

# Intravenous Immunoglobulin Treatment of the Complex Regional Pain Syndrome

## A Randomized Trial

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**Background:** Treatment of long-standing complex regional pain syndrome (CRPS) is empirical and often of limited efficacy. Preliminary data suggest that the immune system is involved in sustaining this condition and that treatment with low-dose intravenous immunoglobulin (IVIG) may substantially reduce pain in some patients.

**Objective:** To evaluate the efficacy of IVIG in patients with long-standing CRPS under randomized, controlled conditions.

**Design:** A randomized, double-blind, placebo-controlled crossover trial. (National Research Registry number: N0263177713; International Standard Randomised Controlled Trial Number Registry: 63918259)

**Setting:** University College London Hospitals Pain Management Centre.

**Patients:** Persons who had pain intensity greater than 4 on an 11-point (0 to 10) numerical rating scale and had CRPS for 6 to 30 months that was refractory to standard treatment.

**Intervention:** IVIG, 0.5 g/kg, and normal saline in separate treatments, divided by a washout period of at least 28 days.

**Measurements:** The primary outcome was pain intensity 6 to 19 days after the initial treatment and the crossover treatment.

**Results:** 13 eligible participants were randomly assigned between November 2005 and May 2008; 12 completed the trial. The average pain intensity was 1.55 units lower after IVIG treatment than after saline (95% CI, 1.29 to 1.82;  $P < 0.001$ ). In 3 patients, pain intensity after IVIG was less than after saline by 50% or more. No serious adverse reactions were reported.

**Limitation:** The trial was small, and recruitment bias and chance variation could have influenced results and their interpretation.

**Conclusion:** IVIG, 0.5 g/kg, can reduce pain in refractory CRPS. Studies are required to determine the best immunoglobulin dose, the duration of effect, and when repeated treatments are needed.

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The complex regional pain syndrome (CRPS) was previously known as *reflex sympathetic dystrophy*, *causalgia*, *Sudeck atrophy*, and *algodystrophy*. It is a painful, usually posttraumatic condition in a limb, and it occurs at an incidence of 2.6 per 10 000 person-years (1). It may be classified as type 1 or 2, on the basis of the absence or presence of injury to major nerves. It is characterized by sympathetic, sensory, and motor dysfunction and skin abnormalities in the affected limb, but the cardinal symptom is severe pain. A range of treatments can enhance early recovery from CRPS (2–4). In patients who do not improve within 6 months, CRPS typically has a lasting, ad-

verse effect on quality of life and the ability to maintain gainful employment (5). Treatment of late CRPS is empirical and often of limited efficacy (6, 7). The cause of CRPS is unknown, and it is not clear what distinguishes patients who recover early from those who do not improve.

There is evidence, however, for immune activation in the affected limb, peripheral blood, and cerebrospinal fluid (8–10). This suggests that modulating the immune system may alleviate CRPS. In keeping with this possibility and stimulated by a chance observation, we examined (11, 12) the benefit of treating CRPS with intravenous immunoglobulin (IVIG). In an open study (11), we found that low-dose IVIG reduced pain intensity by 30% or more in approximately 50% of patients. Other groups (13) have since corroborated these clinical observations, yet to our knowledge, no study has assessed these effects in a trial with an advanced design. In this study, we evaluated the efficacy of IVIG in long-standing CRPS under randomized, controlled conditions.

## METHODS

### Setting and Participants

The trial center was an academic pain management center. After approval by the ethics committee at University College London Hospitals, we identified patients from

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those recently seen at the trial center or at a collaborating supraregional inpatient CRPS rehabilitation center and from patients referred from other pain centers in the United Kingdom. We confirmed the diagnosis of CRPS by using the Bruehl/Budapest clinical criteria (14). The study physician judged whether eligible patients had stable CRPS of 6 to 30 months' duration. Patients with a longer duration of disease were eligible if they reported that disease had spread to a previously uninvolved limb within the past 30 months. We required all patients to have tried acetaminophen, nonsteroidal anti-inflammatory drugs, opioids, tricyclic antidepressants, gabapentin or pregabalin, and physiotherapy with an unsatisfactory outcome (either insufficient pain relief or unacceptable side effects). Patients received their ongoing standard medical therapy during the study, but we did not allow any new analgesic drugs. We excluded pregnant or breastfeeding women and patients with contraindications to IVIG.

