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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, olHDF) 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 olHDF 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 olHDF 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 olHDF 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 olHDF 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 olHDF 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 (olHDF) 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 olHDF (at least 6 months olHDF). 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	%
Application of ESA	37	39.4	4	11.4	7	6.7	48	**20.6**
without ESA								
At least 1 ESA dosage	57	60.6	31	88.6	97	93.3	185	**79.4**

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

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

		Dialysis unit			
		1	2	3	Total
All patients	**N**	94	35	104	233
	Mean	3550	5934	9177	6420
	SD	4443	5316	8487	7129
	Min	0	0	0	0
	Median	1577	5077	6500	4692
	Max	18667	26769	46538	46538
Patients with at least one ESA dosage	**N**	57	31	97	185
	Mean	5855	6700	9840	8086
	SD	4365	5170	8409	7109
	Min	231	167	308	167
	Median	4714	5538	6769	6231
	Max	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			
			1	2	3	Total
Patients without ESA	**Mean Hb**	**N**	37	4	7	48
		Mean	7.63	7.76	7.74	**7.66**
		SD	0.46	0.61	0.63	0.49
		Min	6.7	6.9	7.2	6.7
		Median	7.5	8.0	7.5	7.5
		Max	8.8	8.3	8.8	8.8
At least one ESA dosage	**Mean Hb**	**N**	57	31	97	185
		Mean	7.38	7.09	7.25	**7.27**
		SD	0.41	0.52	0.53	0.50
		Min	6.2	6.0	5.1	5.1
		Median	7.5	7.2	7.4	7.4
		Max	8.6	8.4	8.3	8.6
Total	**Mean Hb**	**N**	94	35	104	233
		Mean	7.48	7.17	7.29	**7.35**
		SD	0.44	0.57	0.55	0.52
		Min	6.2	6.0	5.1	5.1
		Median	7.5	7.2	7.4	7.4
mmol/l		**Max**	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, olHDF) 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 olHDF group and the required ESA dosage to reach the Hb concentration lower (Hb olHDF 7.56± 0.35 mmol/l, HD 7.25± 0.52 mmol/l, p= 0.01; ESA/week olHDF 4407± 4660 U/l, HD 6809±7293 U/l, p= 0.1): Table 6.

			Dialysis unit			
			1	2	3	Total
Treatment mode						
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 olHDF group the intraindividual Hbvar was significantly lower than in HD (HD 0.66±0.28 mmol/l vs olHDF 0.53±0.16 mmol/l, p<= 0.05): Table 7.

				Dialysis unit			
				1	2	3	Total
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 olHDF compared to HD (p = 0.04): Table 8:

			Dialysis unit			
			1	2	3	
HD	**Mean treatment efficacy (spkt/V)**	**N**				**Total**
		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			
		1	2	3	Total
Mean CRP [mg/l]	**N**	87	33	98	218
	Mean	15.82	14.77	13.58	**14.65**
	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			
		1	2	3	Total
Mean albumin [g/l]	**N**	93	35	104	232
	Mean	40.28	39.44	38.81	**39.49**
	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 0.2115 218	-0.23764 0.0004 218
albmean Albumin	-0.23495 0.0003 232	0.30050 <.0001 232
tsatmean TSAT	-0.12875 0.0497 233	0.19808 0.0024 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 olHDF vs HD (albumin olHDF 40.63+/-2.23 g/l, HD 39.11± 2.76 g/l, p< 0.05; CRP olHDF 9.96± 8.28 mg/l, HD 16.07 ± 16.26 mg/l, p< 0.05): Tables 12 and 13:

			Dialysis unit			
			1	2	3	Total
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			
			1	2	3	Total
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 olHDF (olHDF+"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 transferrrin 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 olHDF treatments compared with HD (1.62±0.28 for olHDF versus 1.48±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.

