Low-dose Intravenous Immunoglobulin Treatment for Longstanding Complex Regional Pain Syndrome, a Randomized Trial

Running Title: 'IVIg in CRPS'

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Abstract

Background
Complex Regional Pain Syndrome (CRPS) is a rare, severe post-traumatic pain condition affecting distal limbs and two small trials have shown efficacy of low-dose intravenous immunoglobulin in longstanding disease.

Objective
To confirm the efficacy of low-dose immunoglobulin treatment when compared to placebo treatment to reduce pain over 6 weeks, in adult patients suffering from CRPS of between 1-5 years' duration.

Design
This was a 1:1 online-randomized, placebo-controlled multi-center trial over 6 weeks, with an optional 6-week open extension. Patients were randomized between 27.08.2013 and 28.10.2015, and the last patient completed follow-up on 21.03.2016. Patients, providers, researchers, and outcome-assessors were blinded to the treatment-assignment (ISRCTN, 42179756).

Setting
Seven secondary and tertiary care pain management centers in the United Kingdom.

Participants
Patients with moderate or severe CRPS of between1-5 years duration.

Interventions
0·5g/kg intravenous immunoglobulin (IVIg), or visually indistinguishable 0.1% albumin in saline placebo, on day 1 and day 22 after randomization. 111 patients were randomized.

Measurements
The primary outcome was the 24h average pain intensity measured daily between days 6 and 42, on an 11-point (0-10) numeric rating scale.

Results
108 eligible patients were analyzed for the primary outcome. The mean of the (average) pain scores was 6.9 (SD 1·5) for Placebo and 7.2 (1.3) for IVIg and the adjusted difference in means was 0·27 (95% CI -0.25 to 0.80; P = 0.30), which excludes the pre-specified clinically important difference of -1.2. In the open extension, 12 of the 67 patients who were treated with two infusions had at least 2 points pain reduction compared to their baseline pain. There were 6 serious

adverse events – two in the blinded phase (1 placebo, 1IVIg) and four in the open phase (4 IVIG).

Limitations

Results do not apply to patients with CRPS >5 years duration.

Conclusion

Low-dose immunoglobulin treatment over 6 weeks was not effective in relieving pain in patients with moderate to severe CRPS of 1-5 years' duration.

Funding source

Medical Research Council/National Institute for Health Research Efficacy and Mechanism Evaluation Program, Pain Relief Foundation, Biotest United Kingdom Ltd

Introduction

Complex Regional Pain Syndrome (CRPS) is a rare chronic pain condition (population prevalence <1:2000) arising after trauma to distal limbs (1, 2). The CRPS diagnosis is clinical, based on the assessment of sensory-, motor- and autonomic abnormalities in the affected limb (3). Most patients improve spontaneously, however those 15% with still ongoing symptoms 1 year after onset have amongst the lowest quality of life in medical conditions, and their prognosis is poor (4, 5). Treatment with analgesic drugs such as antidepressants, or anticonvulsants is rarely effective (6). Recommended is multidisciplinary care, however many patients will not achieve pain relief (7).

Following a chance observation, we conducted a prospective open study, and a small randomized crossover trial, where low-dose intravenous immunoglobulin substantially reduced pain in this patient group. The proportion of patients with profound pain relief of >50% was 25% in both studies (8, 9).

The phase III 'Low-dose Immunoglobulin in longstanding Complex Regional Pain Syndrome' (LIPS) randomized controlled trial was conducted to confirm the efficacy of repeated-dose treatment with low-dose intravenous immunoglobulin (IVIg) over placebo in a large group of patients with longstanding CRPS. The primary outcome was the pain intensity measured daily over a 6-week period following infusion. This was compared between immunoglobulin and placebo groups.

