

# Influence of Online Hemodiafiltration on Hemoglobin Level, ESA-Dosage and Serum Albumin – A Retrospective, Multicenter Analysis

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## 1. Introduction

In renal replacement therapy (RRT) a wide range of uremic toxins have to be removed (Vanholder et al., 2003; Vanholder et al., 2008). It is well known that the combination of diffusive and convective dialysis strategies (online hemodiafiltration, oHDF) improves the removal of uremic toxins, i.e. middle molecules, hydrophobic substances and protein (albumin) bound materials (Krieter et al., 2005; Ahrenholz et al., 2004; Ronco et al., 1999; Kim, 1994; Testa et al., 2006; Meyer et al., 2005; Mandolfo et al., 2006; Kanter et al., 2008). In the presence of ultrapure dialysis fluid which is ultrafiltrated by endotoxin restraint systems (Weber et al., 2000; Canaud et al., 2001; Minetti et al., 1985; Hakim et al., 1984) and biocompatible high flux dialysis membranes the convective diffusive treatment significantly prevents the complement activation (Braun et al., 1995; Savica et al., 2006; Jorres et al., 1999; Hörl et al., 1986) in the first minutes of oHDF session and removes proinflammatory substances (cytokines) too (Bellomo et al., 1991; Filiopoulos et al., 2008; Haas et al., 2007; Libetta et al., 2007; Mariano et al., 2005). The intra and interdialytic inflammations are reduced (Ramirez et al., 2007; Ramirez et al., 2007; Carracedo et al., 2006). The suppressed inflammatory process during oHDF leads to an increasing serum albumin concentration via an increased synthesis rate. In spite of a varying albumin removal caused by different dialysis membranes with/without adsorptive character and pore size (Pichaiwong et al., 2006; Yamashita, 2007; Tomo et al., 2008; Winchester et al., 2003; Winchester et al., 2004) the albumin synthesis rate increases by absent inflammation (Giordano et al., 2001). It is shown that in oHDF the ESA dosage needed to reach the hemoglobin goal is reduced (Vaslaki et al., 2006; Bonforte et al., 2002; Eiselt et al., 2000). The efficacy of dialysis measured by single pool Kt/V could be improved (Ahrenholz et al., 1997; Ding et al., 2002). There is evidence of longer survival of patients treated by oHDF versus hemodialysis (HD) independently of dialysis dosage (Canaud et al., 2008; Panicchi et al., 2008). The cycling of hemoglobin levels depends on inflammatory episodes and malnutrition (Del et al., 2005; Brimble et al., 2005). This retrospective, non randomized, multicentre, descriptive clinical evaluation examined the influence of oHDF on hemoglobin concentration (Hb), ESA dosage (ESA), Hb variability (Hbvar), albumin and CRP.

