gd/L for the iHD and the SLEDD groups, respectively (*p* > 0.05). After 3 dialysis sessions, Gd-serum concentrations fell to 5 ± 4 μmol Gd/L in the iHD and to 10 ± 8 μmol Gd/L in the SLEDD group (*p* > 0.05; Fig. 1). The Gd-reduction rate for the first dialysis session was 83 ± 9 and 67 ± 9% for the iHD and the SLEDD groups, respectively (*p* = 0.0083; Fig. 2). The Gd-reduction rate for the second and third dialysis sessions was 94 ± 4 and 98 ± 1% in the iHD group and 89 ± 5 and 96 ± 3% in the SLEDD group, respectively (*p* > 0.05; Fig. 2).

When corrected for VS changes during dialysis, the Gd-reduction rate for the first dialysis session was 82 ± 7 and 68 ± 10% for the iHD and the SLEDD groups, respectively (*p* = 0.0197).

Table 2. Gd-Clearance (Gd_{clear}) of each patient, mean urine volume per 24 h, total amount of creatinine, BUN, and Gd in urine

Group	Patient	Gd_{clear} 1st HD, mL/ min	Mean Urine volume, mL/24 h	Total amount of U-Crea, mg	Total amount of U-BUN, mg	Total amount of U-Gd, μ mol	Percentage of total Gd, %
iHD	2	94.9	0	0	0	0	0
	3	119.2	567	56	649	649	4.6
	5	91.9	267	123	757	153	2.2
	6	129.9	0	0	0	0	0
	10	79.6	533	–	–	5	0.05
	11	64.6	527	1,532	16,763	1,702	34.1
	12	103.8	267	273	2,037	361	5.2
	Median	94.9	267	89.5	703	153	2.2
SLEDD	1	63.0	2,300	177	16,437	1,024	13.7
	4	108.1	434	190	1,710	268	2.7
	7	61.8	0	0	0	0	0
	8	72.2	0	0	0	0	0
	9	94.4	0	0	0	0	0
	13	72.0	433	170	4,539	300	3.8
	Median	72.1	216.5	85	855	134	1.35

iHD, intermittent hemodialysis; SLEDD, sustained low efficiency daily dialysis.

Fig. 1. Mean serum Gd concentration before and after each dialysis session during iHD (blue line) and SLEDD (red line). iHD, intermittent hemodialysis; SLEDD, sustained low efficiency daily dialysis.

The Gd-reduction rate for the second and third dialysis sessions was 94 ± 4 and $98 \pm 1\%$ in the iHD group and 90 ± 5 and $96 \pm 3\%$ in the SLEDD group, respectively ($p > 0.05$).

Prior to the second dialysis session, there was a rebound of Gd-plasma concentration in the iHD group ($+22 \pm 25\%$) which was absent in the SLEDD group ($-18 \pm 12\%$, $p = 0.0052$; Fig. 3a). The rebound was reduced prior to the third dialysis session in the iHD group ($13 \pm 22\%$) and statistically not different from that seen in the SLEDD group ($-3 \pm 25\%$; $p > 0.05$). When corrected for VS changes, the rebound of Gd-plasma concentration in the iHD group persisted ($+16 \pm 19\%$) and was also absent in the SLEDD group ($-16 \pm 27\%$; $p = 0.0384$). Again the rebound was reduced prior to the third dialysis session in

Fig. 2. Gd reduction rates during the 3 consecutive dialysis sessions in patients treated with SLEDD or iHD. * Significant difference between the groups ($p < 0.05$). iHD, intermittent hemodialysis; SLEDD, sustained low efficiency daily dialysis.

Fig. 3. Gd rebound rate between first and second dialysis sessions (a) and Gd clearance rate during first dialysis session in mL/min (b). * Significant difference between the groups ($p < 0.05$). iHD, intermittent hemodialysis; SLEDD, sustained low efficiency daily dialysis.

the iHD group ($13 \pm 27\%$) and statistically not different from that seen in the SLEDD group ($4 \pm 32\%$; $p > 0.05$).