Methods

Design Overview

In this parallel group trial patients with Complex Regional Pain Syndrome were randomly assigned in 1:1 allocation to receive either of two infusions of 0·5 g/kg intravenous immunoglobulin (IVIG), or placebo; all patients were offered an open label extension of two IVIg infusions. Providers, researchers, and outcome assessors were blinded to the treatment assignments. Ethics approval was given (12/EE/0164, East of England Ethics, Welwyn). Patients were provided with patient information leaflets about the trial, and interested patients gave written informed consent. The study protocol has been published (10)

Setting and participants

The study recruited across 7 UK secondary and tertiary care pain treatment centers. Participants were recruited from the study centers' internal databases, and from new patients referred to these seven study centers. To enhance recruitment, the study was regularly publicized in UK Pain Medicine professional

journals, through letters to each English Specialist Pain Clinic, on social network sites, and with UK CRPS patient organizations.

Eligible participants were non-pregnant adults with moderate or severe CRPS (Budapest research criteria(3)). The CRPS severity cutoff was concealed, and determined by a mean pain intensity of five or higher on an 11-point (0-10) Numeric Rating Scale (NRS) over the first seven daily entries into pain diaries during screening, with no single entry below 4. A pain intensity of 4/10 is considered a cut point between mild and moderate pain (11). The Budapest research criteria require the presence of at least one regional sign, in at least 2 of 4 diagnostic categories, i.) sensory abnormalities such as allodynia, ii.) swelling or sweating, iii.) colour or temperature changes, iv.) motor or trophic changes; additionally required is the report of symptoms in all 4 categories. All recruitment centers used these criteria. Patients with either CRPS type I (without-), or II (with nerve injury) were eligible. Patients had between 1-5 years' disease duration, and no other pains which in the study doctor's opinion might interfere with the patients' own assessment of CRPS-pain changes. Before enrolment, patients had tried tricyclic antidepressants, gabapentinoids, mild and strong opioids, and they had received specialized pain physiotherapy, if not refused by them, or contraindicated. Patients with implanted spinal cord stimulator were eligible if they met pain intensity criteria with the stimulator turned on. Patients continued with their usual exercises and medications. Further detail on inclusion and exclusion criteria is provided in the study protocol (10).

After consent and screening for eligibility, suitable patients completed a screening diary for 7 days, and were then telephoned to ascertain their diary values; the suitable patients were randomized 10-21 days after screening (=day 0).

Randomisation and Interventions

Participants were individually randomly assigned (1:1) to IVIg or placebo by site staff via an independent online randomization system, using block randomization with randomly varying block sizes, stratified by study center. Blinding was achieved by preparing the IVIg (0·5 g/kg IVIg) or placebo solution (0·.1% albumin in normal saline) into bottles of identical appearance. Upon notification, non-blinded dispensing site pharmacists removed the bottle-label indicating the trial arm before dispensing. All other study site staff, the trial manager / site monitor, statistician and Chief Investigator remained blinded to the patients' treatment assignments until database-lock. No participants required emergency un-blinding.

Blinded infusions were scheduled on days 1 and 22 post-randomization. A pre-determined time window around the infusion days provided flexibility (first infusion up to 5 working days, second infusion day 22 +/- 1day). The primary outcome period, days 6-43 after randomization, remained fixed and was thus independent of the actual infusion dates.
Patients who completed the blinded phase were offered a choice to have open label immunoglobulin infusions on days 43 and 64 post-randomization. The dosages prescribed were within normal, weight-determined clinical limits (0.5g/kg) for low-dose treatment.

