Tandem plasmapheresis and haemodialysis as a safe procedure in 82 patients with immune-mediated disease

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Abstract

Background. A number of medical, mostly immune-mediated conditions call for a combination therapy consisting of plasmapheresis and haemodialysis. While the two treatments are most commonly applied separately, we describe here the technical details of providing a combined ‘tandem’ treatment.

Method. The components of a dialyzer (polysulfon membrane) and plasma filter are serially connected by a continuous arteriovenous haemofiltration (CAVH) system. In an extracorporeal circulation, using a blood pump the patient’s blood is led first to the plasma filter and then into the dialyzer. The substituate connection is located behind the plasma filter and before the dialyzer. At the beginning it is obligatory to carry out an inspection of tubing system leakages. Afterwards, the system is flushed with a heparinized (5000 IE) sodium chloride solution that is removed thereafter.

During the treatment, a blood flow of 150–200 ml/min is possible. In each case, the plasmafiltration and the ultrafiltration should not exceed 25% of the blood flow. The whole time, an intermittent check of blood pressure and heart rate is necessary. The total procedure does not take longer than a routine haemodialysis (3–4 h).

Results. In 82 patients we performed 483 tandem treatments during the last 16 years. None of the patients had volume disturbances caused by plasma shifts and derangements of electrolytes and acid–base balance were immediately equalized. There were no episodes of hypotension or bleeding. Back-filtration did not occur.

Conclusion. Providing both haemodialysis and plasmapheresis at the same time reduces treatment time and thus, overall cost of the treatment. This retrospective analysis shows the tandem treatment to be safe and effective.

Keywords: combined extracorporeal treatments; haemodialysis; plasmapheresis; thrombotic microangiopathy; vasculitis

Introduction

A number of nephrological diseases are immune mediated and under certain circumstances require both plasmapheresis (PE) and the simultaneous initiation of kidney replacement therapy. The effective removal of pathogenic large molecular plasma components and the treatment of uraemia are significant therapeutic goals. A combination consisting of haemodialysis (HD) and PE unites both goals.

PE, for example, is an established procedure for treating, among other things, thrombotic microangiopathies. In cases with renal affect, haemodialysis treatment is required at the same time. Goodpasture’s syndrome is caused by specific pathogenic antibodies that are directed against structural antigens of the glomerular and alveolar basal membrane. PE together with immunosuppression with steroids and cyclophosphamide is also standard therapy for Goodpasture’s syndrome. Although PE used to be viewed as indicated even before the initiation of dialysis, it is often performed in spite of necessary kidney replacement therapy, both for renal and extra-renal indications [1,2]. Rapidly progressive glomerulonephritis is another indication for PE that may, for example, occur in the context of vasculitis (c-ANCA, p-ANCA) [3,4]. A similar approach is taken with essential cryoglobulinaemia with precipitating immunoglobulin complexes that induce vasculitis with complementary activity [5]. Here, too, PE may be performed as a last resort.

In individual cases, PE is used to treat multiple myeloma and Waldenström’s globulinaemia with hyperviscosity syndrome to decrease the concentration of monoclonal immunoglobulin [6,7]. In recent years, PE has been increasingly performed in addition to increased immunosuppression in cases of humoral-mediated rejection after kidney transplants. Often these patients also require haemodialysis [8,9].

Combined PE and haemodialysis most commonly means consecutive treatment, which poses considerable strain on human and financial resources. Several authors have small case series of ‘tandem’ treatments [10–12]. Simultaneous PE and haemodialysis has become the treatment modality of choice in our department over the past 16 years, with good clinical outcomes. This technical report describes in
detail the structural and technical requirements to provide good-quality tandem treatments, and briefly reports on the outcome in 82 consecutive patients who underwent this treatment in our centre.

