Background: Complex regional pain syndrome (CRPS) is a severe chronic pain condition that most often develops following trauma. Some investigators have postulated CRPS to be a post-traumatic neuralgia associated with distal degeneration of small-diameter peripheral axons. Intravenous immunoglobulin treatment (IVIG) has been shown to be efficacious in the treatment of painful polyneuropathies. Some CRPS patients have been reported to respond to IVIG. Based on a recent hypothesis proposing an autoimmune etiology for CRPS, we decided to offer plasma exchange therapy (PE) to CRPS patients with a clinical presentation suggestive of a small fiber neuropathy.

Objectives: To evaluate the efficacy of PE in a group of CRPS patients with a clinical presentation suggestive of a small fiber neuropathy that were either non-responders or poor responders to their current treatment.

Study Design: This is a retrospective case series study of CRPS patients that met the Budapest diagnostic criteria for CRPS and received PE as treatment for their illness between September 2012 and June 2014. Approval for this review was granted by the Drexel University Institutional Review Board.

Setting: Drexel University College of Medicine pain clinic

Methods: Thirty-three CRPS patients that received PE treatment were retrospectively studied. The workup for these patients consisted of a complete medical and pain evaluation, the completion of the short-form McGill questionnaire, quantitative sensory testing (QST), and skin punch biopsy. The PE protocol was as follows: all patients had a series of PE therapies (range 5 to 11 with a mean of 7.2) performed over a 2 to 3 week period. Following the PE series, the patients had a pain evaluation and completed the short-form McGill questionnaire. Patients that responded to PE were offered maintenance therapy consisting of either weekly PE or other immune modulating agents. In these patients, their pain was evaluated during the maintenance phase.

Results: Thirty of the 33 patients demonstrated significant ($P < 0.01$) median pain reduction of 64% following the initial series of PE. Three patients demonstrated no improvement. Twenty-four patients are receiving maintenance therapy, the pain reduction in these patients following the initial PE series has been maintained with either weekly PE ($n = 15$), oral immune modulating agents ($n = 8$), or IVIG ($n = 1$). The remaining 6 patients are not receiving maintenance therapy and their pain has returned to pre-treatment levels. In addition, this study suggests that patients with the greatest loss of small fibers and the greatest temperature sensory deficits are most likely to benefit from PE therapy.

Limitations: The major limitation of this study is its retrospective nature which includes non-randomization, non-blinding, and an uncontrolled design.

Conclusions: This study shows that PE is effective in a subset of patients with severe long-standing CRPS and that the reduction in pain following the initial series of PE treatments can be maintained on a weekly PE schedule, IVIG, or with other immune modulating drugs. Large, randomized, placebo controlled studies may be required to confirm and expand these results. Such studies may lead to new therapies for this severe life-altering condition.

Key words: Complex regional pain syndrome, small fiber neuropathy, plasma exchange, skin punch biopsies, immune modulating therapies

Pain Physician 2015; 18:383-394
Complex regional pain syndrome (CRPS) is a chronic pain condition that most often develops following trauma (1). The pathophysiology of chronic neuropathic pain conditions such as CRPS is not fully understood, but evidence suggests a maladaptive response to nervous system damage involving immune and inflammatory pathways as well as abnormalities in both peripheral and central processing of afferent inputs (2,3). At this time, there is no single therapy that wholly addresses the effects of this varied condition (4-6).

Some investigators have postulated CRPS to be a post-traumatic neuralgia associated with distal degeneration of small-diameter peripheral axons (7). We have reported that some CRPS patients demonstrate reduced epidermal nerve fiber density, consistent with a small fiber neuropathy (SFN) (8). An autoimmune etiology has also been postulated for CRPS (9-11). These investigators have shown that at least half of their patients demonstrate immunoglobulin G (IgG) serum-autoantibodies directed against and activating autonomic receptors (12), and that CRPS serum-IgG, when transferred to mice causes signs of clinical CRPS (13). Intravenous immunoglobulin (IVIG) has been shown to be efficacious in the treatment of painful polyneuropathies and some patients with CRPS have also been reported to respond to IVIG (14-16).

