RHEOPHERESIS AND ITS USE IN THE TREATMENT OF DISEASES WITH IMPAIRED MICROCIRCULATION. A REVIEW

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The author of the study declares that no conflict of interests exists in the compilation, theme and subsequent publication of this professional communication, and that it is not supported by any pharmaceuticals company. The study has not been printed or sent to any other journal, with the exception of congress abstracts and recommended procedures.

Received: 16 August 2022
Accepted: 18 November 2022
Available online: 20 February 2023

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SUMMARY

Rheopheresis ranks among apheretic methods. It is a selective, extra-corporeal double cascade filtration treatment. First, the plasma is separated from blood elements in extra-corporeal circulation by passing through membrane filter. The plasma is then filtrated through the second filter in order to remove proteins with a high molecular mass, e.g. lipids, fibrinogen, α2-macroglobulin, von Willebrand factor, immunoglobulin IgM. The purified plasma is then returned together with the blood elements back to the patient. The aim of the procedure is to improve the microcirculation and rheological properties of the blood. Rheopheresis is well established method for the treatment of age-related macular degeneration, acute sensorineural hearing loss, calciphylaxis, systemic sclerosis or peripheral vascular disease.

Key words: apheresis, plasmapheresis, rheopheresis, macular degeneration

Čes. a slov. Oftal., 79, 2023, No. 1, p. 3–5

Therapeutic aphereses are extra-corporeal methods of purifying the blood used as a part of the treatment of certain immunologically conditioned, haematological, nephrological diseases, in transplantation medicine or in patients with progressive atherosclerosis. Fig. 1.

The least selective apheretic method is plasmapheresis, which has been in use the longest of all the procedures, and is still used today. In plasmapheresis the plasma is separated from the blood elements by a membrane filter, and subsequently liquidated. The removed plasma may be replaced with fresh frozen plasma from a donor or a colloid solution with albumin. This is a non-selective method in which substances with a high molecular density such as autoantibodies, alloantibodies, immunoglobulins, antigen-antibody complexes, endogenic toxins and other components present in the plasma are removed together with the plasma [1]. The development of apheretic methods has been in a direction towards more selective procedures. Rheopheresis is a technique which is intended to improve the rheological properties of blood. It differs from plasmapheresis in the fact that the separated plasma then passes through a second, rheopheretic filter, which filters out a precisely defined spectrum of proteins with a high molecular density. For this reason, it is also referred to as double filtration plasmapheresis (DFPP). The molecules trapped by the rheopheretic filter include α2-macroglobulin, fibrinogen, LDL-cholesterol, Lp(a), von Willebrand factor, IgM, fibronectin, multimeric vitronectin [2]. There is a reduction of the activity of all three complement pathways. This leads to an improvement of blood and plasma viscosity, and a reduction of the aggregation of erythrocytes. An improvement of microcirculation is achieved independently of the underlying pathology. Fibrinogen and other globulins such as α2-macroglobulin are determinants of blood viscosity, and serve as macromolecular bridges for the aggregation of erythrocytes. Plasmatic viscosity is reduced by the procedure by approximately 20%, and aggregability of erythrocytes by 60%. The rheopheretic effects on microcirculation are pleiotropic [3]. In addition to the removal of macromolecules, changes occur in the levels of cytokines, adhesive molecules, there is an increase in the production of endothelial nitrous oxide (NO), a reduction in the aggregability not only of erythrocytes but

also thrombocytes [4]. Some components of the coagulation cascade are capable of activating the complement cascade, the terminal membrane complex of which leads to endothelial damage to the capillaries. In rheopheresis there is a reduction of fibrinogen, which plays an important role in the coagulation cascade and its relationship to the complement. Upon modification of microcirculation, the complete interactive environment between the plasma, blood cells, vascular wall, cellular and extracellular interstitial structures is stabilised and modified [5].

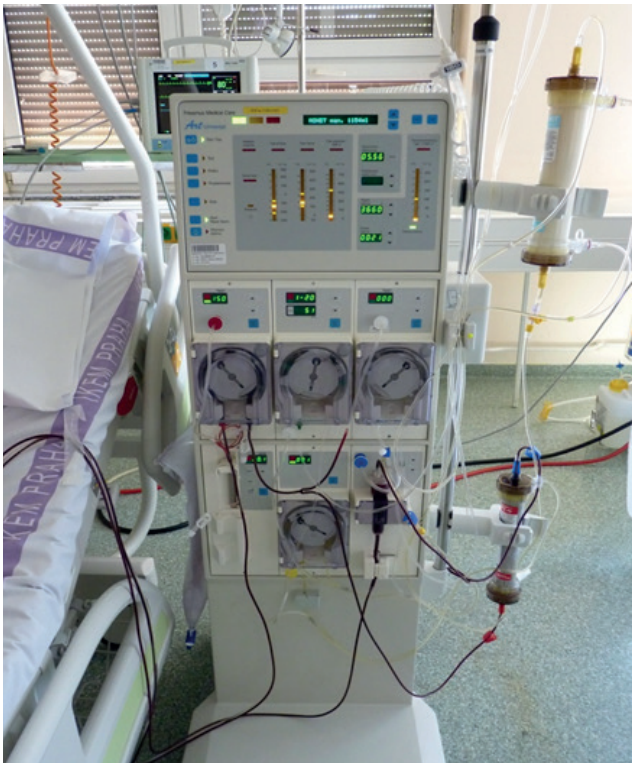

Figure 1. Apheretic device set for rheopheresis. Underneath a membrane filter for plasma separation, above a rheopheretic filter that captures macromolecules. Extracorporeal circulation set lines attached to the bed, draining from the patient and returning whole blood back to the patient´s circulation

