

The Potential of Heparin-induced Extracorporeal LDL/fibrinogen Precipitation (HELP)-apheresis for Patients with severe acute or chronic COVID-19

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Basic concept

In COVID-19 pandemic, the key question is: Which therapeutic approach should be favoured in order to save seriously sick patients? What kind of approach is suitable to prevent looming acute lung failure involving microthrombi and inflammation of the endothelium (1–5) as a result of an excessive immune response of the body when the first lines of the host defence have already failed? We know that SARS-CoV-2

uses the angiotensin-converting enzyme 2 (ACE2) receptor and the transmembrane serine protease 2 (TMPRSS2) as gateways (6–8) to infect cells of the alveolar epithelium (1–4) and endothelial cells in the lungs, heart, kidneys, intestines, and liver (5). This is why cardiac patients, those with hypertension, diabetes, or obesity exhibit a higher mortality risk (3) as their receptor density is up-regulated. Moreover, the binding of the SARS-CoV-2 spike protein inhibits and down-regulates ACE2 function which in turn promotes the inflammatory response (6–8).

Histological studies confirmed the presence of the virus in both cell types: alveolar epithelium and endothelial cells (1–5). Alveolar tissue and adjacent capillaries reveal massive inflammatory and procoagulatory activation together with cell necrosis, thrombi and massive fibrinoid deposits (1–5,9-10). It results in the clinical picture of an obstructed gas exchange. The enlargement of the diffusion barrier limits the benefits of artificial ventilation and extracorporeal membrane oxygenation (ECMO). Additionally, the latter promotes formation of radicals as a side effect.

The application of HELP apheresis could significantly contribute to the restoration of microcirculation in the lungs and other affected organs. The method, developed by Seidel and Wieland in 1984 primarily for patients with severe hyperlipidemia or familial homozygous hypercholesterolaemia (11–17), has not only been proven beneficial as an ultima ratio treatment of arteriosclerosis and its atherothrombotic sequelae. It also has been successfully applied in coronary heart disease (11–14,18–20), to prevent and treat graft vessel disease following heart transplantation (20–26), acute thrombotic graft occlusion following aortocoronary bypass surgery (27), preeclampsia (28–29), strokes (30–33), unstable angina pectoris (34), and hyperlipoproteinaemia (a) (19). It exhibits anti-inflammatory effects in chronic as well

as acute inflammatory processes of the endothelium in the micro- and macrocirculation (13–23, 27, 35-36) and has anticoagulant properties (12, 37-38).

Methodology

During HELP apheresis, blood cells are first separated from plasma in the extracorporeal circuit, then 400.000 units of unfractionated heparin are added to the plasma, and the pH is lowered to 5.12 using an acetate buffer. That is the isoelectric point for the optimal precipitation of the apolipoproteins from LDL cholesterol, lipoprotein(a) (Lp(a)) and VLDL, which are precipitated in the precipitation filter together with fibrinogen. The excess heparin is adsorbed and bicarbonate dialysis balances the pH again. Patient's blood cells are reinfused in parallel with a saline solution (11,37). The duration of treatment – two hours at average – can be shortened or extended to meet individual needs (37).

Indications for HELP apheresis

COVID-19 patients most probably will benefit from HELP apheresis due to the following reasons:

1. It has no allocation problem and allows direct access to the entire macro- and microcirculation due to its extracorporeal access.
2. It uses 400,000 units of unfractionated heparin in the extracorporeal circuit, which was shown of being capable to bind SARS-CoV-2 spike protein and thereby could directly remove the virus during viraemia (10).

3. The large quantity of unfractionated heparin allows the dissolution of forming microthrombi without a bleeding risk due to the heparin adsorber (37).
4. HELP apheresis removes about 50% to 60% of fibrinogen, the most important coagulation protein, within two hours, that in turn immediately improves oxygen supply in the capillaries (37,38).
5. Additionally, it partially removes the precursors of both the procoagulatory and the fibrinolytic cascade by 35% to 50%, thus deescalating the entire haemostaseological system (37). However, antithrombin III is only eliminated by 25% (37) ensuring minimised bleeding risk complications.
6. From the very beginning, HELP apheresis is rheologically effective (17-18,20,39): It increases myocardial (17,39), cerebral (40) and pulmonary blood flow rates, and coronary flow reserve (39). These effects facilitate oxygen exchange in the capillaries sustainably (38).
7. It removes cytokines such as interleukin (IL)-6, IL-8 and TNF- α , and reduces C-reactive Protein (CRP) concentration by more than 50% (28,35,36). The heparin adsorber completely eliminates endo- and ectotoxins (35), so that the excessive inflammatory response, the so-called cytokine storm, can calm down (9,10,35,36).
8. HELP apheresis has already been successfully applied for septic multi-organ failure in pilot studies by Bengsch et al. (35,36). In modified form, it showed a successful outcome in the EHEC epidemic in patients suffering from the haemolytic-uraemic syndrome (HUS) (41).
9. HELP apheresis is an established commercially available system (B. Braun AG, Melsungen, Germany) that has been in clinical use for 36 years. It is easy to handle and has been shown to reduce complication rates in acute and chronic cardiac

patients very effectively by 82% to 97% (14,16-17,19,21,23). Long-term clinical experience with HELP apheresis suggests with a probability close to certainty that it cannot inflict harm upon COVID-19 patients.

10. It does not remove protective IgM or IgG antibodies and does not affect leukocyte or platelet function. In the past, the therapy has been shown to be well-tolerated and safe during treatment with antiviral drugs, antibiotics, anticoagulants, or antihypertensive drugs.