### Screening, Randomization, and Interventions

The study was a randomized, placebo-controlled, double-blind, single-center, 2-period crossover trial. We screened patients to determine whether pain was severe enough to qualify for the study by using a pain diary in which patients recorded on a daily basis how much pain they had had during the preceding 24 hours. Patients rated their pain by using an 11-point numerical rating scale (0 = no pain; 10 = pain as bad as you can imagine). Patients reported their diary entries over the phone after 1 week. If pain intensity was 5 or higher for all 7 days, patients were eligible for random assignment, although they were unaware of this threshold. We randomly assigned eligible patients to receive either the intervention in the first period and placebo in the second period or placebo first and the intervention second (**Figure 1**). Patients continued to use the numerical rating scale to measure their pain on each day of the study. There was a washout period between the 2 infusion periods to ensure reduction of the immunoglobulin plasma level by more than half. We scheduled patients for crossover infusions 28 days after the initial infusions. If at that time a patient reported ongoing pain relief, we extended the washout until pain intensity was stable for 7 days at a level similar to that during screening (plus or minus 1 point and not <5). Patients stopped keeping pain diaries 28 days after the crossover infusions and were then followed for another 8 weeks to identify some secondary outcomes and any late adverse events.

The same investigator enrolled all patients. We obtained informed consent according to the Declaration of Helsinki and took samples for blood count, serum immunoglobulin level (to exclude IgA deficiency), and urine human chorionic gonadotropin level. Patients also completed the Brief Pain Inventory (short form) (15). The trial statistician provided the trial pharmacy with a computer-generated, blocked randomization code that ensured approximately equal numbers of patients in each study

### Context

Several years ago, the researchers gave intravenous immunoglobulin (IVIG) to a patient with primary hypogammaglobulinemia and widespread pain of unknown cause that was not the complex regional pain syndrome (CRPS). The patient had unexpected pain relief that was temporary but reproducible when IVIG treatment was repeated. Since then, the researchers have tried IVIG treatment in other patients with chronic pain syndromes of unknown cause.

### Contribution

In this randomized, placebo-controlled, double-blind, crossover trial in 13 patients who had CRPS for 6 to 30 months, patients reported that their pain level was lower after IVIG than after placebo.

### Caution

Because the study is so small, it is difficult to know whether these results apply to most other patients with CRPS. Also, the small number of patients increases the possibility that chance may affect the results.

### Implication

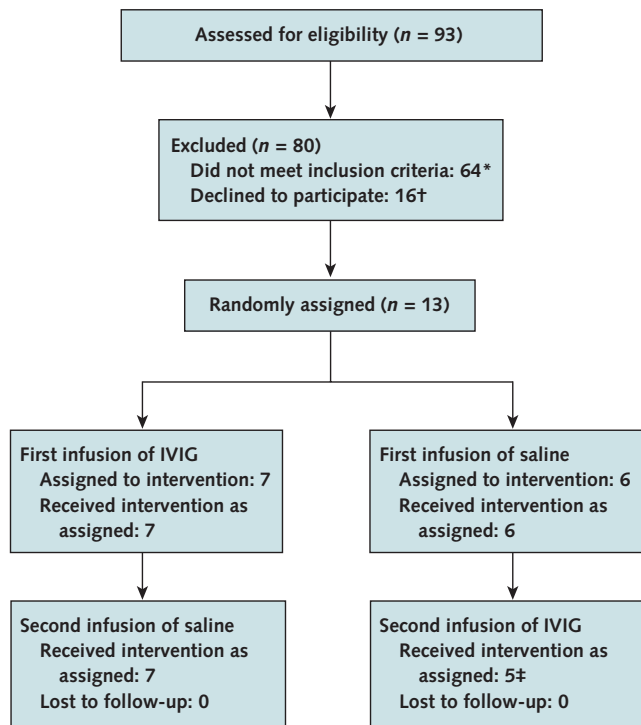
Therapy with IVIG reduced pain in patients who have CRPS for 6 to 30 months. Additional studies are needed to determine which patients are likely to benefit and which IVIG doses and schedules are most effective.

