

## Therapeutic Plasma Exchange for the Treatment of Raynaud's and Digital Ulcers in Systemic Sclerosis: A Systematic Review

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### Abstract

**Background/Purpose.** Raynaud's phenomenon (RP) is an early marker of microvascular damage in systemic sclerosis (SSc) and digital ulcers (DU) are a serious complication of vascular dysfunction, occurring in about 50% of SSc patients. DU are painful, difficult to heal, and in some cases progress to gangrene and autoamputation.

Current treatments for RP and DU focus on improving distal blood flow using vasodilators, vasoconstrictor antagonists, or drugs which reduce vasospasm. Nevertheless, many patients continue to develop DU over time, suggesting the need for alternative treatment options.

**Method.** We reviewed all publications between 1978 and 2016 on the use of therapeutic plasma exchange (TPE) to treat patients with SSc. Out of the 40 papers reviewed, 13 reported effects on RP and DU. Four studies were confounded by simultaneous use of drug therapies and were excluded from the analysis shown in the table.

**Results.** A commonly reported finding was that a single course of a small number of weekly TPE treatments (typically four) had significant effects on both RP and DU as well as blood flow, microvessel patency, and blood rheology. In many patients, RP disappeared or was significantly improved, and even long-standing digital ulcers began to heal. Several studies documented abnormal blood rheology pre-treatment (elevated whole blood viscosity (WBV) and RBC aggregation) that was significantly reduced after four weekly TPE treatments. The improvements in symptoms and blood rheology were surprisingly long lasting: at least six months and in one study no reoccurrence of DU was observed at three-year follow-up.

**Conclusion.** In patients diagnosed with SSc, a limited course of TPE treatments appears to lead to significant improvements in RP and DU symptoms as well as objective improvements in blood flow, microvessel patency, and blood rheology that persist for several months. Since TPE treatments have no known direct effects on blood vessels, these results suggest that TPE may have an entirely different mechanism of action. Volkov (2006) noted that WBV is highest in patients with active DU, raising the possibility that the long-lasting normalization of whole blood viscosity and significant reduction of RBC aggregation may directly lead to enhanced microvascular blood flow and thus to improved microvessel patency and SSc symptoms. We recommend that a randomized, double blind, placebo-control study of TPE that includes measurements of blood rheology be conducted to better understand these effects.

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## About Systemic Sclerosis

- Systemic Sclerosis (SSc) is an umbrella term for a family of rare diseases with the common factor being abnormal thickening (fibrosis) of the skin. SSc is a complex autoimmune disease that affects internal organs as well as the skin.
- Estimated incidence (US): 20/million adults (4800/year new cases), prevalence: 240/million (58,000 diagnosed cases). SSc may occur at any age, but the symptoms most frequently begin in mid-life (25-45). SSc is very rare in children. The disease is about 4 times more common in women than men.
- SSc is divided into two general categories: diffuse (dcSSc) and limited (lcSSc). dcSSc patients usually have rapid onset of symptoms and significantly reduced survival, mostly due to lung, heart, and kidney involvement. lcSSc patients have a slower onset and progression rate, often live near normal lifespans but with steadily increasing disability and disfigurement over time.
- Current treatment approaches focus on using immunosuppressants to slow the disease process plus interventions targeted at specific symptoms. Neither approach is currently very effective.

## Background: Raynaud's and Digital Ulcers

- About 95% of patients with diagnosed SSc develop Raynaud's symptoms.
- Raynaud's phenomenon (RP) and digital ulcers (DU) are directly related symptoms that result from extensive microvascular damage that is characteristic of SSc. RP is an earlier manifestation of the vascular involvement.. DU are a severe complication of microvessel involvement and also of persistent vasospasm from RP.
- DUs are a major clinical problem in SSc, with about 50% of patients eventually developing DU. Current treatments are largely ineffective and persistent DU leads to reduced quality of life, pain, disability, and disfigurement that can lead to gangrene and amputation.