## 2. Materials and methods

233 chronic hemodialysis patients were included in this clinical evaluation (dialysis center 1 (D1) n= 94, D2 n= 35, D3 n= 104 patients). 54.9% were male; the mean age was 63.8 years (range 22 - 89). The patients in all three centers were comparable with regard to gender distribution, mean age, mean time on dialysis, and distribution of underlying kidney disease. The clinical evaluation was carried out for 12 months retrospectively. Laborchemical parameters were estimated for hemoglobin (Hb) every 2 weeks (labanalyzer), CRP (turbidometry), albumin (alb; nephelometry) and ferritin (chemiluminescence technique) every three months. Serum iron (photometry) and transferrin (turbidometry) were necessary to calculate the transferrin saturation (every 4 weeks). Single pool kt/V was evaluated every 3 months with the Daugirdas technique (Daugirdas, 1993). Intraindividual variability of hemoglobin (Hbvar) was defined as the difference between minimal and maximal concentration (range) and by time to reach the target between Hb 6.8 mmol/l and 8.0 mmol/l within 9 months. Relevant changes in ESA dosages were defined as an elevation greater than two fold and lowering of a half of the ESA dosage, the end of ESA application or the start with more than 4200 U/week. Hemodialysis (HD) was performed by MTS 5008 (Fresenius Medical Care), low flux dialyser FX8, FX10 (helixone, Fresenius Medical Care),  $Q_B$  300 ml/min,  $Q_D$  500 ml/min, ultrapure dialysis fluid, online hemodiafiltration (oHDF) by MTS 5008 (Fresenius Medical Care; automatic procedure with factor 1.2), high flux dialyser FX 60, FX80 (helixone, Fresenius Medical Care),  $Q_B$  300 ml/min,  $Q_D$  350.....360 ml/min,  $Q_S$  51...60 ml/min, ultrapure dialysis fluid and Nikkiso DBB 05 (Nikkiso Medical Ltd.), high flux dialyser FDY 15 G (PEPA, Nikkiso Medical Ltd.),  $Q_B$  300 ml/min,  $Q_D$  700 ml/min,  $Q_S$  60 ml/min, ultrapure dialysis fluid ( $Q_B$ ... blood flow;  $Q_D$ ...dialysate flow;  $Q_S$ ...substitution flow). The group "mixed" contained patients started with HD and switched to oHDF (at least 6 months oHDF). We compared the mean values of collected serum parameters three times a month. Descriptive statistical evaluation was calculated by mean, standard deviation and significance by Wilcoxon test, correlation by Spearman rang correlation. The level of significance was defined as  $p < 0.05$ .

## 3. Results

The distribution of ESA applications in the three observed dialysis centers can be seen in table 1. Totally 185 of 233 patients received at least one ESA dosage. The mean value of ferritin was 538 mg/L. The transferrin saturation (TSAT) did not differ significantly in the observed dialysis units.

	Dialysis unit						Total	
	1		2		3		N	%
	N	%	N	%	N	%		
<b>Application of ESA without ESA</b>	37	39.4	4	11.4	7	6.7	48	<b>20.6</b>
<b>At least 1 ESA dosage</b>	57	60.6	31	88.6	97	93.3	185	<b>79.4</b>

Table 1. Application of ESA per dialysis unit and overall.

The mean weekly ESA dosage can be seen in table 2:

		Dialysis unit			Total
		1	2	3	
<b>All patients</b>	<b>N</b>	94	35	104	233
	<b>Mean</b>	3550	5934	9177	6420
	<b>SD</b>	4443	5316	8487	7129
	<b>Min</b>	0	0	0	0
	<b>Median</b>	1577	5077	6500	4692
	<b>Max</b>	18667	26769	46538	46538
<b>Patients with at least one ESA dosage</b>	<b>N</b>	57	31	97	185
	<b>Mean</b>	5855	6700	9840	8086
	<b>SD</b>	4365	5170	8409	7109
	<b>Min</b>	231	167	308	167
	<b>Median</b>	4714	5538	6769	6231
	<b>Max</b>	18667	26769	46538	46538

Table 2. Mean weekly ESA dosage

In nearly all patients (98.9%) an adjustment of ESA dosage was essential. Relevant changes in ESA dosages were defined as an elevation greater than two fold and lowering of a half of the ESA dosage, the end of ESA application or the start with more than 4200 U/week. The mean value of Hb (measured per patient over the whole study time) was 7.35 mmol/l (Table 3). In patients without ESA application during the 12 months study the mean value of Hb was larger (7.66 mmol/l) in comparison to patients with ESA dosage (7.27 mmol/l).