Considering the evidence of immune system involvement in CRPS (9) and the reported positive response to IVIG in some CRPS patients (14), we tested the efficacy of IVIG in 4 refractory CRPS patients that showed reduced epidermal nerve fiber density, consistent with a SFN. Following IVIG, 3 patients showed little or no improvement, whereas one patient demonstrated a 25% reduction in overall pain level. This patient also tested positive for IgA monoclonal-gammopathy and since plasma exchange therapy (PE) has been shown to be efficacious for this condition in a randomized double-blind trial (17), it was felt that it would be a suitable potential therapy for this patient. PE or plasmapheresis is an extra corporeal therapy that comprises the extraction of the patient’s whole blood which is separated into plasma and blood cells. The plasma is removed and replaced with another solution such as human albumin in saline or specially prepared donor plasma. The reconstituted plasma substitute along with the blood cells is then returned to the patient.

Following PE, this patient had a greater than 60% reduction in pain level. Consequently, we decided to offer PE to CRPS patients with a clinical presentation suggestive of a SFN that were either non-responders or poor responders to their current treatment. This initial report describes our experience with the first 33 CRPS patients from our pain clinic that received PE.

**Methods**

This is a retrospective case series study of CRPS patients seen at the Drexel University College of Medicine pain clinic that met the Budapest consensus criteria for CRPS (18) and received PE as treatment for their illness between September 2012 and June 2014. Approval for this review was granted by the Drexel University Institutional Review Board. Patient records were reviewed from which data regarding demographics, CRPS signs and symptoms, duration of illness and response to PE were obtained. The patient’s workup consisted of a complete medical and pain evaluation, the completion of the short-form McGill questionnaire (19), quantitative sensory testing (QST), and skin punch biopsy. The QST methods used for the determination of thermal detection thresholds and thermal pain thresholds have been previously described (20).

All patients had a double lumen indwelling central catheter inserted at the subclavian vein through which the PE was performed. During the PE patients continued their medications, no changes were made to their regular dosage, and no new medications were started. For most patients (n = 30) the PE was performed at Hahnemann University Hospital, Philadelphia, PA. For 3 patients PE was performed at medical centers near their home.

The skin punch biopsies were performed using a 3 mm circular puncher, to a depth of 4 mm under standard sterile technique and local anesthesia. The biopsies were taken at the calf and proximal thigh to evaluate epidermal and sweat gland nerve fibers which are often affected in SFNs (21,22). The epidermal nerve fiber density and autonomic fiber count in sweat glands was determined as previously described (22-24).

The PE protocol included a series of PE (approximately 7) performed over a 2 to 3 week period provided that the plasma fibrinogen was greater than 100 mg/dl, the hematocrit greater than 24, and the ionized calcium greater than 1.02 mmol/L. If these conditions were not met, PE was discontinued until the values normalized. Following the initial series, all patients had another pain evaluation and completed the short-form McGill questionnaire. For patients that chose to continue PE, the initial series was followed by twice a week PE for a period of 4 weeks. These patients were then placed on
a maintenance protocol of weekly PE. The patients that elected weekly PE had a pain evaluation and completed the short-form McGill questionnaire during this period.

Statistical Analysis: Paired difference testing was performed with the paired student’s t-test for parametric variables and the Wilcoxon signed-rank test for non-parametric variables. Correlation between variables was determined by evaluating the Spearman’s rank correlation coefficient (rho). The data was considered significantly different if \( P < 0.05 \). Statistical calculations were performed with SPSS version 20 (IBM SPSS Statistics for Windows, Armonk, NY).