—The Editors

group. The trial pharmacist concealed the random assignments from other persons involved in the study. Because bubbles and foam in the bottles and drip chamber occur only with the IVIG solution, we blinded patients and physicians during drug infusions by concealing the infusion bottles and the drip chamber of the intravenous line with small inflatable covers and then covering the infusion equipment and the inflatable cover with a cotton bag. In addition, a screen separated the infusion equipment from the patient. Because IVIG solution is stickier than saline, we primed the infusion line with normal saline to prevent the patient or study physician from identifying the study drug if it dripped from the end of the intravenous line. The color of the IVIG preparation (Sandoglobulin NF, CSL-Behring, Bern, Switzerland) was indistinguishable from saline when it was in the intravenous line. A nonblinded administration nurse not otherwise involved in the trial gave the infusions. The study physician remained outside the treatment room unless the patient requested assistance. To determine whether blinding was successful, we asked both patient and study physician immediately after each infusion administration to guess the treatment allocation and to explain the guess.

We gave each infusion to patients for 2 consecutive days. We used a total immunoglobulin dose of 0.5 g/kg (0.25 g/kg per day), which is lower than that commonly

Figure 1. Study flow diagram.



IVIG = intravenous immunoglobulin.

\* 11 patients improved, 23 had had complex regional pain syndrome for too long, and 30 did not meet inclusion criteria for other reasons.

† 4 patients had travel problems, 2 declined for other reasons, and 10 declined for unknown reasons.

‡ 1 patient withdrew after becoming pregnant.

used for other conditions, because our preliminary results (11) showed that this dose had good efficacy with minimal adverse effects. Before each infusion administration, we told patients, “Both treatments, or 1 of the treatments, or none of the treatments may provide significant pain relief. Both IVIG and normal saline may cause an initial pain increase, but this will not predict treatment outcome. Both IVIG and normal saline may cause similar adverse symptoms. Pain relief may last as little as a few days, or as long as a month, or even longer in some cases.” Study personnel called each patient every 2 to 3 days after each infusion to confirm adherence to the pain questionnaires and to ask about possible adverse events.

## Outcomes

The primary outcome was pain intensity, measured with our numerical rating scale, from days 6 to 19 after each period. Day 1 was the day of the first infusion administration in each period. We selected these days because we believed that they would include the period of maximum drug effect and exclude the period immediately after the infusion, during which preliminary studies (11) indicated that some patients had headache from the drug that could

complicate assessment of CRPS pain relief. We asked patients to provide 1 score for each 24-hour period.

We also measured 2 secondary outcomes: the report by the patient of which treatment was more efficacious and the score on a CRPS “limb-symptom” scale. We asked patients to rate their involved limbs every day from days 6 to 19 in each period on the basis of temperature, color, swelling, sweating, muscle power, and nail and hair growth. Patients rated limb status for the previous 24 hours by comparing it with the status before the infusion by using the following scale: 0 = complete subsidence, 1 = a lot of improvement, 2 = moderate improvement, 3 = slight improvement, 4 = no change, and 5 = worse. During the 8-week follow-up, patients completed a global impression-of-change scale, a 7-point verbal rating scale in which 0 = very much improved, 3 = no change, and 6 = very much worse (16). The **Appendix** (available at [www.annals.org](http://www.annals.org)) lists additional outcome measures. We also asked patients about adverse events, which they rated as mild, moderate, or severe. We defined adverse events as serious in accordance with the International Conference of Harmonisation guideline (17).

## Statistical Analysis

We calculated the sample size by using a paired *t* test based on a single outcome measure in each period. A sample size of 11 patients was needed to detect an average difference of 2 units between pain intensity after IVIG and pain intensity after saline with 90% power and 5% statistical significance, assuming an SD of 2 units. We assumed that about one third of participants would withdraw and scheduled 16 patients for enrollment.

We used a regression model with random effects to estimate the treatment effect on the primary outcome (**Appendix**, available at [www.annals.org](http://www.annals.org)). This model describes pain intensity as a function of treatment and treatment period and uses random intercepts to adjust for the correlation between outcome measures from the same patient. To investigate whether the treatment effect was constant over each period, we fitted terms for day and for the interaction between day and treatment and tested them for statistical significance.

We performed a simpler summary statistics analysis for the limb-symptoms outcome. For each patient, we dichotomized the data from each treatment period into either “reported some improvement over the treatment period” or “no improvement reported.” We then analyzed these outcomes by using the McNemar test. We summarized the more efficacious treatment outcome by using proportions. We performed all analyses on an intention-to-treat basis. We used Stata, version 10 (StataCorp, College Station, Texas; `xtreg` command for the main analysis) to fit the model and check the residuals for normality. We used Graphpad InStat and Prism 4 (GraphPad Software, San Diego, California) to calculate summary statistics and create the figures.