			Dialysis unit			Total
			1	2	3	
<b>Patients without ESA</b>	<b>Mean Hb</b>	<b>N</b>	37	4	7	48
		<b>Mean</b>	7.63	7.76	7.74	<b>7.66</b>
		<b>SD</b>	0.46	0.61	0.63	0.49
		<b>Min</b>	6.7	6.9	7.2	6.7
		<b>Median</b>	7.5	8.0	7.5	7.5
		<b>Max</b>	8.8	8.3	8.8	8.8
<b>At least one ESA dosage</b>	<b>Mean Hb</b>	<b>N</b>	57	31	97	185
		<b>Mean</b>	7.38	7.09	7.25	<b>7.27</b>
		<b>SD</b>	0.41	0.52	0.53	0.50
		<b>Min</b>	6.2	6.0	5.1	5.1
		<b>Median</b>	7.5	7.2	7.4	7.4
		<b>Max</b>	8.6	8.4	8.3	8.6
<b>Total</b>	<b>Mean Hb</b>	<b>N</b>	94	35	104	233
		<b>Mean</b>	7.48	7.17	7.29	<b>7.35</b>
		<b>SD</b>	0.44	0.57	0.55	0.52
		<b>Min</b>	6.2	6.0	5.1	5.1
		<b>Median</b>	7.5	7.2	7.4	7.4
		<b>Max</b>	8.8	8.4	8.8	8.8

Table 3. Mean Hb concentrations

Table 4 shows the intra-individual variability of hemoglobin (Hbvar):

			Dialysis unit			Total
			1	2	3	
ESA without ESA	Hb range (min-max)	N	37	4	7	48
		Mean	1.98	1.35	1.93	1.92
		SD	0.92	0.68	1.11	0.93
at least one ESA dosage	Hb range (min-max)	N	57	31	97	185
		Mean	2.20	1.74	2.41	2.23
		SD	0.73	0.85	0.88	0.86
Total	Hb range (min-max)	N	94	35	104	233
		Mean	2.11	1.70	2.37	2.17
		SD	0.81	0.83	0.90	0.88

Table 4. Means of haemoglobin variability

The relation between the treatment mode (HD, oHDF) and ESA dosage as well as Hb is shown in the tables 5 and 6:

			Dialysis unit			Total
			1	2	3	
HD	All patients	N	40	32	74	146
		Mean	3608	6132	8833	6809
		SD	5058	5511	8313	7293
	Patients with at least one ESA dosage	N	22	28	69	119
		Mean	6560	7009	9473	8354
		SD	5217	5339	8248	7234
HDF	All patients	N	15	.	4	19
		Mean	3515	.	7750	4407
		SD	4160	.	5535	4660
	Patients with at least one ESA dosage	N	9	.	4	13
		Mean	5859	.	7750	6441
		SD	3853	.	5535	4287
Mixed	All patients	N	39	3	26	68
		Mean	3505	3821	10378	6147
		SD	3960	1500	9441	7313
	Patients with at least one ESA dosage	N	26	3	24	53
		Mean	5257	3821	11243	7887
		SD	3775	1500	9314	7410

Table 5. Relationship between treatment mode and required weekly ESA dosage

Hb was larger in the oHDF group and the required ESA dosage to reach the Hb concentration lower (Hb oHDF  $7.56 \pm 0.35$  mmol/l, HD  $7.25 \pm 0.52$  mmol/l,  $p = 0.01$ ; ESA/week oHDF  $4407 \pm 4660$  U/l, HD  $6809 \pm 7293$  U/l,  $p = 0.1$ ): Table 6.

			Dialysis unit			Total
			1	2	3	
HD	Mean Hb [mmol/L]	N	40	32	74	146
		Mean	7.37	7.16	7.23	7.25
		SD	0.43	0.59	0.53	0.52
HDF	Mean Hb [mmol/L]	N	15	.	4	19
		Mean	7.58	.	7.50	7.56
		SD	0.38	.	0.25	0.35
Mixed	Mean Hb [mmol/L]	N	39	3	26	68
		Mean	7.56	7.22	7.41	7.49
		SD	0.46	0.11	0.61	0.52
Total	Mean Hb [mmol/L]	N	94	35	104	233
		Mean	7.48	7.17	7.29	7.35
		SD	0.44	0.57	0.55	0.52

Table 6. Relationship between treatment mode and Hb value

In the oHDF group the intraindividual Hbvar was significantly lower than in HD (HD  $0.66 \pm 0.28$  mmol/l vs oHDF  $0.53 \pm 0.16$  mmol/l,  $p < 0.05$ ): Table 7.