The mean dialyzer Gd clearance was 95 and 77 mL/min for iHD and SLEDD groups, respectively ($p > 0.05$; Fig. 3b; Table 2).

The total amount of eliminated Gd in all 3 dialysis sessions was $89 \pm 14\%$ of the applied dose in the iHD group and $91 \pm 4\%$ in the SLEDD group, respectively ($p > 0.05$). The percentage of eliminated Gd with urine was 7 ± 12 and $3 \pm 5\%$ in the iHD and SLEDD groups, respectively ($p > 0.05$).

After 30 days of follow-up, 4 out of 6 patients in the SLEDD group had died and all patients in the iHD group were alive. There was no case or suspicion of NSF in any patient. One patient in the iHD group died during the next 12 months due to pneumonia. After a follow-up of 12 months, none of the patients developed NSF or another adverse event that could be related to Gd toxicity.

Discussion/Conclusion

Our study is the first to analyze the elimination of a cyclic GBCA by SLEDD in ICU patients in comparison with iHD. Our results indicate that SLEDD eliminates gadobutrol with similar efficacy as iHD and achieved elimination rates of more than 90% of the administered Gd dose after 3 consecutive dialysis sessions. The remaining amount was excreted by residual kidney function. These data indicate that SLEDD is an adequate modality to eliminate GBCA in ICU patients who are usually hemodynamically compromised and poorly tolerate iHD. In these patients, dialysis modalities with a low blood flow such as SLEDD or continuous RRT are associated with improved hemodynamic stability. For continuous RRT, it is noteworthy that there are still no studies investigating the efficacy of Gd elimination [32]. Another advantage of SLEDD in the ICU over iHD is that it is more cost-effective and does not require dialysis personnel during treatment since SLEDD is usually monitored by the ICU staff.

The plasma gadobutrol reduction rates achieved with iHD were higher than that reported by Tombach et al. [21], who reported values of 68% using a low-flux membrane with 1.2 m². The difference can be explained by the longer dialysis time in our study. The Gd-RR of iHD was also higher compared to SLEDD, particularly in the first session indicating a more rapid clearance of Gd from the plasma compartment. This can be explained by the higher blood and dialysate flow during iHD. However, this was followed by a higher rebound as a result of Gd redistribution from the interstitial space. In an earlier study, we observed the same during dialysis with the drug dabigatran, which had higher reduction rate and rebound in iHD compared to SLEDD [33]. However, when looking at the eliminated Gd amount during the first session, there was no difference between SLEDD and iHD. These findings indicate that SLEDD eliminates Gd equally effectively due to the prolonged dialysis time that offsets the reduced blood and dialysate flow. It also shows that assessment of dialysis efficacy should not solely rely on plasma reduction rates that can overestimate clearance, especially when tissue deposition may occur [7, 9]. Calculating dialyzer clearance from blood and dialysate samples also overestimate the true clearance [34]. The best way to assess the efficacy of any dialysis modality is the analysis of the spent dialysate as was done in this study. However, for the latter, sensitive quantification methods must be available given the large dialysate volume in which the analyte is diluted. So further studies on Gd elimination should take into account that a simple reduction rate is easy to use but is prone to overestimate the real clearance.

In conclusion, our study demonstrates that SLEDD is an adequate modality to effectively remove Gd in ICU patients with dialysis-dependent AKI and can be used to eliminate GDCA in ICU patients after Gd-enhanced MRI.

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Statement of Ethics

The study was approved by the IRB and Ethics Committee (No: 281/2016MPG23). Fully informed and signed consent was obtained from each patient or his caregiver.

Disclosure Statement

The authors have no conflicts of interest to declare.

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The study was carried out with own funds.

Author Contributions

H.B.: designed the study, was responsible for IRB approval, supervised the study and wrote main parts of the manuscript. N.H.: was involved in study design and manuscript revision. M.H. and R.R.: was involved in patient inclusion and data sampling. O.T.: was involved in study design pre-analytics and ethical approval. F.A.: was involved in study design, supervision, statistical analysis, and manuscript preparation.

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