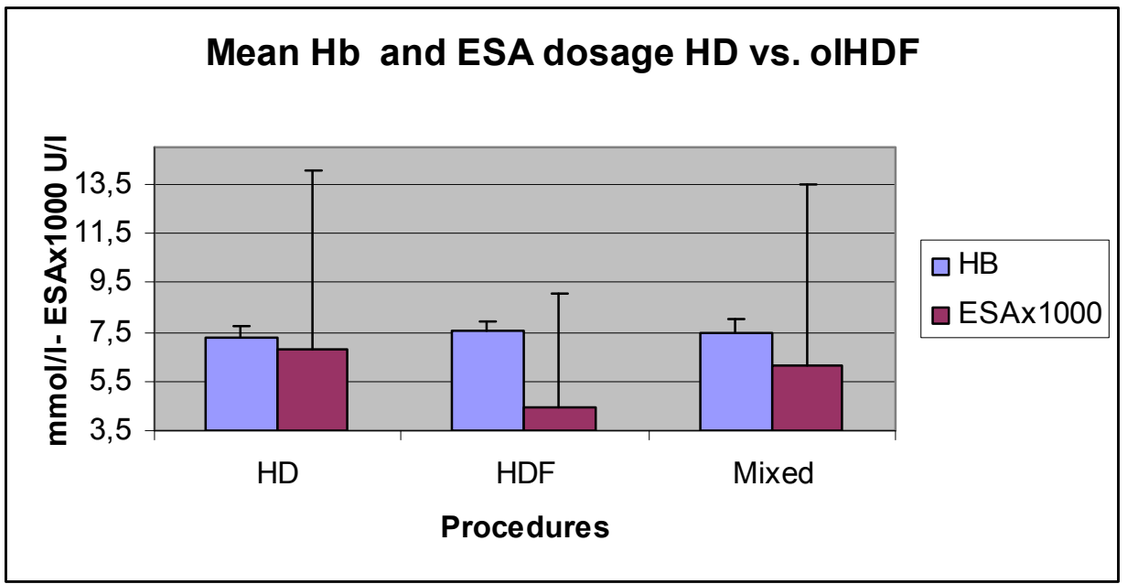

Fig. 1. Mean Hb level and ESA dosage HD vs. HDF (ESA: p=0.1, ns., Hb: p=0.01)

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 olHDF sessions (Ahrenholz et al., 2004; Samtleben et al., 2003; Combarnous et al., 2002). In low flux dialysis protein removal only occurs with adsorptive membranes (PMMA, polyacrilonitrile) 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).

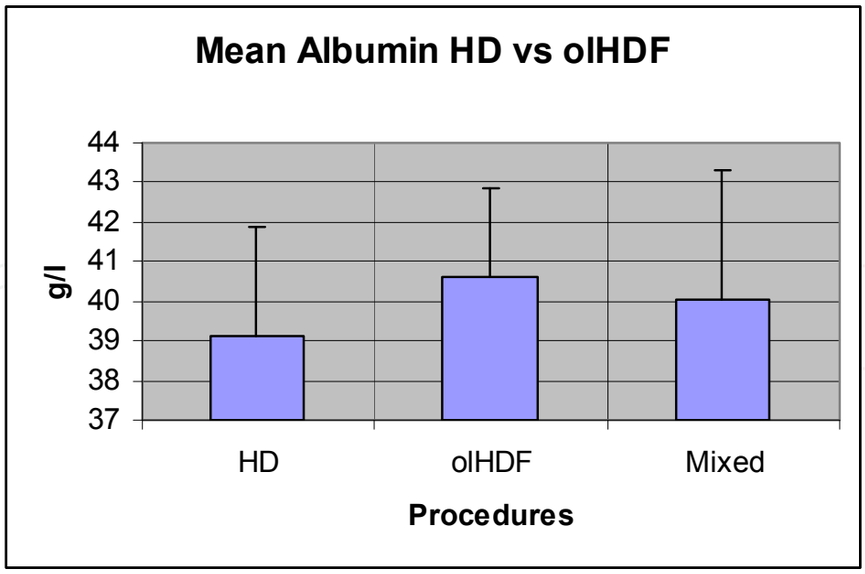

Fig. 2. Mean serum albumin concentration HD vs. olHDF (p=0.01)