				Dialysis unit			Total
				1	2	3	
HD	All patients	Intra-individual standard deviation of the Hb-value	N	40	32	74	146
			Mean	0.69	0.51	0.71	0.66
			SD	0.29	0.24	0.26	0.28
HDF	All patients	Intra-individual standard deviation of the Hb-value	N	15	.	4	19
			Mean	0.52	.	0.57	0.53
			SD	0.11	.	0.30	0.16

Table 7. Intra-individual standard deviation of the Hb-values as a function of the treatment mode

In the subanalysis the single pool Kt/V (spkt/V) was  $>1.2$  on average in all centers. But there is a significant improvement of spKt/V for oHDF compared to HD ( $p = 0.04$ ): Table 8:

				Dialysis unit			Total
				1	2	3	
HD	Mean treatment efficacy (spkt/V)	N					
		Mean	1.46	1.32	1.55	1.48	
		SD	0.60	0.29	0.38	0.44	
HDF	Mean treatment efficacy (spkt/V)	N	15	.	4	19	
		Mean	1.57	.	1.82	1.62	
		SD	0.17	.	0.52	0.28	
Mixed	Mean treatment efficacy (spkt/V)	N	38	3	26	67	
		Mean	1.48	1.16	1.45	1.45	
		SD	0.24	0.04	0.31	0.27	

Table 8. Single Pool Kt/V as a function of the treatment mode

Further analyses regarded the relationship between CRP and albumin. The tables 9 and 10 show the mean levels of CRP and albumin:

		Dialysis units			Total
		1	2	3	
Mean CRP [mg/l]	N	87	33	98	218
	Mean	15.82	14.77	13.58	<b>14.65</b>
	SD	19.48	8.75	9.67	14.30
	Min	3.6	4.5	3.1	3.1
	Median	10.2	13.1	10.4	10.6
	Max	160	47.6	40.5	160

Table 9. Mean CRP level per dialysis unit and overall

		Dialysis unit			Total
		1	2	3	
Mean albumin [g/l]	N	93	35	104	232
	Mean	40.28	39.44	38.81	<b>39.49</b>
	SD	3.10	2.17	2.84	2.93
	Min	30.4	35.8	31.0	30.4
	Median	40.5	39.6	39.0	39.6
	Max	47.1	43.7	45.9	47.1

Table 10. Mean albumin level per dialysis unit and overall

For all patients the Hb level was negatively correlated to CRP ( $r = -0.24$ ,  $p < 0.0005$ ) and positively to Albumin ( $r = 0.30$ ,  $p < 0.0001$ ) and TSAT ( $r = 0.20$ ,  $p < 0.005$ ): see table 11:

Spearman Correlation Coefficients		
Prob >  r  under H0: Rho=0		
Number of Observations		
	esamean	hbmean
crpmean CRP	0.08497	-0.23764
	0.2115	0.0004
	218	218
albmean Albumin	-0.23495	0.30050
	0.0003	<.0001
	232	232
tsatmean TSAT	-0.12875	0.19808
	0.0497	0.0024
	233	233

Table 11. Correlation of the total values for CRP, Albumin and TSAT with Hemoglobin

In a subanalysis we found significantly larger albumin levels and lower CRP concentrations in oIHDF vs HD (albumin oIHDF  $40.63 \pm 2.23$  g/l, HD  $39.11 \pm 2.76$  g/l,  $p < 0.05$ ; CRP oIHDF  $9.96 \pm 8.28$  mg/l, HD  $16.07 \pm 16.26$  mg/l,  $p < 0.05$ ): Tables 12 and 13:

			Dialysis unit			Total
			1	2	3	
Mode HD	albumin [g/l]	N	40	32	74	146
		Mean	39.89	39.35	38.58	39.11
		SD	3.10	2.11	2.72	2.76
HDF	albumin [g/l]	N	14	.	4	18
		Mean	40.74	.	40.24	40.63
		SD	2.32	.	2.17	2.23
Mixed	albumin [g/l]	N	39	3	26	68
		Mean	40.51	40.35	39.24	40.02
		SD	3.35	3.06	3.21	3.30