## Role of the Funding Source

The study was funded by the Association of Anaesthetists in Great Britain and Ireland, the University College London Hospitals Trustees, and CSL-Behring. The funding sources had no role in the design, conduct, or analysis of the study; writing of the manuscript; or the decision to publish. We notified CSL-Behring of the results of the study and provided them with a copy of the manuscript before submission.

## RESULTS

### Demographic Characteristics

From December 2005 to May 2008, we enrolled 13 patients in the study and stopped enrollment when our target of 11 patients completed the study. One patient completed the first period of the study but did not receive treatment in the second period because she became pregnant (Figure 1). Table 1 shows patients' overall baseline characteristics (individual data are shown in Appendix Table 1, available at [www.annals.org](http://www.annals.org)).

### Success of Blinding

When asked about drug identity immediately after their 4 infusion administrations (2 drug and 2 saline), 12 patients answered "don't know" on all occasions and 1 patient incorrectly guessed saline after both the first and second infusion administration. The study physicians answered "don't know" on all occasions, with 1 exception, who correctly guessed after the first infusion administration that the infusion was IVIG because he saw bubbles in the infusion line. The patient on this occasion guessed "don't know." Both study physician and patient guessed "don't know" after the second infusion administration.

### Primary Outcome

Only 1 patient had missing outcome data with no measurements for the crossover period. Clear evidence existed for a treatment effect, with an average decrease of 1.55 units in pain scores after IVIG compared with saline (95% CI, 1.29 to 1.82;  $P < 0.001$ ) (Figure 2). No evidence indicated that the effect of treatment varied during the observation period ( $P = 0.38$ ). Five patients (42%) had median pain scores that were at least 2 points lower with IVIG than with saline, and 3 of these patients had median pain scores that were at least 50% lower. One patient reported a median pain score 2 points lower after saline administration than after IVIG. Ongoing pain relief after the first infusion required delay of the second infusion in 4 patients (3 patients after IVIG and 1 patient after saline). Two patients who received IVIG as the second infusion reported "much improved" or "very much improved" pain after day 28 following the second infusion: one patient for 2 weeks, and the other patient for 3 weeks. Appendix Table 2 and the Appendix Figure (available at [www.annals.org](http://www.annals.org)) list additional information about the primary outcome.

## Secondary Outcomes

Eight of the 12 patients (66%) who received both types of infusion believed that one infusion period was more efficacious than the other. The better period was IVIG in 7 cases and saline in 1 case. Of the 11 patients with limb-symptom measurements for each treatment period, 1 patient reported some improvement in both periods, and 3 patients reported no improvement in either period. The remaining 7 patients reported an improvement after IVIG but not after saline ( $P = 0.016$ ). Appendix Table 3 (available at [www.annals.org](http://www.annals.org)) lists results of additional outcomes.

## Safety

Patients reported no serious adverse events. Table 2 lists adverse events rated by patients as severe or moderate. Of the 9 severe adverse events, 4 occurred after IVIG and 5 occurred after saline. Severe or moderate headaches were self-medicated with acetaminophen at home, and patients did not use the emergency help-line set up for the trial.

## DISCUSSION

Our 13 patients with long-standing, refractory CRPS reported that, compared with saline, IVIG at 0.5 g/kg substantially reduced pain over 14 days and improved auto-

Table 1. Patient Characteristics at Baseline

Characteristic	Value
Patients, <i>n</i>	13
Mean age (SD), <i>y</i>	41 (10)
Women, <i>n</i>	10
Initiating trauma, <i>n</i>	
None or trivial	4
Trauma without fracture	4
Fracture or surgery	5
CRPS type, <i>n</i>	
Type 1	12
Not determined	1
Limb affected, <i>n</i>	
Lower	4
Upper	6
Lower with spread to lower	1
Upper with spread to lower	1
Upper with spread to upper, then lower	1
Mean disease duration (SD), <i>mo</i> *	19 (8)
Patients with autoimmunity, <i>n</i> †	2
Patients with CRPS signs on first presentation, <i>n</i>	
Allodynia or hyperalgesia	13
Temperature or color abnormality	10
Swelling or sweating	10
Motor or trophic changes	11
Dystonia	1
Mean numerical rating scale score (SD)‡	7.9 (1.1)
Mean Brief Pain Inventory interference score (SD)§	7.1 (1.7)

CRPS = complex regional pain syndrome.