Outcomes and Follow-up

Paper diaries documenting the participants' average 24h pain score on a 11-point (0-10) numeric rating scale were self-administered by the participants from day 1 to 43 post-randomization (example diary provided in the Appendix), and a weekly pain score was documented for 9 weeks further. Those who decided to have two open infusions after the end of the blinded phase completed 24h diaries to day 84, and nine weekly diaries thereafter. These were 11-point numeric rating scale scores, with 0=no pain, 10=pain as bad as you can imagine.
Patients completed questionnaires at screening, and day 43, assessing their multidimensional pain experience. At these two time-points we also measured skin temperature of both the CRPS affected and contralateral limbs (protocol in the Appendix).
Safety bloods (serum immunoglobulin, full blood count, creatinine, urea and electrolytes), and where applicable pregnancy tests were collected at the screening visit to determine the patient's eligibility. Site staff contacted participants twice following each infusion, to confirm adherence to completing the pain diaries, and to document any adverse events.

The primary outcome measure was the average 24h pain intensity measured daily from day 6 to 42. The interval starting day 6 was pre-specified to exclude the time period of early, unspecific, temporary pain increases, such as headaches (8). Secondary outcomes were the pain interference measured using the interference subscale of the Brief Pain Inventory (12), and quality of life (Euroqol EQ-5D-5L) (13). All other outcomes were exploratory.
Multidimensional assessment tools were used, in line with consensus recommendations for pain trials (14). Details are provided in the Appendix, and in the published protocol (10).

Reasons for withdrawal from randomized treatment were reported at days 22 and 43 post-randomization. Adverse events and reactions were recorded by patients in their diaries, and were transcribed at 22 and 43 days post randomization. In addition, study nurses queried adverse events using open

ended questions as part of scheduled telephone calls at 2 and 5 days after each infusion. A study doctor rated the severity and causality of each event in categorical scales. Open label infusion adverse events, reported from 43 to 85 days post randomization, were tabulated separately. Serious Adverse Events (SAEs) were monitored for 21 days after the final dose of IVIg (or placebo) or until resolution.

Statistical Analysis

The sample size was based on the following assumptions from a pilot study (8): 122 participants were required to detect a clinically meaningful difference on a group level (15)) in pain score of 1.2 using a two-sample t-test assuming 5% statistical significance, 85% power and a common standard deviation of 2·2 (as in this previous study). Assuming 10% loss to follow-up and a 5% non-compliance increased this number to 152 participants. We intended to collect 37 measurements of pain intensity (the primary outcome) per participant and analyze the outcome using a mixed effects regression model. Therefore, the sample size was reduced based on these extra measurements. From the pilot study (8) the correlation between a patient's measures was assumed to be 0.7, hence the multiplying factor was (1+(37-1)x0.7)/ 37 =0.71) Therefore the total required sample size was calculated at 152 x 0.71 = 108 participants (54 participants per study arm).

All statistical analyses were conducted using Stata version 14. The primary outcome was analyzed using a random-intercepts mixed model (Stata: *mixed*) to establish any difference between pain scores after IVIg and placebo. In detail, this model contained fixed effects for treatment and study center and assumed an exchangeable correlation structure between the 37 repeated outcome measurements for a patient. Modeling assumptions were checked: level 1 and 2 residuals were checked for normality. The primary analysis sample was an intention to treat (ITT) sample based on all randomized, eligible patients. No imputation was performed. As a secondary analysis, we calculated the proportion of participants in each arm that achieved 50% or 30% pain relief based on the average pain level entered on days 6-42, compared to their baseline level of pain (the average pain level recorded during the first 7 days of the screening period). Pain reduction of 30% represents a clinically meaningful effect on an individual level (16)).

The following sensitivity analyses were performed: (i) A fixed effect was added to the mixed model for baseline pain score; (ii) A fixed effect was added to the mixed model for disease duration; (iii) Three patients who were incorrectly consented into the trial after not meeting the inclusion criteria were included in the analysis. Possible subgroup effects based on study center, disease duration,

gender, allergy status, IgG plasma level, anxiety and depression, and CRPS type were investigated separately using exploratory plots and by fitting mixed models that included interaction terms between the factor and treatment.

The secondary outcomes Brief Pain Inventory interference scores and Quality of Life (EQ-5D-5L), and also McGill Pain Questionnaire (Short Form) descriptor terms (17) and limb temperature were analysed using linear regression models (Stata: *regress*) with covariates for treatment and study center.