Table 12. Relationship between albumin levels and treatment mode

			Dialysis unit			Total
			1	2	3	
Mode HD	CRP [mg/l]	N	39	30	71	140
		Mean	18.56	15.52	14.94	16.07
		SD	26.70	8.82	10.05	16.26
HDF	CRP [mg/l]	N	12	.	2	14
		Mean	10.81	.	4.81	9.96
		SD	8.68	.	0.22	8.28
Mixed	CRP [mg/l]	N	36	3	25	64
		Mean	14.52	7.36	10.43	12.59
		SD	10.79	2.55	7.81	9.66

Table 13. Relationship between CRP levels and treatment mode

#### 4. Discussion

Our retrospective analysis was performed in three different dialysis centers for 12 months. The D1 center had the largest percentage of patients treated with oHDF (oHDF+“mixed”) (57 % in D1 vs. 9 % in D2, 29 % in D3). In D1 the lowest dosage of ESA to reach the Hb target was used (Table 2; D1 vs D2 p= 0.003; D1 vs D3 p< 0.0001), the smallest number of D1 patients were treated with ESA and the time in target was longer than in D2 and D3. In addition, it could be demonstrated that in D1 patients the frequency of adaptation of ESA dosage and Hbvar were reduced in comparison to the other centers.

Concerning the ferritin values and the transferrin saturation (TSAT) there were no noticeable differences between the observed centers. But the subanalysis shows a positive correlation of the overall TSAT values with the Hb values (p = 0.002, see Table 11) and a negative one with the mean ESA consumption (p = 0.05). These results comply with the expectation because an improved Hb value is connected with a larger TSAT level and reduced ESA needs.

The treatment efficacy (single pool and equilibrated Kt/V; spKt/V, eKt/V), which was measured periodically in the 3 dialysis units, did not show any significant influence on ESA

dosage and Hb levels. But the subanalysis calculating the impact of the different treatment modes on Kt/V resulted in a significant increased spKt/V for oIHDF treatments compared with HD ( $1.62 \pm 0.28$  for oIHDF versus  $1.48 \pm 0.44$  for HD; Table 8).

Interestingly the correlation analysis also shows a highly significant positive correlation of the mean albumin level with the mean Hb values ( $p < 0.001$ , Table 11) and a negative one with the mean ESA dosage ( $p = 0.0003$ ). Simultaneously CRP is negatively correlated with Hb ( $p = 0.0004$ , Table 11).

The significant difference in albumin concentration most likely played the decisive role for ESA dosage and Hb level (Ward, 2005). It is known that in patients who underwent convective-diffusive treatment the ESA dosage could be reduced (Vaslaki et al., 2006; Bonforte et al., 2002; Eiselt et al., 2000). That observation was confirmed by our results, reaching an economically interesting level of savings in ESA costs: Fig. 1.