\* All patients had had CRPS for 6 to 30 mo in one limb, but 2 patients had longer duration of disease in another limb.

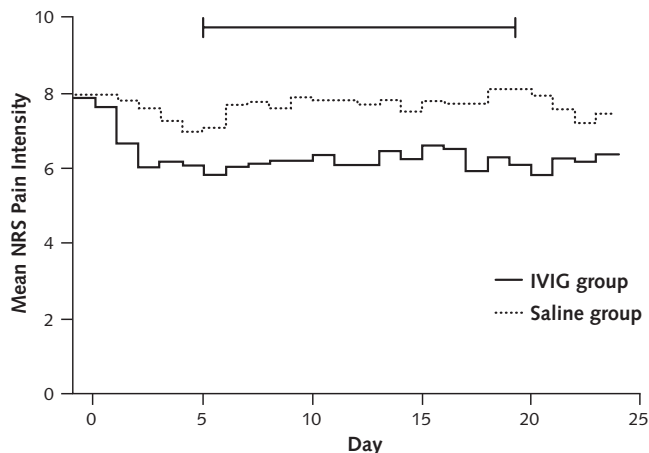
† 1 patient had resolved hemolytic anemia and thyrotoxicosis and ongoing pernicious anemia, psoriasis, and gluten-sensitive enteropathy, and 1 patient had relapsing-remitting multiple sclerosis.

‡ Average of 7 pain diary entries recording 24-h average pain on an 11-point scale (0 = no pain; 10 = pain as bad as you can imagine).

§ In patients with only upper-limb CRPS, interference with the ability to walk was not included in the calculation.



**Figure 2. Mean pain intensity for each day after the infusion.**



Intensities were recorded on an 11-point NRS (0 = no pain and 10 = pain as bad as you can imagine). The horizontal bar marks the 14-day observation period when pain intensities were included in the analyses. Patients received infusions on days 1 and 2. NRS = numerical rating scale.

nomic limb symptoms. To our knowledge, this is the first randomized, controlled trial to show the efficacy of an immune intervention in long-standing CRPS. In long-standing CRPS, only a few medical interventions are effective; except for local anesthetic blockade of the stellate ganglion, epidural clonidine, and intravenous ketamine, no drug treatment has been shown to provide benefit. These treatments have cumbersome modes of administration, are associated with serious adverse reactions, and help only subgroups of patients (18–20). Nondrug treatments of long-standing CRPS include spinal cord stimulation, which can confer symptomatic pain relief, and physiotherapy (4, 6, 7, 21, 22). In this context, IVIG seems to be an important new treatment possibility.

Because late CRPS pain is often refractory to medical treatment and because patients have frequently lost early autonomic signs, including swelling and color changes (23, 24), some observers suggest that the condition may pre-

dominantly be sustained by neuroplasticity mechanisms. These mechanisms are believed to occur both at spinal cord and cortical levels and to represent maladaptive neuronal memory, with no or minimal need for ongoing peripheral noxious drive (25). Our results suggest that immune mechanisms play an important role in sustaining long-standing CRPS, but the precise nature of the immune contribution or how it might relate to the putative central drive is unknown. Experimental models suggest that both peripheral and central glia-mediated neuroimmune activation temporarily sustain posttraumatic pain (26, 27), and an analogous augmented immune activation may play a role in CRPS (8, 10). Intravenous immunoglobulin treatment may reduce this immune activation (28).

Autoimmune mechanisms may also play a role. We and others (12, 29–31) have reported that some cases of CRPS may be mediated by pathogenic autoantibodies. Patients may be predisposed to CRPS after trauma because of the presence of serum autoantibodies, and IVIG may neutralize these antibodies. A recent population-based study (32) found immune-mediated disorders with higher frequency in nonresolving CRPS than in resolving CRPS, which adds credence to this interpretation.