### Results

#### Demographics and Disease Characteristics

Thirty-three CRPS patients received PE during the review period. Patient demographics are listed in Table 1 and co-morbidities listed in Table 2. Patients who were septic, could not tolerate central line placement, were hemodynamically unstable, or were allergic to albumin or heparin were not offered PE.

All patients met the Budapest diagnostic criteria for CRPS (18), demonstrated overall pain greater or equal to 6 on a 0 – 10 numerical rating scale (NRS) with duration of disease greater than 2 years and re-

<table>
<thead>
<tr>
<th>Case</th>
<th>Painful conditions or procedures exacerbated by pain</th>
<th>Comorbidities that are being actively treated</th>
<th>Reported comorbidities not being actively treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>bilateral knee replacement</td>
<td>hypertension, hyperlipidemia</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>grade i medial collateral ligament sprain-right knee</td>
<td>migraine headaches</td>
<td>postural orthostatic transient tachycardia syndrome, gastroparesis</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>hypothyroidism</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>lumbar spinal canal stenosis □</td>
<td>diabetes mellitus type 2, hypothyroidism, gastroesophageal reflux, migraine headaches, major depression</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>lumbar and cervical spinal canal stenosis □</td>
<td>dilated cardiomyopathy, esophageal reflux, hyperlipidemia, hypertension</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>osteoarthritis of the cervical spine ●</td>
<td>migraine headaches</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>osteoarthritis of spine, cervical and lumbar ●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>lumbar spine osteoarthritis ●, complete tear of anterior cruciate ligament of the left knee</td>
<td>bronchial asthma, chronic active hepatitis c, esophageal reflux, hypothyroidism, systemic lupus erythematosus</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>lumbar disc replacement, lumbar spondylosis ●, status post cervical spine fusion at c4-5-6 and c7 fusion ●</td>
<td>major depression</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>hyperthyroidism</td>
<td>irritable bowel syndrome</td>
</tr>
</tbody>
</table>
sponded poorly to standard treatment. Prior to PE, the level of pain in all of the subcategories of the McGill questionnaire were scored as severe (Table 3). All patients showed decreased sensation to pin-prick and cold temperature in a glove-stocking-shield distribution. Otherwise, the patients were physically healthy and fulfilled the American Society of Anesthesiologists Physical Status Classification Class I or II. The patients did not have a history of substance or drug abuse, psychiatric illness or suspected somatoform pain disorder.

Thirty-two patients reported a clear precipitating event and their symptoms were initially restricted to one extremity. The remaining patient described no precipitating event; the onset of pain was sudden, localized to both feet, with a clear burning quality. In all patients the pain spread beyond the original affected extremity. In one patient the pain spread to the proximal one third of the contralateral extremity. In the remainder 32 patients the pain spread to all 4 extremities.

Twenty-four patients underwent QST, 9 patients

---

**Table 2 (cont.). Patient comorbidities.**

<table>
<thead>
<tr>
<th>Case</th>
<th>Painful conditions or procedures exacerbated by pain</th>
<th>Comorbidities that are being actively treated</th>
<th>Reported comorbidities not being actively treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>neurosarcoaidosis, migraine headaches, major depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>factor v leiden</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>thyroid nodule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>thrombophlebitis of the left upper extremity</td>
<td>migraine headaches, grave’s disease, von willebrand disease, polycystic ovarian syndrome, gastroesophageal reflux</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>neuroma status post removal, non-healing fractured right 5th metatarsal **</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>osteoarthritis of the cervical spine ●</td>
<td>migraine headaches, iga polyclonal gammopathy</td>
<td>posture orthostatic transient tachycardia syndrome, irritable bowel syndrome</td>
</tr>
<tr>
<td>21</td>
<td>chronic pancreatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>hypothyroidism, hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>hypertension, chronic obstructive pulmonary disease</td>
<td>interstitial cystitis, gastroparesis</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>hypothyroidism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>polyneuropathy, organomegally, endocrinopathy/ edema, m spike and skin changes (poems) syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>major depression</td>
<td>gardner-diamond syndrome, osteodystrophy, anterior scleritis, gastroparesis</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>gastroesophageal reflux</td>
<td>gastroparesis</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>osteoarthritis of the cervical spine ●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>lumbar spondylosis ● &amp; radiculopathy ○</td>
<td>major depression, migraine headaches</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>osteoarthritis of spine, cervical and lumbar ●</td>
<td>rapid eye movement sleep disorder, major depression, obstructive sleep apnea</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td></td>
<td>migraine headaches, major depression, hypercholesterolemia</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td></td>
<td>major depression</td>
<td>irritable bowel syndrome</td>
</tr>
<tr>
<td>33</td>
<td>osteoarthritis of spine, cervical and lumbar ●</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This table lists patient comorbidities that are being actively treated, comorbidities reported by the patient that are not being actively treated as well as painful conditions or procedures that exacerbated their CRPS pain. The key for the location of the pain due to painful conditions or procedures is ** the pain was localized to the dorsum of the foot, ○ the pain was axial in nature, ● the pain was radicular in nature.
Plasma Exchange Therapy in Patients with CRPS