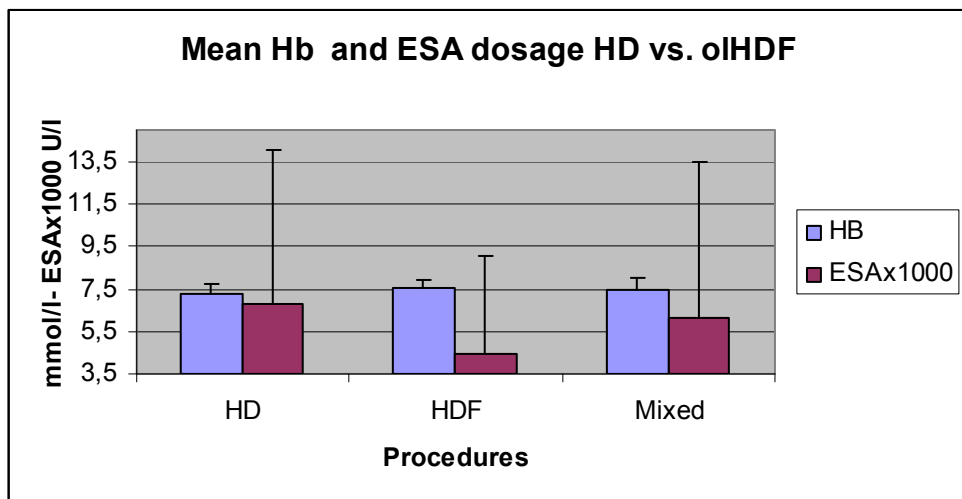


Fig. 1. Mean Hb level and ESA dosage HD vs. HDF (ESA:  $p=0.1$ , ns., Hb:  $p=0.01$ )

Typically, convective diffusive procedures are characterized by an additional removal of hydrophobic middle molecules and protein (albumin) bound uremic toxins depending on the membrane characteristics (hydrophobic areas, pore size, adsorptive properties, biocompatibility) (Ahrenholz et al., 2004; Panicchi et al., 2008). The loss of protein bound substances leads to a membrane determined loss of albumin during oIHDF sessions (Ahrenholz et al., 2004; Samtleben et al., 2003; Combarrous et al., 2002). In low flux dialysis protein removal only occurs with adsorptive membranes (PMMA, polyacrylonitrile) with decreasing dialysis efficacy for water soluble toxins (Parzer et al., 1993). This removal of albumin can be compensated after a time of about 12 weeks in the absence of relevant inflammation (Ding et al., 2002; Kaysen et al., 1997). In chronic ambulant peritoneal dialysis protein losses are in-between 6 to 10 g/d and albumin losses up to 5 g/d over the peritoneal membrane (Kaysen et al., 1984).



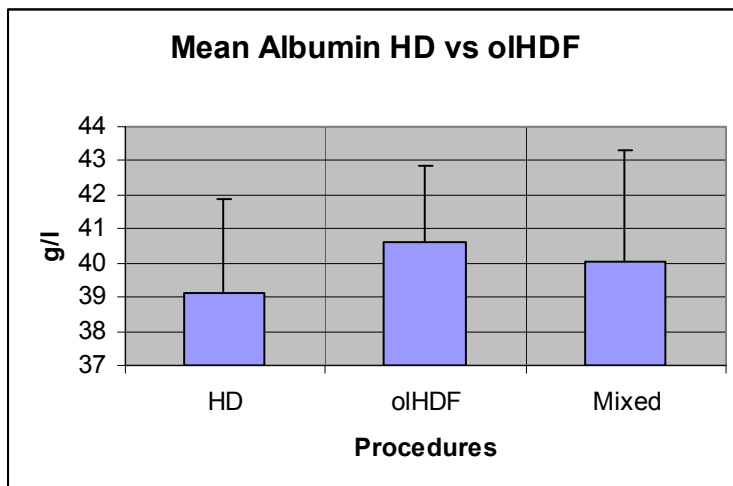


Fig. 2. Mean serum albumin concentration HD vs. oHDF (p=0.01)

Albumin losses during renal replacement procedures are generally thought of being unwanted, as low serum albumin correlates with poor outcome in dialysis patients. Therefore, oHDF, that technically spoken is an albumin-losing therapy, might carry the danger of exposing the treated patients to threads associated with low albumin levels.

It is striking that in our analysis the oHDF group had the largest serum albumin concentration (Fig. 2, Table 12). All patients of the “mixed” group (containing patients that had switched from HD to oHDF) showed an increase in albumin level rather than a decrease.