**Methods**

**Structural preconditions**

The performance of tandem plasmapheresis and haemodialysis (TPH) requires specialized personnel, equipment and space conditions. Experience in dealing with extracorporeal procedures and knowledge of potential complications are basic requirements. Qualifications for performing dialysis and PE must be guaranteed. Only examined nurses and dialysis specialists should be entrusted to perform TPH. The preconditions conform to the standards for haemodialysis and apheresis therapy that are recommended by the Deutsche Arbeitsgemeinschaft Klinische Nephrologie eV (German Society for Clinical Nephrology) (http://www.nephrologie.de/Apheresestandard.html).

In the treatment environment, the technical and hygienic conditions must conform to those of dialysis. The minimum typical equipment for emergencies must be in place. Non-invasive monitoring with EKG and RR controls are recommended. Equipment to control activated clotting time and space conditions. Experience in dealing with extracorporeal procedures and knowledge of potential complications are basic requirements.

**Preparation and treatment method**

**Vascular access and plasma exchange solution**

TPH requires placement of a temporary double-lumen catheter in the vena cava. The jugular vein is preferred to the subclavian vein for sonographically guided puncture.

In patients with disorders associated with an increased bleeding risk, fresh frozen plasma is chosen for plasma exchange. Treatment is usually initiated with 100% exchange volume. Other than that, we use an iso-oncotic solution mixed from albumin 20% with haemofiltration solution. We calculate each patient’s plasma volume using weight, height, gender and haematocrit. Oncotic pressure is estimated using total plasma protein concentration and percentage of serum albumin.

**Implementation**

The necessary equipment such as the haemodialysis and PE machines may be placed next to each other. This enables an overview and ideal operation (Figure 1). However, this generally limits the size of the treatment space. Because of this, it is recommended that the equipment be set up in front of the other. The PE machine is then placed in front of the dialysis machine because it controls the treatment and displays the treatment parameters and important alarm functions. This facilitates inputting and monitoring. A volumetrically and gravimetrically balanced machine should be used for the PE. The pumps work by occlusion; scales control the balancing. A blood leak detector is also required. The dialyzing fluid is prepared in accordance with the manufacturer’s specifications with bicarbonate and acetate. In order to ensure the best possible microbiological quality, a sterile filter removes potential bacteria and endotoxins from the dialyzing fluid [13,14]. The dialysate flows according to the reverse flow principle. A closed balancing system with volumetric balance chambers (semi-single-pass system) is needed to withdraw the ultrafiltrate from the patient. All machines are equipped with the necessary safety protections for patient safety.

**Machine setup**

A specific blood tubing system is used for the machines (Figure 2). The membrane plasma separator consists of polysulfone with a surface of 0.6 m² and a pore size of 0.6 µm. The size of the capillary dialyzer (polysulfone) is determined individually and is between 1.4 and 1.6 m²; all filters are steam sterilized. The arterial blood tubing system (PE) is threaded into the blood pump segment (PE) and connected to the plasma filter input port. For plasma filters that are prefilled with fluid, the arterial system (PE) must be bled beforehand.

The venous blood tubing system (HD) is attached to the plasma filter outflow port. The venous drip chamber is placed in the air trap of the dialysis machine, and one attaches the pressure conduit (HD) firmly to the pressure sensor. Bypassing the venous tube clamp (HD), the system is guided over the light–dark detector (HD) and connected to an arterial CAVH system. This is done with a recirculator (Female Luer Lock®). A system consisting of a filter replacement set can be used instead of a CAVH system. This system combination is the bridge between the plasma filter and the dialyzer.

Finally, the dialyzer is connected to the venous blood tubing system (PE). The filtrate and the substitute system are placed according to the manufacturer’s specifications. When flushing and bleeding the system, the sodium chloride solution (1000 ml) is heparinized with 5000 IU. In the preparation, substitution occurs as post-dilution. Once the treatment begins, the substitution, in contrast, is attached before the dialyzer as pre-dilution. The heparinized solution is flushed out before treatment with a 500-ml sodium chloride solution.