In those who decided to receive both *open* infusions, and who had at least 30% or 2 NRS points average pain relief from 6 to 20 days after their last open infusion as compared with baseline, the time between the last open infusion, and the first period with average weekly pain equaling or exceeding baseline -1NRS point was calculated as the IVIg effect duration. As the study ended on day 148 (12 weeks after the second open infusion), later effects were not recorded.

A Data Monitoring Committee had access to the un-blinded data and monitored the progress of the trial in terms of safety and ethical issues. A blinded interim analysis was performed for safety after half of participants completed the trial. The stopping rule was based on detecting an effect in favor of placebo at the 5% significance level. The Data Monitoring Committee reviewed the results of the analysis and recommended continuation of the trial.
This trial is registered with ISRCTN, 42179756.

Role of the funding source

This project was funded by the Efficacy and Mechanism Evaluation Program, an Medical Research Council and National Institute for Health Research partnership, and the Pain Relief Foundation Liverpool. Biotest United Kingdom Ltd provided the active study medication at no cost. The funders had no role in the study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author and the Trial Statistician had full access to all the data in the study and the corresponding author was responsible for the final submission of the publication.

Results

Patients

Between 27th August 2013 to 28th October 2015, 121 patients from 7 sites were screened for eligibility. Of these, 111 were randomized to one of the two trial arms. 56 were randomized to Placebo and 55 were randomized to IVIg. Three

patients were randomized in error. Two had an average baseline pain score (over the first 7 days of screening) below 5 and one had a disease duration of less than 12 months. These 3 patients (all randomized to IVIg) are excluded from the primary analysis. Twelve patients withdrew from study medication before the end of the blinded phase (day 42). Two of these patients did not receive their first infusion and supplied no outcome pain data and three further patients received their first infusion but also did not supply any outcome pain data. The remaining 7 patients received their first infusion and all completed their pain diaries for at least 2 weeks. Six of these 12 patients indicated an adverse event as reason for their withdrawal (3 on Placebo and 3 on IVIg), one patient wished to pursue an alternative therapy, two patients stated problems with travel arrangements, and three patients gave no reason. The primary analysis was performed on 108 patients, with 56 in Placebo and 52 in IVIg (Figure 1 near here).

Figure 1.