The initial series of treatments were performed over a 2 week period in 28 patients and over a 3 week period in 5. All PEs were performed with 1.5 plasma exchange volumes. An isotonic solution containing 5% albumin with a sodium content of 145 ± 15 mEq/L was used as the replacement fluid. Of the 30 patients, for whom PE was performed at Hahnemann University Hospital, one was treated as an outpatient; the remainder were admitted and remained in-house for their entire initial treatment. The 3 patients treated at other institutions received PE in an outpatient setting.

During the PE, the first reported improvement was an increase energy level usually before the third PE session. Prior to any report of decreased pain, patients reported improvement in morning joint stiffness, muscle spasms, and muscle contractions, especially at night time. In addition, decreased sensitivity to touch was described by some patients.

Following PE, the patients demonstrated a statistically significant reduction in their pain level ($P < 0.001$). Only 3 patients demonstrated no improvement. The remaining 30 patients demonstrated a NRS median pain reduction of 64%, and in each case the reduction was at least 2 NRS points (Fig. 1). The NRS pain score throughout the initial 7 exchanges, for the 30 patients where such data was available, is illustrated in Fig. 2. The 3 non-responders did not show any change in their daily NRS pain score (Fig. 2A). The patients that responded to PE showed a progressive decrease in their pain that reached statistical significance by the third PE and continued to improve throughout the therapy (Fig. 2B). In the 30 patients that responded to PE therapy, there was no significant difference ($P > 0.05$) in the degree of pain reduction between punch biopsy positive and negative patients or between QST positive and negative patients. However, there was a significant correlation (rho = 0.558, $P = 0.009$) between pain reduction following PE and increased temperature detection thresholds.

<table>
<thead>
<tr>
<th>Table 3. Short Form McGill scores.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td><strong>Pre (n=33)</strong></td>
</tr>
<tr>
<td><strong>Post (n=33)</strong></td>
</tr>
<tr>
<td><strong>Maintenance (n=20)</strong></td>
</tr>
<tr>
<td><strong>Total Score (0-220)</strong></td>
</tr>
<tr>
<td><strong>Continuous (0-60)</strong></td>
</tr>
<tr>
<td><strong>Intermittent (0-60)</strong></td>
</tr>
<tr>
<td><strong>Neuropathic (0-60)</strong></td>
</tr>
<tr>
<td><strong>Affective (0-40)</strong></td>
</tr>
</tbody>
</table>

This table lists the pre and post short-form McGill median scores and 95% confidence interval of the mean for all 33 patients that received PE. Also included are the scores from the 20 patients that continued with weekly PE maintenance therapy. Statistically significant differences ($P < 0.01$) between groups are denoted as (**).