Albumin losses during renal replacement procedures are generally thought of being unwanted, as low serum albumin correlates with poor outcome in dialysis patients. Therefore, olHDF, that technically spoken is an albumin-loosing 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 olHDF 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 olHDF) showed an increase in albumin level rather than a decrease.
Moreover, olHDF 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 olHDF group vs. HD group (9.96+/- 8.28 mgl/l vs. HD 16.07+/- 16.26 mg/l, p=0.02), see Fig. 3, and Table 13:

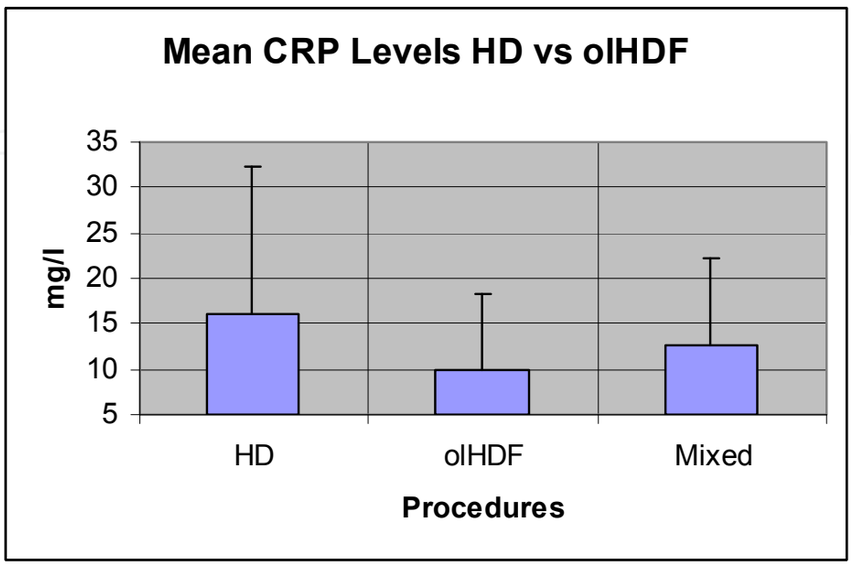

Fig. 3. Mean CRP concentration HD vs. olHDF (p=0.02)

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 olHDF 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 olHDF 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 olHDF 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 olHDF in the dialysis departments followed by varying parameters of inflammation (CRP) and nutrition (albumin). It can be demonstrated that patients who underwent olHDF 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 ol HDF vs HD. Due to the reduced inflammation Hbvar was improved in olHDF vs HD. There is a correlation between serum albumin concentration, Hb level and ESA dosage. OlHDF could be the gold standard for prevention of inflammation because of removal of proinflammatory substances and hydrophobic and protein bound uremic toxins. OlHDF influences positively inflammation, nutrition, Hb level, Hb variability and required ESA dosage in chronic renal replacement therapy.

6. References

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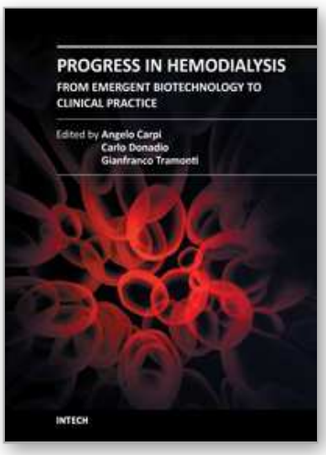

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Hemodialysis (HD) represents the first successful long-term substitutive therapy with an artificial organ for severe failure of a vital organ. Because HD was started many decades ago, a book on HD may not appear to be up-to-date. Indeed, HD covers many basic and clinical aspects and this book reflects the rapid expansion of new and controversial aspects either in the biotechnological or in the clinical field. This book revises new technologies and therapeutic options to improve dialysis treatment of uremic patients. This book consists of three parts: modeling, methods and technique, prognosis and complications.

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