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Long-term therapeutic efficacy of lipoprotein apheresis on circulating oxidative stress parameters − A comparison of two different apheresis techniques

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Abstract

Background: A chronic lipoprotein apheresis therapy leads to an expressed reduction in the incidence of cardiovascular events in high-risk patients. In addition to the elimination of atherogenic lipoproteins such as LDL and lipoprotein(a), an antioxidative effect of lipoprotein apheresis has been suspected.
Objectives and methods: We investigated long-term biochemical effects in sixteen patients undergoing lipoprotein apheresis − lipid filtration (LF, n = 7) or dextran sulfate adsorption (DSA, n = 9). Systemic oxidative stress markers (blood phagocyte chemiluminescence, levels of oxidized LDL and antioxLDL antibodies) were examined at the 1st, 40th and 80th apheresis sessions.
Results: In DSA patients, the 80th apheresis session was associated with significantly higher LDL cholesterol removal and lower HDL cholesterol deprivation as compared to LF patients. In contrast to LF patients, DSA patients showed a long-term progressive decrease in circulating oxidant generating activity as evaluated by whole blood chemiluminescence ($p < 0.05$). Moreover, a single LF apheresis session was associated with higher systemic generation of reactive oxygen species over time.
Conclusion: Compared to LF, long-term DSA apheresis is associated with a gradual reduction of circulating oxidative burden and may be considered a beneficial molecular mechanism of this technique.

Keywords: Lipoprotein apheresis; Systemic oxidative stress; Long-term biochemical effects

1. Introduction

Previous studies have reported that beyond affecting peripheral lipoprotein status various apheresis techniques induce changes in systemic oxidative stress markers. These studies were mostly conducted over a short period of time [1,2]; investigations of long-term effects of apheresis treatment on oxidative balance are rare [3]. In the present study, we examined the long-term effects of two lipoprotein apheresis techniques − (1) plasma lipidfiltration (LF, Diamed, Cologne, Germany, Octo Nova) and (2) whole blood dextran sulfate adsorption (DSA, Liposorber® D, Kaneka Corporation, Osaka, Japan) on circulating oxidative stress markers for up to two years. Both lipoprotein apheresis methods are capable of effectively eliminating

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LDL cholesterol and lipoprotein(a) (Lp(a)) and their advantages have been demonstrated in several clinical studies [4–8].

2. Methods

Sixteen patients with a history of previous apheresis treatment were enrolled in the study, seven received LF and nine received DSA in a total period of 80 subsequent apheresis sessions. All subjects gave written consent to the study, which was approved by the local Ethics Committee (EK 199052011). Baseline clinical characteristics are given in Table 1.

Mean treated plasma volume in LF was 3929 ± 170 ml (session 1). It remained constant during the study period with one exception – in one patient treatment volume was increased by 500 ml at sessions 40 and 80. Mean treated blood volume in DSA was 7711 ± 409 ml (session 1). During the study period it was increased in two patients by 400 ml and 1700 ml, respectively.

Blood for measurement of the conventional lipid status, phagocyte count, whole blood chemiluminescence, oxidized LDL, and antioxLDL antibodies was drawn immediately before and after the 1st, 40th and 80th apheresis sessions. Details of blood lipid measurement, whole blood chemiluminescence, estimation of circulating parameters of the oxidative and antioxidative balance have been described previously [1]. Statistical analysis was performed using IBM SPSS Statistics, version 22. Differences between pre-apheresis and post-apheresis values on session one, forty and eighty were calculated for each biochemical parameter from each patient. Differences between groups were assessed by one-way analysis of variance (ANOVA). P values of <0.05 were considered significant.

Table 1
Clinical characteristics of lipoprotein apheresis patients undergoing 80 apheresis sessions.

Parameter	LF (n = 7)	DSA (n = 9)	Significance p
Age	64 ± 4	62 ± 3	0.716
Gender (M/F)	5/2	6/3	–
Body Mass Index (kg/m^2)	28.0 ± 1.6	27.4 ± 1.5	0.803
Waist-to-Hip-Ratio	0.93 ± 0.38	0.91 ± 0.22	0.605
Blood pressure (mm Hg)			
systolic	125 ± 5	126 ± 6	0.950
diastolic	72 ± 1	72 ± 3	0.984
Inflammatory markers			
Leukocyte count (Gpt/l)	5.9 ± 0.6	5.6 ± 0.5	0.771
C-reactive protein (mg/l)	2.4 ± 0.6	1.6 ± 0.7	0.440
Drugs (patients)			
Statins/Fibrates	7	9	–
Antihypertensive agents	6	6	–
Anticoagulants	4	2	–
Analgetics	4	7	–
Duration of apheresis treatment (weeks)			
40 sessions	48 ± 3	46 ± 2	0.617
80 sessions	98 ± 3	97 ± 3	0.825

Data are means ± SEM; univariate analysis of variance (ANOVA).

3. Results

There were no significant changes from baseline in pre apheresis Lp(a), total cholesterol, triglyceride, HDL cholesterol and LDL cholesterol levels at sessions 40 and 80 in both apheresis groups. Table 2 shows absolute changes in lipid and lipoprotein parameters at different time points.

Both LF and DSA technique were effective in elimination of LDL cholesterol, total cholesterol, triglycerides and Lp(a) (significant pre to post apheresis changes at 1st, 40th and 80th session) and in conservation of HDL cholesterol (no significant pre to post apheresis changes over time).

Percentage changes during a single apheresis treatment are documented in Table 3. Compared to LF, percentage LDL cholesterol reduction was significantly higher in DSA at sessions 1, 40 and 80. Furthermore, at session 80 patients treated with DSA showed a significantly lower HDL and triglyceride reduction compared to LF procedure.

LF and DSA procedures exerted distinct effects on circulating capabilities of generation of reactive oxygen species (ROS), mostly independent of the time-point of follow-up. Due to opposite changes in phagocyte count (pre-to post-apheresis increase in LF, decrease in DSA) circulating blood of LF patients generated a higher amount of ROS than observed in DSA patients. Fig. 1 displays percent changes of parameters of the oxidative and antioxidative potential during session 80.

Similar changes were observed in session 1 and 40 (data not shown) with two exceptions – the significantly greater percent declines in levels of oxidized LDL (−59.3% LF vs. −68.0% DSA, p = 0.013) and antioxLDL antibodies (−12.6% LF vs. −38.6% DSA, p = 0.012) in DSA patients (session 1) were no more detectable in sessions 40 and 80. Changes in lipid and lipoprotein parameters and ROS generating activities did not correlate over time.

Absolute values of whole blood chemiluminescence are shown in Fig. 2. In contrast to LF patients, subjects treated with DSA showed a significant gradual decrease in circulating ROS generating activity over time. This decline from session 1 to session 80 could be demonstrated by stimulation of phagocytes with zymosan (Fig. 2A) or with zymosan plus the chemotactic peptide formyl-methionyl-leucyl phenylalanine (maximum stimulation, Fig. 2B).

4. Discussion

In patients with severe hypercholesterolemia or combined dyslipoproteinemia and/or with an elevation of Lp(a) levels the reduction in atherogenic lipoproteins is the critical determinant for clinical outcome. LDL is the best established risk factor for cardiovascular disease. In addition, several epidemiological studies document an