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Adverse events of lipoprotein apheresis and immunoadsorption at the Apheresis Center at the University Hospital Dresden

J. Dittrich-Riediger, U. Schatz, B. Hohenstein, U. Julius*

Department of Internal Medicine III, University Hospital Carl Gustav Carus at the Technische Universität Dresden, Fetscherstr. 74, 01307 Dresden, Germany

Abstract

Background: Lipoprotein apheresis and immunoadsorption methods have a firm place among therapeutic approaches in order to treat disorders of lipoprotein metabolism or anti-body induced diseases. The extracorporeal treatment is associated with adverse effects, we wanted to report the Dresden experience.

Methods: In this study we retrospectively analyzed the adverse events of several lipoprotein apheresis and immunoadsorption methods at the Apheresis Center in Dresden (Germany). We carefully looked into all available documents. The first extracorporeal lipoprotein apheresis was performed in 1990 and the first extracorporeal immunoadsorption was executed in 1995. Throughout the 23 years study period, 10 different methods were employed in treating 268 patients for a total of 25,293 treatments.

Results: Adverse events of varying severity occurred in 1948 of the treatments (7.7%). We subdivided them into mild (61.3% no treatment was necessary), moderate (37.0% oral medication or infusion was given) and severe (1.7% emergency hospitalization was necessary). Therapy had to be stopped prematurely in 1.5% of the treatments. We compared adverse events profiles among the different methods and evaluated for differences by gender. Females were found to have a significantly higher risk of adverse events than male patients. In males, the rate of adverse events ranged from 3.3% (Liposorber® D) to 11% (Therasorb™ Ig); in females the minimum rate was 7.8% (DALI) and the maximum 30% (rheopheresis). Adverse events were evenly distributed between the ages of 30–69, the age range at which most of the therapies were performed. We also found that all methods had a higher rate of adverse events during the first year of treatment. Puncture problems and hypotension were the most common adverse events.

Conclusion: It can be stressed that in general the extracorporeal methods used can be regarded as safe.

Keywords: Lipoprotein apheresis; Immunoadsorption; Adverse events; Heparin allergy; Gender differences

1. Introduction

Extracorporeal treatment of hypercholesterolemia using plasma exchange was first performed by de Gennes in 1967 [1] with other groups following in the early 1970s [2]. In the 1980s and 1990s, numerous apheresis techniques were developed to selectively remove preferably those particles from plasma or whole blood which play a role in the pathophysiology of atherosclerosis, particularly LDL and lipoprotein(a) [3]. Lipoprotein apheresis (LA) is an accepted and effective tool in preventing the incidence of new cardiovascular events in patients at high risk for cardiovascular disease due to severe hyperlipoproteinemia not adequately controlled by diet and medication [4–9]. In Germany, three indications have been accepted for extracorporeal LA therapy: 1) homozygous familial hypercholesterolemia; 2) severe hypercholesterolemia, if a maximum documented dietetic and drug therapy for more than one year

* Corresponding author. Tel.: +49 351 458 2306; fax: +49 351 458 5306.
E-mail address: ulrich.julius@uniklinikum-dresden.de (U. Julius).

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failed to lower LDL cholesterol (LDL-C) sufficiently; and 3) elevation of lipoprotein(a) (LP(a)) above 600 mg/l together with progressive cardiovascular disease documented clinically or by imaging techniques [10]. At the Dresden center, most patients are treated once a week, although some patients are treated bi-weekly or even larger intervals.

Several diseases like pemphigus vulgaris, systemic lupus erythematosus, macular degeneration and other diseases can be treated with immunoadsorption (IA) and rheopheresis (Rheo) respectively. For such cases, an individualized treatment regimen was used.

Here we describe the frequency and severity of adverse events of all extracorporeal methods that had been performed in our center.

2. Patients and methods

2.1. Patients

Starting with the first treatment in 1990, all patients treated at our center until December 31, 2013 were included. Treatments and adverse events of 268 patients were reviewed for every treatment method.