After the plasma has passed through the rheopheretic filter, blood elements are returned to it, and it is subsequently returned back into the patient's circulation. During a single procedure, 1.5 times the plasmatic volume is processed. In the treatment of macular degeneration, patients undergo 8 procedures over the course of 10 weeks [6]. Extra-corporeal circulation requires anticoagulation. The anticoagulants used are citrate, unfractionated heparin or low molecular weight heparin. The patient's own veins can be used as the vascular access Fig. 2. In the case of inadequate quality of the veins, a central venous catheter is used, most commonly inserted into the jugular veins, less commonly into the subclavian vein. The incidence of clinically manifest adverse reactions is approximately 4%, the majority of them less severe. Severe complications (incidence less than 1%) include allergic reactions, fever, haemolysis, dyspnoea, shock and arrhythmia. Bradykinin may form on the membranes of the filters, an excess of which in patients receiving therapy by ACE inhibitors (ACEI) may lead to severe hypotension and anaphylaxis. Administration of ACEIs should be discontinued at least one day before the procedure, they can be substituted with angiotensin II blockers (ARB). Pregnancy is not a contraindication for the performance of the procedures [7].

Since 2018, when the rheopheresis programme was launched, 25 patients have been treated for macular degeneration at the Dialysis Centre of the Institute of Clinical Experimental Medicine. After being referred for rheopheresis by an ophthalmologist, patients are invited to attend an initial examination, where their capacity to undergo the treatment is assessed from an internal medical perspective, and the therapeutic procedure is explained in detail. The most frequent contraindications are severe cardiac dysfunction, upon which the haemo-

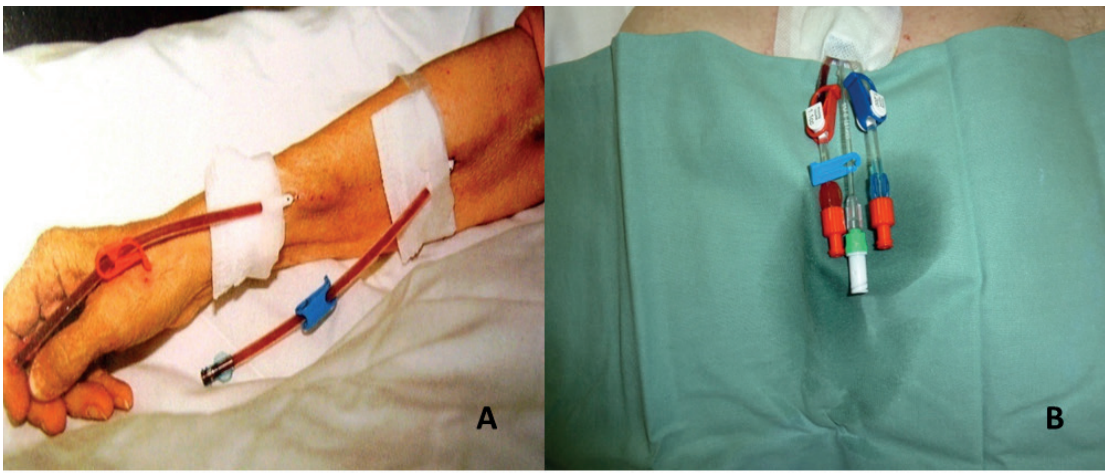

Figure 2. Possibilities of venous access to extracorporeal circulation connection. **(A)** arterio-venous fistula, **(B)** central venous catheter

dynamic instability during the procedures outweighs the benefits of treatment. If no impediments are found in any aspect, dates are arranged for the treatment sessions. For the majority of patients, in order to ensure the smooth course of the procedure it was necessary for us to insert a central venous catheter. We use a permanent catheter, which is inserted by our physicians under local anaesthesia on the dialysis unit on the day of the first procedure. The advantage of a permanent catheter is that it does not need replacing after 2–3 weeks as in the case of temporary catheters. After the end of the treatment the catheter is extracted by the surgeons in the operatingroom, due to the necessity of preparing the ingrown dacron cuff into the hypodermis. The catheter is inserted in antibiotic prophylaxis, which is administered to the patient directly before the procedure. Procedures last 2–3 hours, all treatment takes place in outpatient care. The majority of patients tolerate the procedures well, and are able to leave the centre and go home unaccompanied. In the weeks when a catheter is not used, flushes are required 1x per week. These are performed either at our centre or following prior arrangement at dialysis centres in the localities of the patients' place of residence.

Rheopheresis is an established component of therapeutic protocols of certain diseases. It is a safe and effective modality within the framework of therapeutic aphereses. It is indicated in the case of diseases with impaired microcirculation, independently of the etiopathogenesis of the disease.

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