Our study has limitations. First, it is small. Chance variations can affect the results (33), and recruitment bias may affect generalizability. It is encouraging that the observed response rate is congruent with that documented in an open trial involving 11 patients with CRPS from a different population (11). Second, both the optimum dose and the best treatment intervals for IVIG remain unclear. Repeated and higher doses may confer additional pain relief. Third, because we excluded patients who had CRPS for less than 6 months, we are not confident about extrapolating our results to this group. Fourth, we did not quantify physical findings or their changes. Physical findings other than allodynia or hyperalgesia are often reduced in long-standing CRPS (23, 24); therefore, the inclusion of quantitative sensory testing, which measures allodynia, may provide more information in future trials.

Low-dose IVIG was associated with few adverse reactions, except for moderate or severe headaches and transient pain increases (Table 2). Preventive measures may

**Table 2. Adverse Events\***

Type of Event	Intravenous Immunoglobulin	Saline
Severe	Headache (n = 2), pain increase (n = 2)	Pain increase (n = 2), chest and back pain, nausea, pins and needles in affected arm
Moderate	Headache (n = 3), nausea (n = 2), infusion site reaction (n = 2), worsening eczema, chills, pain increase, tiredness, unusual CRPS pain, symptoms in the unaffected hand (cold, color change, or stiffness [but no pain]), dizziness, "feeling hot," abdominal pain, depression	Headache (n = 2), light-headedness (n = 2), tiredness (n = 2), pain increase (n = 2), infusion site reaction (n = 2), worsening of autonomic signs, queasiness, dizziness
Significant†	Gum infection, subjective improvement of multiple sclerosis relapse	NA

CRPS = complex regional pain syndrome; NA = not applicable.

\* Adverse events were patient-rated as severe or moderate. Numbers of patients are listed in parentheses if greater than 1.

† Not rated by patients, but rated by the investigators after unblinding as significant and as possibly related to the intravenous immunoglobulin infusion.

ameliorate headaches (34), but administration of preventive drugs was not feasible in this trial because it would have complicated interpretation of the study results. Patients should be warned of the possibility of a temporary pain increase with IVIG treatment.

Future research should determine the best IVIG doses, the duration of effect, the need for repeat treatment, and whether treatment response varies with disease duration. In addition, the efficacy of immune modulation with IVIG should perhaps be assessed in other severe, treatment-refractory chronic pain.

To our knowledge, we have shown for the first time that low-dose IVIG reduces pain in patients with long-standing, refractory CRPS, with few adverse reactions. Intravenous immunoglobulin may emerge as an effective and safe novel clinical treatment option for otherwise refractory disease, but confirmatory trials are required.

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**Potential Conflicts of Interest:** Disclosures can be viewed at [www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M09-1292](http://www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M09-1292).

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## EXPEDITED REVIEW

*Annals* invites authors of clinically important randomized, controlled trials to request expedited review and publication of their manuscripts. Send requests to Christine Laine ([chrisl@acponline.org](mailto:chrisl@acponline.org)), Michael Berkwits ([mberkwits@acponline.org](mailto:mberkwits@acponline.org)), Cynthia Mulrow ([cmulrow@acponline.org](mailto:cmulrow@acponline.org)), or Sankey Williams ([swilliams@acponline.org](mailto:swilliams@acponline.org)). We take extra efforts to provide thorough, high-quality, and timely critiques of trials that we expedite. Expedited trials that are accepted are published early online. We also provide readers ancillary material about selected trials, including registered protocols, lists of other ongoing and published relevant trials, lists of relevant published systematic reviews, and links to clinical sources that provide physicians and patients information about the topic of the trial.

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## APPENDIX

### Regression Model With Random Effects Used to Calculate the Primary Outcome

The primary model was  $Y_{ijk} = \mu_0 + \beta_T X_{ij} + \gamma_j + u_i + \epsilon_{ijk}$ , in which  $Y_{ijk}$  is the 24-hour pain intensity score for patient  $i$  in treatment period  $j$  and daily episode  $k$ .  $\mu_0$  represents the mean 24-hour pain intensity score in the population with no treatment,  $\beta_T$  is the fixed effect of treatment,  $X_{ij}$  is the design matrix indicating the treatment assignment (placebo = 0, treatment = 1),  $\gamma_j$  is the period effect,  $u_i$  is the random effect of patient  $i$ , and  $\epsilon_{ijk}$  is the variation within the patient. The 2 random terms  $u_i$  and  $\epsilon_{ijk}$  are assumed to be normally distributed with a mean of zero and variance  $\sigma_u^2$  and  $\sigma_\epsilon^2$ , respectively. Estimates from this model are given in Appendix Table 2.