Before starting the extracorporeal treatment, each patient gave written informed consent after he was informed about the expected benefits and possible adverse events of the planned treatment method.

2.2. Methods

All treatment protocols and medical records for each patient undergoing LA, IA and Rheo were reviewed. Adverse events documented in the medical records included the following: hypotension, hypocalcemia, bleeding/hematoma, heparin-allergy, discomfort, edema, bradykinin syndrome, puncture problems, applying of an arteriovenous fistula, abdominal pain, pain at the puncture site, hypertension, patch-allergy, numbness in the arm and hand, feeling of heat, hearing loss, angina pectoris attack, nausea, vertigo, headache, cardiac arrhythmias, thrombosis of the AV fistula, pain from the AV fistula, AV fistula insufficiency, syncope, shortness of breath, speech disorder and an increase of INR after HELP apheresis sessions.

We subdivided the severity of these adverse events into mild (no treatment was necessary), moderate (oral medication or infusion was given) and severe (emergency hospitalization was necessary).

2.2.1. Lipoprotein apheresis (LA), immunoadsorption (IA) and rheopheresis (Rheo) methods

The six ***LA methods*** used in Dresden are based on different techniques (precipitation, filtration and adsorption) [11].

- **Precipitation**: HELP (heparin-induced extracorporeal LDL precipitation treatment; B. Braun, Avitum AG, Melsungen, Germany)
- **Filtration**: Lipidfiltration (LF; DIAMED Medizintechnik GmbH, Cologne, Germany) and MONET (Membrane Filtration Optimised Novel Extracorporeal Treatment; Fresenius Medical Care, Bad Homburg Germany)
- **Adsorption**: DALI (Direct adsorption of lipoproteins; Fresenius Medical Care, Bad Homburg, Germany), Liposorber® D (Kaneka Pharma Europe N.V., Eschborn, Germany), TheraSorb™ LDL (antibodies; Miltenyi Biotec GmbH, Bergisch Gladbach, Germany).

The three ***IA methods*** are:

- **Adsorption**: TheraSorb™ Ig (antibodies; Miltenyi Biotec, GmbH, Bergisch Gladbach, Germany), TheraSorb™ Ig flex (antibodies; Miltenyi Biotec, GmbH, Bergisch Gladbach, Germany) and Immunosorba (Protein a; Fresenius Medical Care, Bad Homburg, Germany).

Filtration and adsorption is used for the ***Rheo***:

- **Filtration**: DFPP (double filtration plasmapheresis; Diamed Medizintechnik GmbH, Cologne, Germany)
- **Adsorption**: TheraSorb™ – Rheo Apheresis (pentapeptide; Miltenyi Biotec, GmbH Bergisch Gladbach, Germany)

2.2.2. Statistical analysis

For the comparison between men and women among the various procedures a logistic regression and chi-square tests was used. The range for the statistical significance was set at a p-value of <0.05 (SPSS version 21).

3. Results

3.1. Patients and time course of treatment

In 1990, the first LA was first performed in Dresden in two patients. Since then, 268 patients (162 men and 106 women) were treated at the Dresden center using 10 different methods. The patients were between 7 and 89 years old, with a mean age of 56 years.

Subsequently, we analyzed four patient groups according to the applied treatment procedure: 1) LA, 2) IA using Therasorb™ Ig, 3) HELP in patients with acute hearing loss or diabetic foot syndrome, 4) other IA treatment methods such as Ig-Flex, Immunosorba and Rheo treatments (Table 1). All data was analyzed until the end of treatment at our center. From groups 1 and 2, eight patients died during the study period. One patient died from a bronchial carcinoma, one from a stroke, one from an embolism and 5 had an unknown cause of death. None of them passed away due to the extracorporeal therapy.

At the end of 2013, 96 patients in groups 1 and 2 were on a regular treatment. For the whole study period the total