Background

In patients who are suffering from severe COVID-19, the computed tomography (CT) scan of the lungs shows ground-glass-like interstitial thickening (5) which presumably leads to acute respiratory distress syndrome (ARDS). As a result of an excessive immune response, it appears uncontrollable. The advanced disease stage develops after initial antiviral defence lines of the innate immune system - such as protective effects of interferons and secretory IgA on alveolar epithelium - have failed to eliminate the virus. In case SARS-CoV-2 causes relevant viraemia, the clinical course turns out to be worse on the other hand, viraemia is the prerequisite of humoral antibody synthesis of IgM and IgG subtypes. They could lyse virus-infected cells in the presence of complement factors. As far as we know, the nature and extent of the cellular immune response to viral antigens is almost entirely dependent on T lymphocytes. The cell-mediated antibody-dependent cytotoxicity is T cell-dependent and currently is being the subject of intensive virological and cell biological research.

Ideally, intervention in the inflammatory cascade takes place as early as possible before the onset of the “cytokine tsunami” in order to prevent an uncontrollable coagulation and inflammatory activity (9,10) harming microcirculation in lungs and other organs. The phenomenon of a “cytokine storm” was first described in 1973 in graft-versus-host disease (GvHD) following organ transplantation, and later in ARDS, sepsis, Ebola, avian flu H5N1, smallpox, systemic inflammatory response syndrome (SIRS), and now in COVID-19 (43).

Cytokines are proteins that coordinate and modulate cellular immune responses: they guide and activate leukocytes – in particular, T-lymphocytes and monocytes – to the site of inflammation where cytokine secretion is regulated by positive feedback. During a “cytokine storm”, leukocytes are activated in such an extent that the immune response seems inexorable. High concentrations of IL-1 β , IL-6, and IL-8 are expressed (9-10,43-45). Furthermore, IL-1 β and IL-6, together with TNF- α – the latter being mainly expressed by macrophages – direct systemic inflammatory effects such as the increase in body temperature and blood flow, capillary permeability and leakage. Due to the complexity of regulation and orchestral functions, IL-6 plays a key role in the transition of mechanisms of innate to acquired immunity (44,46). CRP triggers IL-6 (45) and IL-6 links procoagulatory activation, especially triggering fibrinogen production in the liver (38).

Whenever the body’s defense is not able clear the virus from all sites, the inflammation may persist in macrophages, in vascular beds, or in the brain stem and chronify, as recently reviewed by Proal and VanElzakker (47) with the consequence of a wide range of longlasting clinical symptoms and an impaired host immunity.

Effects of HELP apheresis

The anti-inflammatory effects of HELP apheresis had been intensively investigated by Bengsch et al. (35,36) in the nineties. It has been applied by them in pilot studies to successfully treat sepsis and sepsis shock patients with multiple organ failure. In 2012, we were able to rescue a patient with EHEC-induced hemolytic uremic syndrome from her comatose state within hours, and from kidney failure within two days (41).

In the case of COVID-19, HELP apheresis could be of immediate benefit because this extracorporeal system can reduce trigger and effector of the overwhelming immune response simultaneously. SARS-CoV-2, circulating cytokines, CRP, on top fibrinogen are reduced drastically, the latter by 50% within two hours. As a result, the rheology of the pulmonary microcirculation will immediately be relieved – without reduction of the erythrocyte concentration. Fibrinogen is the effector of plasmatic coagulation and decisive determinant in the microcirculation, plasma viscosity and erythrocyte aggregability (38). Due to the use of unfractionated heparin, the antithrombotic effect is maximal.

Previous studies using positron emission tomography in heart transplant patients showed that the median coronary blood flow rate remains significantly increased by 17.5% for 24 hours after a single two-hour apheresis procedure. It increases by 27% under simulated exposure to administration of adenosine (20). Principally, the decreased fibrinogen concentration causes the rheologically significant effects and facilitates oxygen exchange. Plasma viscosity is reduced at average by 19%, and erythrocyte aggregability is significantly decreased by 60% (20). In addition, the vascular endothelial growth factor (VEGF) and nitric oxide (NO) release are favourably influenced (20). The improvements have been also demonstrated for the

cerebral blood flow in cardiac patients profit from an 63% increase in the CO₂ reserve capacity (40).

HELP apheresis reduces LDL cholesterol and Lp(a) concentrations with similar efficacy as fibrinogen (11-12), thereby improving endothelial function (20, 39-40). In regard to LDL reduction through apheresis, it remains unclear whether SARS-CoV-2 resembles delta coronavirus, which uses cholesterol as a vector due to its lipid envelope (42).

For practical reasons it is important to mention that HELP apheresis is not restricted to a two-hour treatment time. The system can be recirculated for many hours – until the precipitate filter that can be replaced easily during the application – so the fibrinogen concentration theoretically could be reduced by up to 99.9999%. In-depth preliminary studies into the influence of HELP apheresis on the kinetics of the procoagulation and fibrinolytic cascades have shown that also the precursors of both cascades are reduced by 35% to 50% within two hours – with the exception of antithrombin III, which is reduced by 25% (37). Taking together, HELP apheresis thus deescalates the coagulation situation of both arms without bleeding risk due to the complete adsorption of unfractionated heparin (37).

The heparin adsorber also has the ability to eliminate endo- and exotoxins regardless of viral or bacterial origin (35,36,41). Even if it is not yet known whether and to what extent toxins play an important in the pathogenesis of COVID-19, it is indisputable that the course of a lung infections aggravated in the presence of toxins. Data from the American Thoracic Society show that pneumonia takes a more severe course in patients with a lung microbiome that contains gram-negative toxin-producing bacteria (48).

The use of HELP apheresis should be considered for the treatment of both acute and chronic COVID patients to avoid suffering. Our first experiences with long COVID patients are promising and summarized in the corresponding article

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