### Additional Outcome Measures and Follow-up Outcome

Patients completed additional outcome measures, including pain unpleasantness, by using an 11-point numerical rating scale (0 = not unpleasant and 10 = most unpleasant feeling possible); pain relief by using a 6-point verbal scale (0 = complete relief and 5 = worse pain); sleep quality by using a 3-point verbal rating scale (0 = good, 1 = fair, and 2 = poor); and a global impression of change scale, a 7-point verbal scale (0 = very much improved, 3 = no change, and 6 = very much worse). These additional outcome measures are reported in Appendix Table 3. At 12 weeks, 9 patients returned their follow-up global impression-of-change questionnaire and reported minimal or no change in their condition compared with before the second set of infusions.

Appendix Table 1. Individual Baseline Characteristics

Patient Number*	Sex	Limb Affected	Duration
1	Female	Lower	16 mo
2	Female	Upper	6 mo
3	Male	Upper	18 mo
		Lower	10 mo
4	Female	Upper	28 mo
5	Female	Lower	29 mo
6	Female	Upper	16 y
		Upper	34 mo
		Lower	22 mo
7	Male	Upper	30 mo
8	Female	Upper	12 mo
9	Male	Lower	12 mo
10	Female	Upper	23 mo
11	Female	Lower	22 mo
12	Female	Lower	10 y
		Lower	12 mo
13	Female	Upper	21 mo

\* Patients 3, 6, and 12 had spreading complex regional pain syndrome.

Appendix Table 2. Results for the Primary Outcome in a Random-Effects Analysis Model

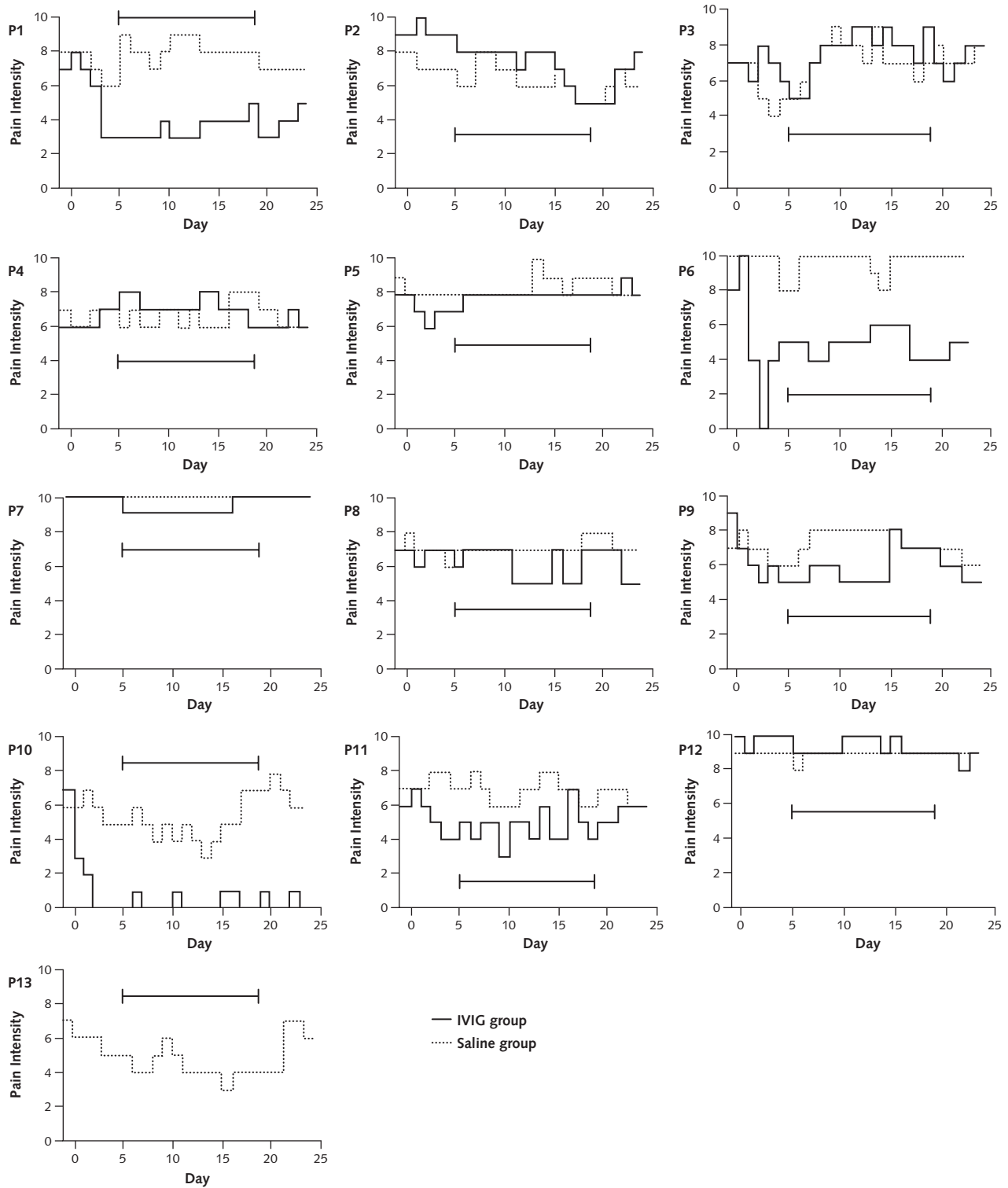
Term	Estimate ± SE (95% CI)*	P Value†
$\beta_T$	-1.55 ± 0.14 (-1.82 to -1.28)	<0.001
$\gamma_j$	-0.48 ± 0.14 (-0.75 to -0.21)	<0.001
$\mu_0$	7.67 ± 0.54 (6.62 to 8.73)	
$\sigma_u$	1.90 ± 0.38 (1.28 to 2.81)	
$\sigma_\epsilon$	1.24 ± 0.05 (1.15 to 1.33)	