### Progression: Raynaud's to Digital Ulcers to Gangrene/Amputation



## Current Treatment Approaches for Raynaud's and Digital Ulcers

Current treatments for RP and DU focus on improving distal blood flow using vasodilators, vasoconstrictor antagonists, or drugs and surgical interventions which reduce vasospasm, as is shown in Table 1 below:

**Table 1: Current Treatment Approaches for RP and DU in SSc**

| RP/DU Treatment Approach           | Target/Technique                           | Examples                                     |
|------------------------------------|--|--|
| <b>Vasodilators</b>                | Calcium channel blockers                   | amlodipine, nifedipine, verapamil, diltiazem |
|                                    | Phosphodiesterase type 5 (PDE5) inhibitors | sildenafil, vardenafil, tadalafil            |
|                                    | Prostaglandins (Prostacyclins)             | Iloprost, epoprostenol, treprostinil         |
|                                    | Topical nitroglycerins                     |  |
| <b>Vasoconstrictor antagonists</b> | Endothelin-1 receptor antagonist           | bosentan                                     |
|                                    | Angiotensin II receptor antagonists        | losartan, candesartan, cilexetil, valsartan  |
| <b>Sympathectomy</b>               | Chemical sympathectomy                     | Botulinum toxin A                            |
|                                    | Localized surgical digital sympathectomy   |  |

## Therapeutic Plasma Exchange for the Treatment of SSc

- A recent review (Harris et al. 2016) of 40 published studies on the use of therapeutic plasma exchange (TPE) to treat SSc concluded that “In contrast to current treatment modalities such as immunosuppression that carry significant risk and show limited efficacy, the results shown in the clinical studies reviewed for this article suggest that long-term TPE may offer a low-risk way to control and in some cases reverse SSc symptoms.”
- The goal of this study was to examine all studies on the use of TPE to treat SSc that included discussions of changes in RP and DU in order to try to better understand how and why TPE impacts these key clinical symptoms in patients with SSc.

## Method

- An initial Google Scholar search of all of the research literature with English language abstracts on the use of therapeutic plasma exchange to treat SSc was conducted using the following search terms:  
(plasmapheresis OR "plasma exchange" OR PEX OR TPE OR apheresis) AND (scleroderma OR "systemic sclerosis" OR PSS OR MCTD OR CREST OR Raynaud's)
- We obtained source copies of all articles identified during the search process and reviewed all references in these article to identify additional candidate articles. This process was

repeated with all newly identified articles until no additional articles meeting our search criteria were found.

- We then reviewed each of the articles that met our initial search criteria to determine if they included discussions on changes in RP or DU following TPE. Out of the 40 papers that met our initial screening criteria, 13 reported effects on RP and DU. Four studies were confounded by simultaneous use of drug therapies and were excluded from our analysis.

## Results

- A commonly reported finding was that a single course of a small number of weekly TPE treatments (typically four) had significant effects on both RP and DU as well as blood flow, microvessel patency, and blood rheology. In many patients, RP disappeared or was significantly improved, and even long-standing digital ulcers began to heal.
- Several studies documented abnormal blood rheology pre-treatment (elevated whole blood viscosity (WBV) and RBC aggregation) that was significantly reduced after four weekly TPE treatments. The improvements in symptoms and blood rheology were surprisingly long lasting: at least six months and in one study no reoccurrence of DU was observed at three-year follow-up.
- Table 2 below summarizes the findings of the key case reports and studies based on our detailed review of the literature.

