The Scleroderma Education Project™

Pulsed Plasma Exchange for the Treatment of Systemic Sclerosis: An Overview for Clinicians

Background: Therapeutic Plasma Exchange

- Therapeutic plasma exchange (TPE) has been used as a mainstream treatment for a number of diseases since 1978. The most common uses are for neurological, hematological, and renal diseases such as Guillain-Barré syndrome, myasthenia gravis, hyperviscosity syndromes, and Goodpasture syndrome. TPE is also called plasmapheresis in the research literature, but in actuality, plasmapheresis is a different but related procedure where plasma is withdrawn but not replaced.
- TPE is typically performed in a hospital outpatient setting. It involves temporary placement of two IVs – one for access and one for return. Blood is withdrawn in a continuous flow process and the plasma is centrifugally separated from red blood cells, white blood cells, and platelets. The extracted plasma is replaced by fresh frozen plasma or sterilized albumin, depending on the specific usage, and the recombined replacement fluid and cells are returned in a process that typically takes 1 1/2 to 2 hours.
- Since TPE is a procedure that does not involve drugs or implanted devices, it is not regulated by the FDA. Every three years, the American Society for Apheresis (ASFA) provides evidence based guidelines on the use of TPE for more than 75 diseases or medical conditions. Currently, ASFA classifies TPE for treating systemic sclerosis (SSc) as a Category III treatment: "Optimum role of apheresis therapy is not established. Decision making should be individualized."
- TPE, when administered in the protocol suggested later in this document, does NOT suppress the overall functioning of the immune system, in contrast to drugs that are commonly used to treat SSc, e.g., methotrexate, mycophenolate mofetil, , cyclophosphamide, or rituximab.
- A recent comprehensive review of the research on the use of TPE as a treatment for SSc noted that: "… in contrast to current immunosuppressive treatments that carry significant risk, long-term TPE appears to be safe, well-tolerated, and associated with only very few, mostly minor side effects." [1]

Potential Mechanisms of Action in TPE

- More than a dozen studies have documented abnormal blood rheology in SSc. These studies document elevated whole blood viscosity (WBV), abnormal clumping of and reduced deformability of red blood cells. Recent studies have shown that digital ulcers and PAH are correlated with increased WBV in SSc patients. Notably, patients with primary Raynaud's have normal blood viscosity and RBC aggregation levels. [2-13]
- As early as 1979, SSc researchers noted that: "Many, if not all, of the manifestations of scleroderma can be explained on the basis of functional and structural vascular

compromise after repeated vascular insults, subsequent healing of vascular walls with proliferative vascular response, and luminal narrowing." [14]

- The RBC clumps/aggregates seen in SSc are highly shear resistant. [15,16] Here is an image that shows what these RBC clumps look like:

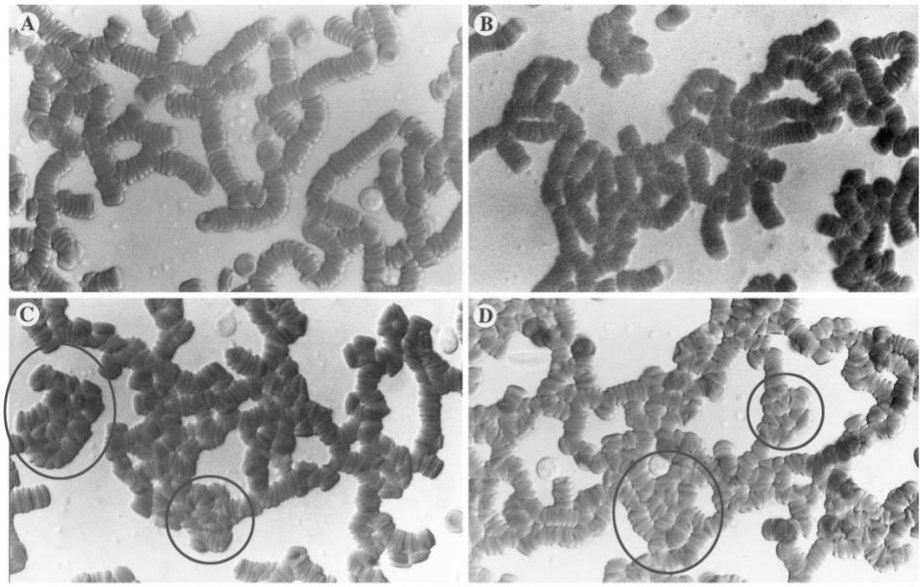

Fig. 6. Photomicrograph of blood at ×640 magnification. *A*: HC *no. 5* at 37%. Linear rouleaux are visible. *B*: SSc *patient 7* at 38%. Same appearance as for *A*. *C*: SSc *patient 6* at 40%. Clusters of compacted red blood cells were observed (*point 1*). *D*: SSc *patient 9* at 45%. Clusterlike aggregates are visible.

Picart, C, P H Carpentier, H Galliard, and J M Piau. 1999. "Blood Yield Stress in Systemic Sclerosis." The American Journal of Physiology 276 (2 Pt 2): H771-7.

- The original rationale for trying TPE back in the late 70s was that reducing plasma circulating levels of potential pathogenic molecules such as autoantibodies might lead to improvements in signs and symptoms. While TPE did lead to these improvements in many cases, early authors noted that these effects lasted much longer than expected after TPE was stopped, suggesting that additional mechanisms of action might be involved.
- A series of four weekly TPE treatments completely normalizes blood rheology including WBV and RBC aggregation/clumping. These effects last for a surprisingly long time. Three months later, RBC aggregation levels are still about half of what they were pre-TPE. [1]
- Hypothesis: the abnormal shear-resistant clumping of red blood cells may directly or indirectly lead to some or all of the endothelial damage that is the hallmark of early SSc. If this is the case, then it is possible that some of the mechanisms of action in TPE may be from improvements in blood rheology in addition to reduction in plasma-circulating molecules that follows each TPE treatment. <u>It is important to understand that while this hypothesis is consistent with existing research, currently there is no definitive research that demonstrates a causal relationship between abnormal blood rheology and endothelial damage.</u>

Pulsed Plasma Exchange

- When TPE is used to treat acute conditions such as Guillain-Barré or Goodpasture syndromes, it is typically administered in an intense, short-term protocol that is designed to remove plasma circulating pathogenic molecules such as autoantibodies.