**Selection of treatment data**

The input of treatment data has two aspects:

- The blood pump velocity can be set between 150 and 200 ml/min. The maximum value depends on the specifications of the plasma filter manufacturer. Because of this, a filter of the proper size should be selected.
- Because of the high plasma rate and ultrafiltration rate, a pronounced haemoconcentration may result at low blood flows. Because of this, it is recommended that the sum of the plasma filtration rate and the ultrafiltration rate do not exceed 25% of blood flow. For example, for a given blood flow of 160 ml/min, 25 ml/min plasma and 15 ml/min ultrafiltrate (900 ml/hr) may be filtered.
Anticoagulation

For anticoagulation, we use only high molecular heparin for this treatment insofar as not contraindicated. Otherwise, the same drugs may be used as for haemodialysis or haemofiltration. The treatment team establishes the maximum heparin dose before each treatment. This depends on the clotting parameters and risk of bleeding (Table 1). Heparin use under combined treatment is comparable to that under conventional PE. The heparin requirements shown in Table 1 conform to the above-cited recommendations for haemoconcentration reduction. If heparinization is performed after the activated clotting time (ACT), these measurements must be taken every half hour. The optimum ACT is 160 s in patients who are not at risk for bleeding.

Monitoring and documentation

Before the patient is hooked up and treatment begins, the system is tested for leaks. Depending on the filter size, the fill volume is between 200 and 350 ml. The re-infusion volumes that were previously input are increased accordingly to 500–750 ml.

EKG and RR monitoring are performed at least during the first two treatments. Depending on the severity of the disease, blood pressure and heart rate are checked and documented every half hour. The treatment requires that Na, K, Ca, glucose, pH and base excess be controlled every hour.

The following treatment parameters are documented: velocity of the blood and plasma pump as well as the indicated treatment pressures for each machine separately. The maximum limit values of the transmembrane pressures conform to the manufacturer’s specifications. These pressures are dependent on the size and surface area of the dialysis machine and plasma filters used.

Allergy prophylaxis

Plasma exchange with fresh plasma increases the risk of side effects [15,16]. Independent of the treatment procedure, allergy prophylaxis consisting of the administration of histamine antagonists and steroids (e.g. Sostril®, Tavegil® and Soludecortin® 75–250 mg) is initiated at our centre.
**Table 1.** The clotting parameters and bleeding risk corresponding to the heparin dose

<table>
<thead>
<tr>
<th>Heparin</th>
<th>Thrombocytes</th>
<th>Quick/INR</th>
<th>Fibrinogen</th>
<th>Bleeding active/risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>No heparin</td>
<td>$&lt;40,000/\mu l$</td>
<td>$&lt;30%/&gt;2.$</td>
<td>$&lt;100$</td>
<td>Active bleeding</td>
</tr>
<tr>
<td>Low-dose heparin 10 IU/kg BW/h</td>
<td>40 000–60 000/\mu l</td>
<td>30–50%/0.8–2.0</td>
<td>100–150</td>
<td>Elevated risk</td>
</tr>
<tr>
<td>Optimal dose heparin 25 IU/kg BW/h</td>
<td>$&gt;60,000/\mu l$</td>
<td>$&gt;50%/&lt;0.8$</td>
<td>$&gt;150$</td>
<td>No risk</td>
</tr>
</tbody>
</table>

**Results**

A total of 82 patients were treated with ‘tandem plasmapheresis–haemodialysis’ at University Hospital in Düsseldorf, between January 1990 and December 2006, and the results were documented. TPH was used to treat thrombotic microangiopathy, vasculitis, Goodpasture’s disease, multiple myeloma, Waldenström’s globulinaemia and acute humoral rejection after kidney transplant. The diseases and the number of tandem treatments of the patients treated are shown in Table 2. No paediatric patients were treated.

Six of the 82 patients died during the course of their inpatient stay. Two patients died of infectious complications, and four of bleeding complications. No death occurred within proximity to the TPH.

To this time point, we did not apply any other anticoagulation substances other than heparin during TPH. Because the plasma filter promotes the formation of a secondary membrane, presumably as a result of its large-pored surface, a single-shot application (single injection at the beginning of treatment) has been shown to work well.