Plasma Exchange

The initial series of treatments were performed over a 2 week period in 28 patients and over a 3 week period in 5. All PEs were performed with 1.5 plasma exchange volumes. An isotonic solution containing 5% albumin with a sodium content of 145 ± 15 mEq/L was used as the replacement fluid. Of the 30 patients, for whom PE was performed at Hahnemann University Hospital, one was treated as an outpatient; the remainder were admitted and remained in-house for their entire initial treatment. The 3 patients treated at other institutions received PE in an outpatient setting.

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Plasma Exchange

The mean number of PEs in the initial series was 7.2 (range 5 – 11). Three patients had 5 treatments, one patient had 6, 24 patients had 7, 2 patients had 8, 2 patients had 10, and one patient 11 treatments.

Plasma Exchange Therapy in Patients with CRPS

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Plasma Exchange

The mean number of PEs in the initial series was 7.2 (range 5 – 11). Three patients had 5 treatments, one patient had 6, 24 patients had 7, 2 patients had 8, 2 patients had 10, and one patient 11 treatments.
There was also a trend between efficacy and loss of small fibers but the correlation was not significant ($\rho = 0.203, P > 0.05$). The correlation results suggest that patients with the greatest loss of small fibers and the greatest temperature sensory deficits are most likely to benefit from PE therapy.

Patients also reported improvement in cognitive abilities, joint stiffness, allodynia, generalized malaise, muscle spasm/jerk, and cramps as well as autonomic manifestations such as edema, erythema, and diaphoresis. The decreased sensation to cold and pin-prick remained unchanged in all patients. Two of the 3 patients that didn't respond to PE reported some changes in their CRPS symptoms. One patient reported improved mobility, less stiffness, and less sensitivity to touch. One patient reported that following a pain flare, symptoms that in the past accompanied a flare (painful bruising, redness, temperature changes, sweating, and swelling) were greatly diminished. The third patient reported no symptom changes.

The short-form McGill scores are tabulated in Table 3. The scores before and after PE showed a similar pattern as the NRS pain scores. The 30 patients that responded to PE demonstrated a median reduction of the total McGill score of 64% (range from 38 to 100%). The subcategories of the McGill score followed a similar pattern, with the neuropathic component demonstrating the greatest (76%) decrease. The 3 patients that didn't respond to PE showed no improvement on their McGill scores.

Results of the complete blood count and fibrinogen plasma concentration before and after the initial series of PE in patients that received PE at Hahnemann University Hospital are shown in Table 4. These patients demonstrated statistically significant decreases ($P < 0.01$) in blood RBC counts, Hg, Htc, and fibrinogen. There was a significant correlation ($\rho = 0.536, P = 0.008$) between the change in plasma fibrinogen level and the percent reduction in pain following treatment (Fig. 4). In addition, there were small but statistically significant increases ($P < 0.05$) in the Red Cell Distribution Width (RDW) and White blood cells (WBC).

**PE Maintenance**

Following the initial series, 20 of the 33 patients elected to continue PE. These patients received twice a week PE for 4 weeks and continued on a weekly PE schedule. The 20 patients on weekly PE retained significant reduction in pain as compared to pre therapy levels ($P < 0.01$) in both the NRS pain score (Fig. 3) and all components of the McGill questionnaire ($P < 0.01$) (Table 3). These patients have maintained the improvement in pain levels for an average of 5.4 months (range one to 16 months). In addition to decreased pain, 3 of
these 20 patients were able to completely discontinue opiates (transdermal fentanyl patch, hydromorphone, and oxycodone) and 2 patients are able to walk without the need of their assisting devices (a 4 point walker and a single leg scooter).