**Table 2: Effects of TPE on RP and DU Symptoms in SSc**

| Study         | Type* | N  | TPE Protocol                         | Follow-Up                   | Summary / Notes  |
|---------------|-------|--|--------------------------------------|-----------------------------|--|
| Cotton 1978   | PS    | 12                                       | Varied                               | Not reported                | Letter. Improved microvessel patency in 10/12 Pts. Gangrene reversed in 1 Pt. after 6 TPE.   |
| Talpos 1978   | PS    | 5  | 1 TPE/week for 5 weeks               | 6 months post TPE           | 4/5 patients with DU before TPE. All DU but 1 healed after TPE. Significant improvement in RP and DU post TPE. Blood viscosity sig improved in 3/3 Pts.  |
| Dodds 1979    | PS    | 8  | 1 TPE/week for 4 weeks               | 6 weeks post TPE            | DU healed in 3/3 Pts. Microvessel patency improved in 6/6 Pts.   |
| O'Reilly 1979 | RCT   | 27 (9 in TPE group)                      | 1 TPE/week for 4 weeks               | 6 weeks, 6 months post TPE  | Microvessel patency significantly improved in TPE group only at 6 week and 6 month follow-up. DU healed after TPE in 3/3 Pts and remained healed at 6 month F/U.                                     |
| Zahavi 1980   | CT    | 37 (9 Pts. with severe SSc in TPE group) | 1 TPE/week for 4 weeks               | 3 months post TPE           | At F/U, microvessel patency improved in 7/8 Pts. and DU healed in 3/3 Pts.   |
| McCune 1983   | PS    | 6  | 1 TPE or "sham" TPE/week for 4 weeks | 3 months, 6 months post TPE | Complicated design with mixed TPE and autologous "sham" TPE. 5/6 maintained improvements in RP and DU at 3 month and 6 month F/U. Some objective measures improved with sham TPE as well as standard |

|                                    |    |   |   |  | TPE.  |
|------------------------------------|----|---|---|--|---|
| Von Rhede<br>van der Kloot<br>1985 | PS | 14 (7<br>primary RP,<br>7<br>secondary<br>RP) | 1 TPE/week<br>for 4 weeks   | Post TPE<br>only                             | RP disappeared or improved in 6/7<br>Pts. in secondary RP group and 2/7<br>in primary RP group, DU improved in<br>3/3 Pts. in secondary RP group.   |
| Ferri 1987                         | PS | 6 (severe<br>SSc)                             | 3 TPE/week<br>for 6 to 8<br>weeks, then<br>tapering down.<br>Total duration<br>6 to 14 weeks. | Post TPE<br>only                             | 5 Pts. completed protocol. DU<br>healed or significantly improved in<br>5/5 Pts. at end of TPE.   |
| Jacobs 1991                        | PS | 18  | 1 TPE/week<br>for 4 weeks   | Three, nine,<br>24, 36<br>months<br>post TPE | Post TPE, all Pts. had either<br>complete elimination of TP or<br>significant reduction. Any DU<br>healed. No reoccurrence of DU at 3-<br>year F/U. In 14 Pts. RP returned<br>after 6 to 9 months post-TPE. In 4<br>Pts, no RP at 3-year F/U. RBC<br>aggregation was significantly less<br>( $p < .001$ ) post TPE and gradually<br>returned to pre-TPE levels after 9<br>months. |

\* PS: Pilot Study RCT: Randomized Controlled Trial CT: Controlled Trial

## Discussion

- Standard treatments for RP and DU in SSc are focused on improving blood flow by either increasing vascular dilation or reducing vasoconstriction or vasospasm.
- Since TPE treatments have no known direct effects on blood vessels, the beneficial effects on RP and DU from TPE treatments suggests that TPE may have an entirely different mechanism of action.

### ***Why Does TPE Improve RP and DU Symptoms in SSc?***

#### Abnormal Blood Rheology May Be Pathogenic in SSc

- Over the past 41 years, a number of published studies have consistently documented that blood rheology is abnormal in patients with systemic sclerosis (SSc). Individual studies have focused on differing aspects of this abnormal rheology including elevated whole blood viscosity (WBV), plasma viscosity (PV), and abnormal red blood cell aggregation.
- The nature of the observed RBC aggregation is not discussed but does not appear to be referring to normal, easily reversible Rouleaux formation.
- While the significance of this abnormal rheology is not yet fully understood, the observation that TPE alone has a striking effect on clinical symptoms such as Raynaud's and digital ulcers and also leads to significant improvements in blood rheology suggests the presence of a plasma related pathogenic factor in SSc (Harris, Moriarty et al. 2016).
- Abnormal rheology in autoimmune diseases is not uncommon. It has been documented in rheumatoid arthritis (Gudmundsson et al. 1993) and systemic lupus erythematosus

(Rosenson et al. 2001). However, TPE does not improve clinical symptoms in RA (Dwosh et al. 1983), suggesting a different mechanism of action in RA pathogenesis.