**Analysis of 300 treatment protocols yielded the following results:**

1. There were no life-threatening complications or side effects that could be traced back to the treatment procedure.
2. The balance goals were achieved; no back-filtration occurred. Controls were performed by checking bodyweight both before and after treatment.
3. The electrolyte and acid–base balance were instantly normalized during the procedure.
4. With simultaneous ultrafiltration, over-hydrated patients with pulmonary congestion underwent plasma separation without problems. There were no cases of fluid displacement from the intra-alveolar to the extra-alveolar space. Breathing problems were quickly relieved and exhaustion prevented.
5. Calcium displacement and enlargement of anion gaps caused by the citrate as occur under high-volume fresh plasma substitution were directly brought into balance by haemodialysis. No calcium had to be substituted.
Table 2. Number of patients and treatments with tandem plasmapheresis–haemodialysis depending on disease that were treated at the hospital between 1990 and 2006

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of patients</th>
<th>Sex (male/female)</th>
<th>Age (years) (mean ± SD, median, min–max)</th>
<th>Number of treatments (mean range)</th>
<th>Outcome: with kidney function/dialysis dependence</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombotic microangiopathy</td>
<td>38</td>
<td>12/26</td>
<td>41 ± 17 (37) 19–80</td>
<td>6.4 ± 3.7 (1–16)</td>
<td>15/23</td>
<td>0</td>
</tr>
<tr>
<td>Vasculitis with rapid progressive kidney disease</td>
<td>27</td>
<td>21/6</td>
<td>54 ± 15 (55) 21–82</td>
<td>6 ± 3 (1–3)</td>
<td>16/11</td>
<td>0</td>
</tr>
<tr>
<td>Goodpasture’s disease</td>
<td>5</td>
<td>5/0</td>
<td>29 ± 12 (29) 29–48</td>
<td>6 ± 4.8 (1–3)</td>
<td>3/2</td>
<td>0</td>
</tr>
<tr>
<td>Plasmocytoma with hyperviscosity</td>
<td>5</td>
<td>4/1</td>
<td>68 ± 10 (74) 52–76</td>
<td>4.6 ± 3.5 (1–8)</td>
<td>3/2</td>
<td>5**</td>
</tr>
<tr>
<td>Cold reactive antibodies and acute renal failure</td>
<td>1</td>
<td>1/0</td>
<td>40 ± 7 (40) 28–49</td>
<td>5 ± 3 (1–5)</td>
<td>3/3</td>
<td>1</td>
</tr>
<tr>
<td>Humoral rejection after kidney transplant</td>
<td>6</td>
<td>4/2</td>
<td>46 ± 17 (42) 19–82</td>
<td>5.9 ± 3.6 (40)</td>
<td>41/41</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>82</td>
<td>47/35</td>
<td></td>
<td>483</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.01 as compared to HUS/TTP.
**P < 0.001.

6. For diseases involving cold-reactive antibodies, the blood temperature was held constant and further haemolysis prevented.

Aside from the medical advantages, the procedure was basically well tolerated by the patients. Some patients, who experienced sequential treatment in earlier years, were welcoming the obvious decrease in treatment time. Total treatment and preparation time—in comparison to conventional procedures—was reduced from 5.75–6.5 h to 3.5–4.0 h. This meant that the dialysis unit’s space and personnel could be used optimally. However, there were no material savings.

There is one technical aspect that needs special consideration. Because of the increased tube volume and the additional filter, the pressure before the plasma filter increases by ~20–30 mmHg; the venous pressure at the PE machine decreases in equal measure. This results in a calculated negative TMP at the PE machine. This must be calculated when setting and interpreting the upper alarm limit.

Summary

Simultaneous PE and haemodialysis can be carried out in patients whose medical condition requires treatment with both techniques. TPH saves time and human resources, and thus indirectly reduces the overall treatment cost. Direct technical treatment cost remains unchanged compared to separate treatment session. While TPH is not an officially approved standard therapy, our positive experience with 82 patients who received a total of 483 treatments clearly makes this an option worthwhile considering.

Conflict of interest statement. None declared.

References


Received for publication: 21.12.07
Accepted in revised form: 7.7.08