**Maintenance with Oral Immunotherapy**

Eight patients that responded to PE are currently on oral immunosuppressants. Seven patients (including 5 that were for a time on PE maintenance therapy) decided to discontinue PE. Five patients discontinued PE because they found the maintenance of the Permacath difficult. Two patients that lived outside the Philadelphia area could not find local hospitals that were able to provide the maintenance PE treatments. When PE was discontinued, their pain gradually (over 6 weeks) returned to pre-treatment values. Given the positive response to PE and the fact that their pain had returned to pre-PE levels we decided to offer them oral immunotherapy. Five patients were placed on mycophenolate mofetil under our care, and one patient was started on adalimumab under the care of her local physician. The patients on mycophenolate mofetil were closely monitored for side effects and titrated to a dose of 1500 mg twice a day over the course of 2 weeks. The reduction in pain level following PE, which had been lost when the therapy was discontinued, has been regained with both adalimumab and mycophenolate mofetil treatment. One patient was placed on prednisone 10 mg daily by the patient’s rheumatologist. The reduction in pain level following PE has also been regained on prednisone therapy.

One patient had been taking 4 mg of dexamethasone daily for leukocytoclastic vasculitis. The dexamethasone did not provide any relief of the pain symptoms. Following PE the patient continued all pre-

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**Table 4. Blood parameters pre and post the initial series of plasma exchanges.**

<table>
<thead>
<tr>
<th></th>
<th>WBC (x10^3 /mL)</th>
<th>RBC (x10^6 /mL)</th>
<th>Hg (g/dl)</th>
<th>Htc (Percent)</th>
<th>MCV (FL/cell)</th>
<th>MCH (pg/cell)</th>
<th>MCHC (g/dl)</th>
<th>RDW (percent)</th>
<th>Fibrinogen (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre PE</td>
<td>7.10</td>
<td>4.06</td>
<td>12.27</td>
<td>36.46</td>
<td>89.96</td>
<td>30.23</td>
<td>33.60</td>
<td>13.82</td>
<td>250.96</td>
</tr>
<tr>
<td>Post PE</td>
<td>7.94*</td>
<td>3.47**</td>
<td>10.53**</td>
<td>31.50**</td>
<td>91.08</td>
<td>30.39</td>
<td>35.90</td>
<td>14.50*</td>
<td>160.54**</td>
</tr>
</tbody>
</table>

The data list blood parameters from the patients that received PE at Hahnemann University Hospital. The abbreviations are as follows: white blood cells (WBC), red blood cells (RBC), hemoglobin (Hg), hematocrit (Htc), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW). Statistically significant changes between pre and post blood values are denoted as (*) P < 0.05 and (**) P < 0.01.
previous medications, including dexamethasone at the same 4 mg/day dose, and the pain level has remained at a 4 for the last 11 months without any additional medication.

In the 8 patients on immunotherapy, the median pain level is 4 (range 3 to 6) which is significantly less (P < 0.01) than pre PE treatment values. There is no statistical difference between the reported pain level after the initial series of PE and their current pain on oral immunotherapy (P = 0.534).

**IVIG Maintenance**

The patient that tested positive for anti-sulfatide antibodies was offered IVIG maintenance therapy given that IVIG is the treatment of choice for this condition (25). This patient's reported a pain reduction from an 8 to a 1 following the initial series of PE. The patient was placed on IVIG (one treatment, 90 grams every 3 weeks) and the pain level has remained at a 1 for the last 6 months.

**No Maintenance Treatment**

The remaining 9 patients elected not to continue PE. The 3 non-responders discontinued PE due to lack of efficacy. The pain level in these patients remains unchanged. One patient found that the pain relief from PE was short lived and also decided to discontinue treatment. The other 5 patients chose to discontinue PE because it was difficult for them to comply with the treatment regimen. The pain level in these 5 patients gradually (over 6 weeks) returned to pre-treatment values. Fig. 5 shows the post PE treatment for all patients.

**Adverse Effects**

The patients that underwent a skin biopsy developed no complications from the procedure. None of the patients had any complications during the catheter placement. However, the surgical procedure caused pain in every patient but it usually subsided by the third day. The pain was treated with intravenous (IV) ketorolac (30 mg every 6 hours as needed). During the PE, patients had no major complications. Minor complications were managed by the staff at the PE suite (symptoms of low calcium, hypotension, symptoms of hypoglycemia, and hyper-somnolence) with simple non-invasive interventions.