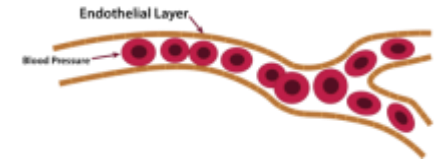

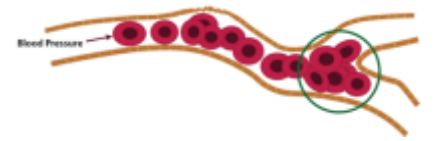
- Volkov et al. (2006) documented that patients with SSc have increased WBV relative compared to matched healthy controls, replicating many previous studies. In addition, they documented that WBV was highest in patients with active DU.

### The Potential Role of RBC Aggregation in SSc Pathogenesis

- In 1979, Kahaleh et al. noted, “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.”
- Hypothesis: abnormally clumped red blood cells may be a significant component of the etiopathogenic processes in SSc, potentially contributing to the vascular damage cited above. Possible endothelial damage mechanisms include biochemical processes or direct mechanical effects tending to re-model vessel walls and changes due to local ischemia caused by abnormal distribution of red cells in the microcirculation.

### Support for RBC Aggregation Hypothesis

- The frequently reported finding that Raynaud’s symptoms usually disappear and digital ulcers start to heal after three or four weekly TPE treatments is consistent with the idea that the microvascular damage seen in SSc is a direct result from aggregated red blood cells. Elimination of RBC aggregation would allow the vascular system to begin to heal due to increased blood flow.

|                                       |  |
|---------------------------------------|--|
| <p><b>Normal Blood Flow</b></p>       | <p>Only one red blood cell at a time can flow through the smallest capillaries.</p>    |
| <p><b>Endothelial Damage</b></p>      | <p>Small clumps of aggregated red blood cells being repeatedly forced through small capillaries may lead to endothelial trauma.</p>    |
| <p><b>Microcapillary Blockage</b></p> | <p>Large clumps of red blood cells may lead to complete capillary blockage, resulting in symptoms such as pain and fatigue, often initial symptoms in diffuse systemic scleroderma.</p>  |

- McCune (1983), when comparing the effects of standard TPE with “sham” TPE that returned the patient’s own separated blood instead of replacing the plasma with sterilized albumin, noted that improvements were seen in several objective measures and clinical symptoms in patients in both the normal treatment group and the “sham” treatment group. Since their “sham” treatment group did not reduce circulating antibody levels, the observed improvements in objective measures and clinical symptoms are likely to be a result of the RBC disaggregation effects that would have occurred in both treatment groups.

## Long-Term TPE: Issues/Concerns

### *TPE Treatments Are Required Indefinitely*

- The beneficial effects from a single round of 4 weekly TPE treatments lasts at least 3 months. Once treatments are stopped, blood rheology and symptoms gradually return to pre-treatment levels. This indicates that TPE treatments need to be continued on a permanent basis in order to provide the maximum possible benefit (Harris, Meiselman et al. 2016). However, this is also true of any other current treatment approach.

### *Safety*

- The safety profile for long-term use of TPE is excellent. The most common side effects are very short term, for example hypotension or fatigue for a few hours following a treatment. An 11-year review of the safety of TPE in 317 patients and 2730 procedures (Cid et al. 2014) showed an adverse event rate of 3%, all of which were mild.