\* Coefficient estimates from our primary random-effects model.

† Wald test.



Appendix Figure. Pain intensity in 13 patients.



Pain intensity for each day after the infusion recorded on an 11-point numerical rating scale (0 = no pain; 10 = pain as bad as you can imagine). The horizontal bars mark the 14-day observation period when pain intensities were included in the analyses. Patients received infusions on days 1 and 2. IVIG = intravenous immunoglobulin; P = patient enrollment number.

**Appendix Table 3. Summary Measures of Individual Patient Outcomes After IVIG and Saline\***

Patient Number	Treatment Allocation†	Pain Intensity‡		Pain Unpleasantness§		Pain Relief		Sleep Quality¶		Limb Symptoms**		Global Impression of Change††	
		IVIG	Saline	IVIG	Saline	IVIG	Saline	IVIG	Saline	IVIG	Saline	IVIG	Saline
1	2	3.5	8	NC	8	NC	4	0	2	1	0	0	3.5
2	1	8	6	8	7	3	2	1	0	1	1	2	1
3	1	8	7	8	7	4	4	NC	NC	NC	NC	NC	NC
4	2	7	6.5	8	5.5	4	4	2	2	0	0	3	3
5	2	8	8	8	8	4	4	1	2	1	0	3	3
6	1	5	10	4	10	1	4	2	2	1	0	1	3
7	1	9	10	10	10	3	5	2	2	0	0	3	5
8	2	6.5	7	7	6	3.5	4	1	1	1	0	3	3
9	1	5.5	8	6	8	3	5	1	2	1	0	3	4
10	2	0	5	0	4	0	3	0	0	1	0	0	2
11	1	5	7	6	7	3	4	1	2	1	0	3	3
12	1	9	9	10	9	4	4	2	2	0	0	4	4
13	2	NC	4	NA	NC	NA	NC	NA	NC	NA	NC	NA	NC

IVIG = intravenous immunoglobulin; NA = not applicable; NC = not completed.

\* Outcome measures were recorded daily via pain diaries during each 14-d observation period. The table shows the median of these daily measures, except for limb symptoms, in which the values represent whether any improvement has been reported over the observation period.

† 1 = IVIG then placebo; 2 = placebo then IVIG.

‡ 24-h pain intensity on an 11-point (0–10) scale.

§ 24-h pain unpleasantness on an 11-point (0–10) scale.

|| Pain relief relative to pain before infusion on a 6-point verbal rating scale (0 = complete relief; 5 = worse pain).

¶ 0 = good; 1 = fair; 2 = poor.

\*\* Overall daily limb symptoms: 0 = no improvement reported; 1 = some improvement reported.

†† 0 = very much improved; 3 = no change; 6 = very much worse.