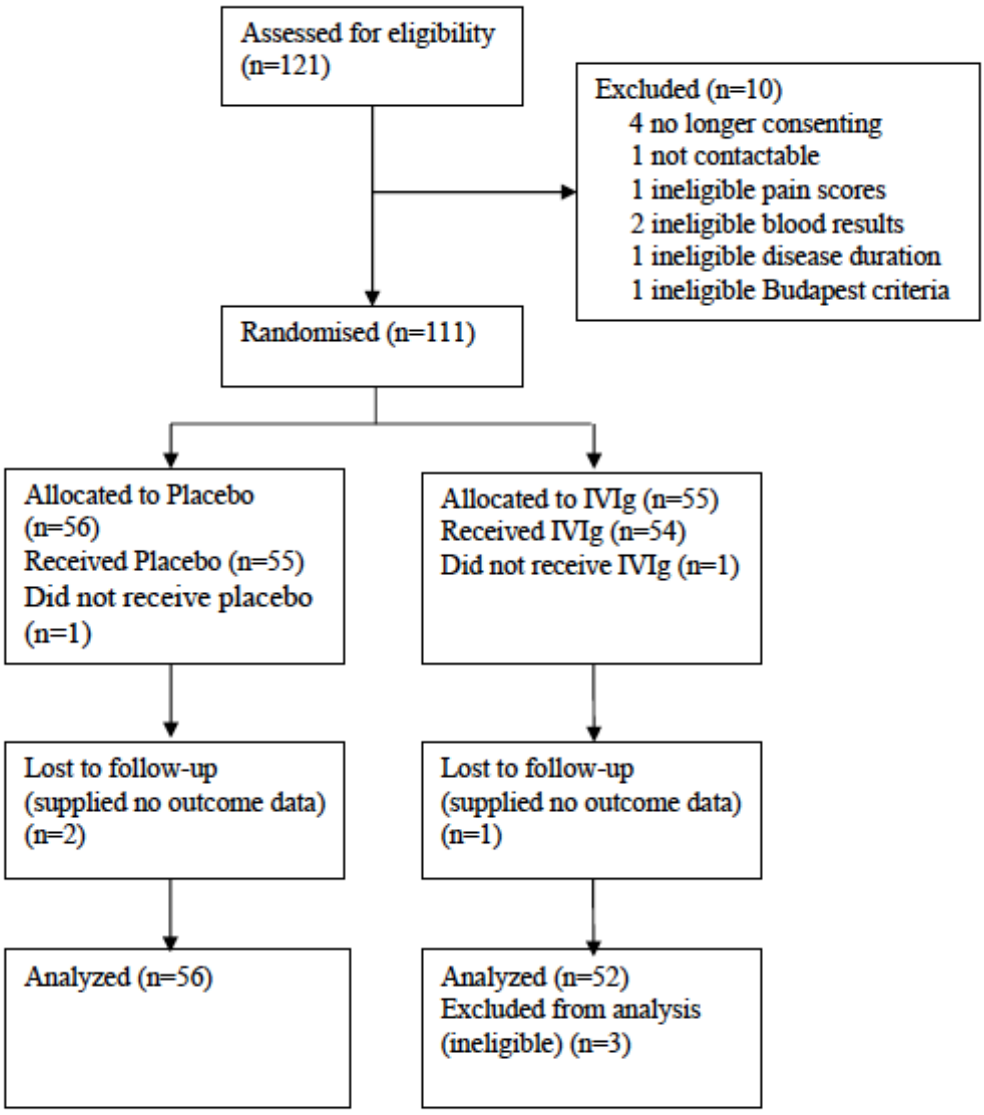

Figure 1. *Consort Flow diagram LIPS trial.* IVIg=intravenous immunoglobulin

Baseline characteristics for the 108 patients included into the primary (ITT) analysis are shown in Table 1. Balance was achieved for most parameters, although there was a slight gender imbalance (Table 1 near here). Apart from one case of stable Crohn's disease, participants had no severe, or multiple concomitant autoimmune disorders (not shown).

Table 1. *Patient baseline characteristics*

	Placebo (n=56)	IVIg (n=52)
Age, years		
Mean (SD)	41·0 (12·5)	43·7 (11·6)
Gender		
Male	14 (25%)	19 (37%)
Female	42 (75%)	33 (63%)
Ethnicity		
Asian	0 (0%)	2 (4%)
White	55 (98%)	50 (96%)
Other	1 (2%)	0 (0%)
Disease duration, years		
Mean (SD)	2·5 (1·2)	2·3 (1·2)
Median (Q1,Q3)	2.5 (1,4)	2 (1,3)
CRPS type		
I	49 (88%)	44 (85%)
II	6 (11%)	6 (12%)
Undecided	1 (2%)	2 (4%)
Limb involvement		
1 limb	43 (77%)	41 (79%)
2/3/4 limbs	10/0/3	8/2/1
Average Baseline Pain		
Mean (SD)	7·4 (1·1)	7·5 (1·0)
Median (Q1, Q3)	7.4 (6.7, 8.1)	7.6 (7, 8.3)
Quality of life		
EQ-5D-5L: Mean (SD)	0·34 (0·28)	0·33 (0·27)
Pain Interference		
Brief Pain Inventory: Mean (SD)	7·32 (1·72)	7·47 (1·63)
Limb Temperature		
Mean (SD) difference with non-affected side	- 0·75 (0.20) C	-0·90 (0.24) C
Percentage of patients with lower temperature in affected side	68%	70%