**Discussion**

We treated 33 CRPS patients with PE and found that a series of PE performed over a 2 to 3 week period can significantly reduce pain levels. We chose an initial series of 7 PE treatments to achieve a decrease in plas-
The efficacy of PE could also be due to reduction of plasma fibrinogen. We found a significant correlation \( (P < 0.01) \) between the reduction of plasma fibrinogen following PE and pain relief. Fibrinogen is a glycoprotein found in blood that is involved in the formation of blood clots and also plays an important role in inflammation (39). Fibrinogen activates macrophages through CD11b/CD18 and toll-like receptor 4 (TLR4) (40). TLR4 is also expressed on nociceptive neurons and its activation results in neuronal sensitization (41). Fibrinogen extravasation into the nervous system has been reported following barrier dysfunction (42,43).

Peripheral nerve injury results in disruption of the BNB and has been implicated in the disruption of the blood spinal cord barrier (BSCB) (43,44). Following barrier disruption, fibrinogen entry into peripheral nerves results in mechanical allodynia whereas extravasation of fibrinogen into the central nervous system (CNS) results in microglia activation and neuroinflammation (42,43). Activated microglia have been shown to be necessary for the initiation of neuropathic pain (45,46). We have shown activated microglia in spinal cord autopsy tissue from a patient with CRPS (47).

In addition, the efficacy of PE could be due to alterations in plasma microRNA (miRNA). We recently reported that blood miRNA profiles differed in CRPS patients compared to healthy controls and that dysregulation of specific miRNAs correlates to symptoms and comorbidities associated with the disease (48). Exosomes are small vesicles that contain diverse classes of miRNAs, mRNAs, proteins, and lipids that are co-expressed, packaged, and secreted from cells into bodily fluids under normal and disease states (49-52). We have also reported that many of the miRNAs that are dysregulated in blood of CRPS patients are associated with exosomes and identified 127 miRNAs whose exosomal concentration were significantly different between CRPS patients and healthy controls (53). One of these miRNAs, miR-29, has been implicated in hereditary neuropathies and several are known to contribute to neuropathic pain (54,55).

The major limitation of this study is its retrospective nature which includes non-randomization, non-blinding, and an uncontrolled design. Not all patients agreed to undergo QST or skin punch biopsy due to fear the procedure would exacerbate their condition. In addition, the only patients that we treated with PE were those whose health insurance carrier considered PE an eligible procedure for their medical condition. This included CRPS patients with a SFN, confirmed by
skin biopsy, or CRPS patients that qualify for Medicare. Due to this limitation, the patients in this study presented with a clinical picture suggestive of a SFN and our findings did not address whether PE is efficacious in all CRPS patients.

In our previous studies, CRPS patients did not respond equally to the same medications (56-58). We have found no agent to be universally efficacious in the treatment of CRPS. Our working hypothesis is that CRPS is composed of different subtypes resulting from more than one etiology and no one treatment is efficacious in all patients. Therefore, the fact that some patients in this study did not respond to PE is consistent with our previous findings.

**Conclusions**

Our study shows that PE is effective in a subset of patients with severe long-standing CRPS. We also showed that in many of these patients the reduction in pain following the initial series of PE treatments can be maintained on either a weekly PE schedule, IVIG, or with other immune modulating drugs. In addition, this study suggests that patients with the greatest loss of small fibers and temperature sensory deficits are the most likely to benefit from PE therapy. Randomized, placebo controlled studies may be required to confirm and expand our results. Additional studies are needed to explore the mechanisms by which PE and other immune therapies reduce pain in all or a subset of CRPS patients. The data obtained from such studies may aid in advancing our understanding of the mechanisms involved in the pathophysiology of CRPS. A better understanding of these mechanisms may lead to new therapies for this severe life-altering condition.

**References**

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