Moreover, oHDF can remove proinflammatory substances such as cytokines (Bellomo et al., 1991; Lee et al., 2004). Again, we could confirm this phenomenon with lower CRP levels in the oHDF group vs. HD group (9.96+/- 8.28 mg/l vs. HD 16.07+/- 16.26 mg/l, p=0.02), see Fig. 3, and Table 13:

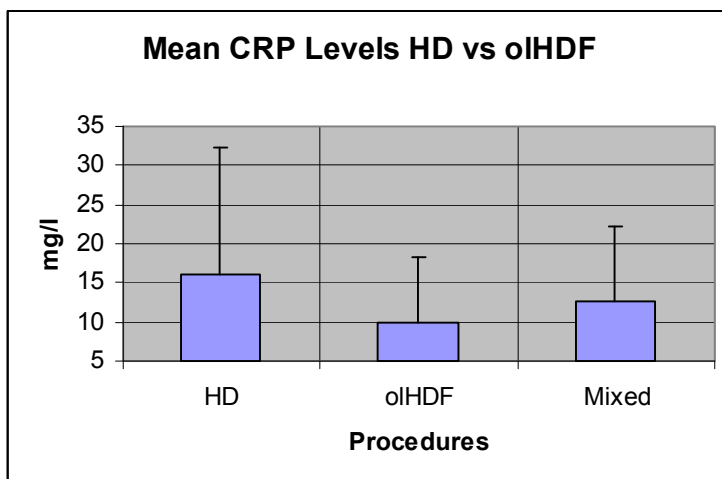


Fig. 3. Mean CRP concentration HD vs. oHDF (p=0.02)

Because albumin is a negative acute phase protein we can, in general, expect higher concentrations at lower inflammation (Panicchi et al., 2006; Kaysen et al., 1997). However, none-biocompatible membranes and partly low flux hemodialysis increases proinflammatory cytokines such as TNF-alpha. Ultrapure dialysis fluid is of relevant importance to prevent inflammation (Panicchi et al., 2008). On the other hand complement activation plays a role for inflammation during the dialysis sessions therefore biocompatible membranes are urgently necessary (Hakim et al., 1984). In the oIHDf method as use in this study, both ultrapure dialysate and biocompatible membrane materials were used, enabling clear attenuation of procedure-associated inflammatory processes. This attenuation of inflammation to us seems the key factor for increased albumin production that even makes up for procedure-associated albumin losses. The nutritional situation (nPCR) has only a secondary influence (Savica et al., 2006; Stenvinkel, 2005). Hbvar also depends on inflammation and albumin concentration (Brimble et al., 2007). Hbvar in oIHDf is lower than in HD because of less inflammation and higher concentration of albumin.

## 5. Conclusions

In a retrospective, descriptive, multicentre study the influence of oIHDf on Hb Level, ESA dosage and Hbvar was evaluated. 233 patients were included in the clinical analysis in three dialysis departments (D1 n=94; D2 n= 35, D3 n= 104). Mean dialysis efficacy expressed as spkt/V by Daugirdas was comparable in all dialysis units. We found differences in the frequency of oIHDf in the dialysis departments followed by varying parameters of inflammation (CRP) and nutrition (albumin). It can be demonstrated that patients who underwent oIHDf showed the highest serum albumin levels and the lowest signs of inflammation (CRP). This combination leads to significantly higher Hb concentrations and surprisingly lower ESA dosages to reach the target Hb in oIHDf vs HD. Due to the reduced inflammation Hbvar was improved in oIHDf vs HD. There is a correlation between serum albumin concentration, Hb level and ESA dosage. OIHDf could be the gold standard for prevention of inflammation because of removal of proinflammatory substances and hydrophobic and protein bound uremic toxins. OIHDf influences positively inflammation, nutrition, Hb level, Hb variability and required ESA dosage in chronic renal replacement therapy.

## 6. References

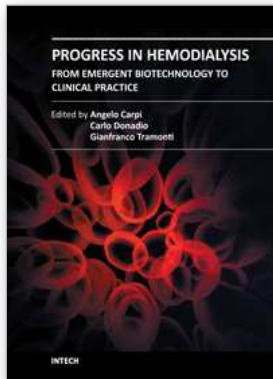
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