Table 1: *Baseline characteristics by trial arm for patients analyzed for the primary Intention to treat (ITT) analysis (n=108)*. SD=Standard Deviation. Values are either Mean (SD), Median (Q1=quartile 1, Q3) or Number (%). Type I/II CRPS is not/is associated with injury to a major nerve. Baseline data are from 108 patients, excepting limb temperature, which was measured only in patients who had a healthy contra-lateral limb, and who could tolerate the procedure (placebo n=47; IVIg n=46).

There was no indication that patients identified their treatments when assessed after the first infusion (Table 2), or after the second infusion (not shown); hence we were satisfied that blinding was successful. (Table 2 near here)

Table 2. *Success of blinding.*

	Trial Arm	
Guess	**Placebo**	**IVIg**
Prescribed IVIg	5 (9%)	5 (10%)
Don't know	44 (80%)	35 (69%)
Prescribed placebo	6 (11%)	11 (22%)
Total	**56**	**52**

Table 2: *Success of blinding at visit 2*, after the first infusion assessed by the 108 patients included into the primary analysis

Primary Outcome

103 patients provided at least 14 daily pain intensity scores for the primary outcome between days 6-42, and 5 supplied none (Appendix Table 1). The average pain scores over days 1-84 for each patient, by trial arm, are shown in Figure 2 for the 108 patients included in the primary ITT analysis (Figure 2 near here).