### *Venous Access*

- The best way to perform TPE is using regular peripheral venous access. Venous access problems were discussed in a number of the articles and was the reason for discontinuation in a number of instances.
- New technologies such as VeinViewer™ or ultrasound guided peripheral venous cannulation significantly improve the likelihood of maintaining peripheral venous access in long-term TPE.
- There is a significant infection risk with central catheters for long-term TPE. Alternatives such as fistulas or newer ports such as Vortex™ may be better options for very-long term use of TPE if peripheral venous access is not an option.

### *Cost*

- Winters (2011) did an analysis of TPE cost and determined that each treatment cost a little under \$1200 when TPE was performed using albumin. This is comparable to Medicare reimbursement rates for TPE treatments.
- Several studies suggest that between 12 and 18 treatments/year may be sufficient to control SSc symptoms. Using the 16 TPE treatment/year protocol discussed in Weiss (2015), this works out to an annual cost of about \$20,000 per year, comparable to the cost of modern biologics commonly used to treat rheumatoid arthritis and other autoimmune diseases (Howe et al. 2014).

## Research and Treatment Implications

Research is needed to determine if: 1) TPE is an effective treatment for some or all variants of SSc, and if so, 2) whether the beneficial effects from using TPE are from: a) temporary reduction in circulating pathogenic factors, b) normalization of blood rheology including disaggregation of red blood cells, or c) a combination of both.

### ***Proposed Initial Clinical Trial:***

- Randomized, double-blinded, placebo controlled trial of anticentromere antibody (ACA) positive lcSSc patients within 5 years from initial diagnosis.
- Two active treatment groups: 1) standard TPE; 2) autologous TPE (patient's plasma recirculated instead of being replaced). Use Harris, Meiselman et al. (2016) protocol: 4 weekly TPE treatments, 2 months' rest, repeat (16 treatments/year). Duration: 1 year.
- Lab measures – baseline: pulmonary function test (PFT), ESR, CBC, WBV, PV. All measures except PFT repeated before/after each treatment round. Other measures: Raynaud's attacks, digital ulcers, GI symptoms, Scleroderma Health Assessment Questionnaire (SHAQ).

### ***Outcome Interpretation***

- Neither Treatment Group is Significantly Better Than the Control Group: TPE is not likely to be an effective treatment for *any* variant of TPE.
- Only the Standard TPE Treatment Group is Significantly Better Than the Control Group: 1) TPE is an effective treatment of ACA-positive lcSSc patients; and 2) TPE effects are mostly from temporary reduction of circulating pathogenic factors.
- Both TPE Treatment Groups Are Significantly Better Than the Control Group: 1) TPE is an effective treatment of ACA-positive lcSSc patients; and 2) TPE effects are primarily from normalization of blood rheology.

## Summary and Conclusion

- RP, frequently leading to DU, is an almost universal manifestation of SSc. DUs are a major clinical problem as they are associated with reduced quality of life, pain, disability, and disfigurement that can escalate to gangrene and amputation.
- Current treatments for RP/DU are focused on improving blood flow by increasing vasodilation and reducing vasoconstriction and vasospasm. Some of these treatments have been shown to be moderately effective on reducing current symptoms and reducing the rate of occurrence of new symptoms. However, no single treatment or combination of treatments is completely effective in stopping the frequent progression of RP to DU, often with severe complications.
- A number of studies have shown that therapeutic plasma exchange (TPE) has a rapid and in some cases long-lasting effect on RP and DU.



- Since there is no known direct on the microvascular system from TPE, this suggests a completely different mechanism of action for these observed improvements in RP and DU following TPE.
- Abnormal blood rheology, including elevated whole blood rheology and increased aggregation of RBC, has been consistently documented in SSc. TPE has been shown to lead to both symptom improvements and normalization of blood rheology, suggesting the presence of a blood circulating pathogenic factor.
- Research is needed to: 1) determine the nature of the abnormal blood rheology in SSc, 2) determine if this abnormal rheology has a etiopathogenic role, and 3) determine if treatments that focus directly on normalizing blood rheology, including TPE and potential pharmacological interventions, may be an effective treatment alternative to current immunosuppressive strategies that are largely ineffective and carry significant risk.

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