- In contrast, the protocol that we are suggesting be used to treat patients with SSc is a pulsed protocol that is primarily focused on improving blood rheology instead of reducing circulating levels of potentially pathogenic molecules such as autoantibodies. While a single TPE treatment does slightly reduce plasma-circulating antibody levels for a few days, overall, it does not reduce circulating antibody levels and does not suppress the overall functioning of the immune system.
- The suggested pulsed plasma exchange (PPE) protocol is simple: one single-blood-volume TPE treatment per week for four weeks followed by eight weeks of rest. The plasma replacement should be 4% to 5% sterilized albumin. This protocol is repeated indefinitely for a total of about 16 TPE treatments per year.
- The goal of this protocol is to try to maintain blood rheology as close to normal as possible while minimizing the number of treatments required to achieve this goal. Research shows that four weekly treatments are needed to completely normalize blood rheology. Eight weeks later, blood rheology maintains significantly improved versions pre-PPE, but is slowly worsening over time.
- A one year trial period (16 treatments) is recommended to determine if PPE is effective. Research literature suggests that patients often see significant improvements in Raynaud's and digital ulcers after a few TPE treatments. Significant improvements in organ systems such as the GI tract or lungs are likely to take significantly longer.
- PPE must be continued indefinitely or any improvements in signs or symptoms will regress towards pre-TPE levels over time.

Safety, Cost, Venous Access

- TPE has an excellent safety profile, especially when the plasma replacement is sterilized albumin rather than fresh frozen plasma, as this minimizes the risk of allergic reactions. Most side effects are short term and are directly related to the procedure itself. The only known side effect of long-term use of TPE is mild iron deficiency anemia, easily treatable by OTC iron supplements.
- The best way to perform TPE is using regular peripheral venous access. Historical data indicates that about 75% of patients undergoing long-term TPE are able to use normal venous access. Modern technologies such as vein illumination systems and ultrasonic-guided venous access are likely to improve this statistic in the future. Where peripheral venous access is not an option, implanted ports such PowerFlow and TidalPort provide alternative access options for long-term therapeutic plasma exchange.
- On average, a single blood volume TPE treatment costs about $1,200 for an average size patient. This is also the approximate Medicare reimbursement rate. At 16 treatments per year for the suggested PPE protocol, this is about $20,000 per year, well below the cost of a biologic drug such as Humira which currently costs about $51,000 per year. Note that hospital charges for this procedure will typically be much higher than the actual cost.
- Many insurance companies in the US now cover TPE as a treatment for SSc, sometimes needing priority authorization. Medicare covers TPE as a treatment for SSc if it is: 1) life threatening, and 2) other treatments are not working.
- The CPT code for TPE (also called therapeutic apheresis) is 36514. ICD 10 diagnosis code for diffuse SSc is M34.0. For limited SSc, it is M34.1.

Additional Resources

If you are considering trying TPE as an intervention for any of your patients, here are five resources that you may find helpful:

- **"Therapeutic Plasma Exchange for the Treatment of Systemic: A Guide for Clinicians".** This slide show handout is a comprehensive overview on TPE for clinicians. It summarizes the information in the published review and includes topics of interest to clinicians such as safety, cost, and insurance coverage.

  Link: sclerodermainfo.org/link/TPE-Slide-Show

- **"Therapeutic Plasma Exchange for the Treatment of Systemic Sclerosis: A Comprehensive Review and Analysis"**. This is a comprehensive review of 46 published papers on the use of therapeutic plasma exchange as a treatment for systemic sclerosis. It is published in the *Journal of Scleroderma and Related Disorders*.

  Link to publisher's website: sclerodermainfo.org/link/TPE-Review

- **"Successful Long-Term (22 Year) Treatment of Limited Scleroderma Using Therapeutic Plasma Exchange: Is Blood Rheology the Key?"** This case report, published in *Clinical Hemorheology and Microcirculation*, documents the effects of very long term TPE as the sole systemic intervention in a patient with diagnosed limited cutaneous systemic sclerosis (CREST).

  Link (US Format): sclerodermainfo.org/link/TPE-Case-Report-US
  Link (A4 Format): sclerodermainfo.org/link/TPE-Case-Report-A4

- **"Suggested Protocol for a One-Year Trial of Therapeutic Plasma Exchange for Treating Systemic Sclerosis"**. This document gives a starting point for clinicians to use if they decide to move forward with a TPE trial. It also includes suggested subjective and objective measures that can be helpful in monitoring treatment effectiveness.

  Link (US Format): sclerodermainfo.org/link/TPE-Guidelines-US
  Link (A4 Format): sclerodermainfo.org/link/TPE-Guidelines-A4

- **"Therapeutic Plasma Exchange: A Guide for Newbies"**. This is a document for patients who are about to start TPE and gives suggestions on how to make the TPE treatment experience as successful and comfortable as possible.

  Link (US Format): sclerodermainfo.org/link/TPE-Newbies-US
  Link (A4 Format): sclerodermainfo.org/link/TPE-Newbies-A4

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Disclosure

The author of this document is the lead author of the above referenced TPE review paper [1].

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