Figure 2

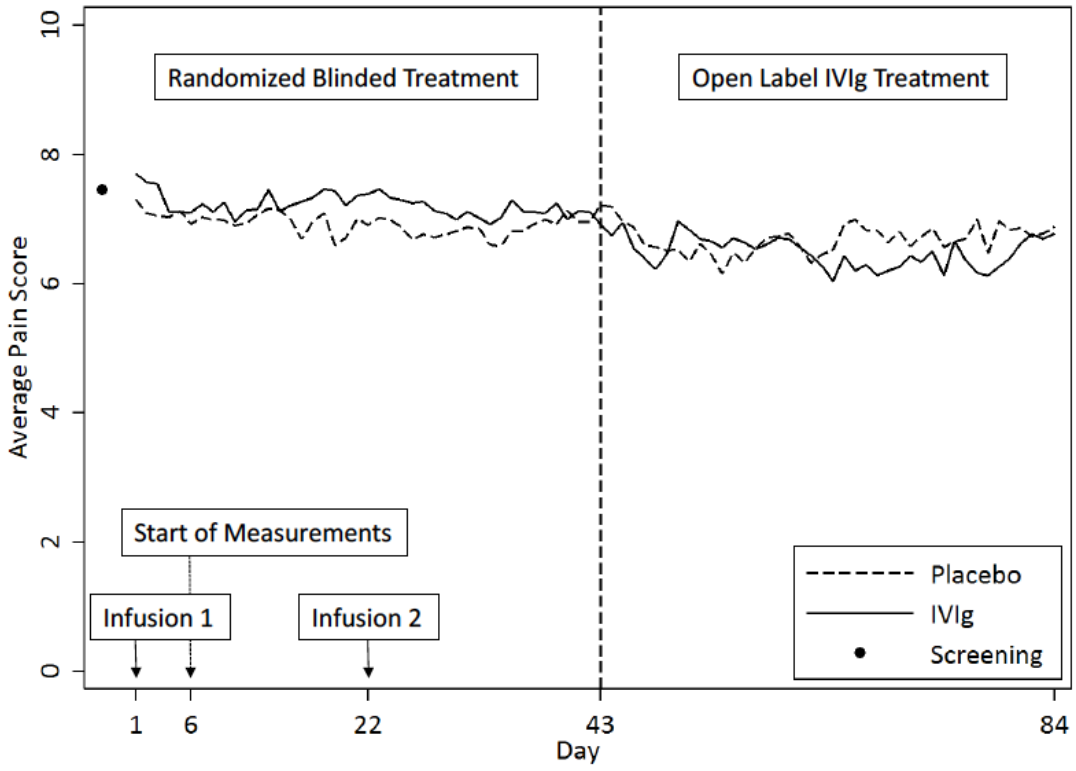

Figure 2. *Average pain for each day by trial arm (day 1 - 84).* Values on the Y-axis reflect average 24h pain intensity numeric rating scale scores (0=no pain, 10=pain as bad as you can imagine). The patient numbers for each time point are as follows: screening n=108; day 1 n=93; day 6 n=101; day 22 n=93; day 43 n=85; day 84 n=62. Note, screening started at most 21 days before randomization (randomization=day 0).

It is clear that average pain scores per patient were very similar for each treatment group. The mean of these (average) pain scores was 6·9 (SD 1·5) for Placebo and 7·2 (1·3) for IVIg and the adjusted difference in means was 0·27 (95% CI -0.25 to 0·80; p = 0·30). Therefore, there is no significant evidence of a treatment effect at the 5% level. In addition, the confidence interval excludes the clinically important difference of -1.2. Sixty-nine (67%) patients had lower pain scores following treatment. This was very similar in both arms: 35/53 (66%) for Placebo and 34/50 (68%) for IVIg. Four patients achieved 30% pain reduction, 3 in Placebo and 1 in IVIg. In addition to these four patients, just one patient, in Placebo achieved 50% pain reduction. The average pain scores during the primary outcome period (day 6 to day 42) were fairly constant (Figure 2).

The treatment effect changed little when the model was adjusted for average baseline pain and disease duration. Similarly, results were only minimally changed when we included the three patients who had been randomized in error. One patient in the placebo group recorded very low pain scores (mean pain = 0·9 from 37 measurements). Omitting this patient from the primary analysis reduces the overall treatment effect in favor of placebo by a third (0·17 (95% CI: -0·30 to 0·64, p=0·49).

There was no evidence of any subgroup effects based on disease duration (p=0·164), gender (P=0·76), allergy status (P=0·49), low baseline IgG (<10/>=10, p=0·19) or HADS sub-scores for anxiety (P = 0·37) and depression (P = 0·77). In addition, there was no statistical evidence for a difference in treatment effects between the 7 study sites (p=0·68), however we note that this study was not powered for these comparisons (Appendix Table 2). There was weak evidence that treatment differs by CRPS type (P=0·016) with a possible positive effect for CRPS II patients (n=14, three patients with 'undecided' CRPS type were omitted from this analysis).

Secondary Outcomes

At baseline, patients had a very low quality of life, and high pain interference, consistent with reports for patients with persistent CRPS (Table 1)(5). The mean quality of life at baseline (EQ-5D-5L) was around 0·33 in both groups. This increased slightly following treatment with means of 0.37 (SD 0.29) for Placebo and 0.41 (0·27) for IVIg. The adjusted difference in means was 0·03 (95% CI -0·08 to 0·15; p = 0·58). The number of patients with a meaningful improvement, of >=0·1 points was similar between groups (20/51 (39%) Placebo, 18/43

(42%) IVIg). At baseline, the mean interference subscale of the Brief Pain Inventory was around 7.3 in both groups. This decreased to 6·89 (SD 2·08) for placebo and 7·24 (1·54) for IVIg and the adjusted difference in means was 0·35 (95% CI -0·43 to 1·13; p = 0·38).

Exploratory Outcomes and open extension

One patient in the IVIg group stopped-, whereas three patients in the IVIg group, and one patient in the placebo group started an analgesic medication.
A summary of exploratory-, and open extension outcomes are given in the Appendix.

Adverse Events

Harms from the study medication in the parallel phase are summarize in Table 3. There were two serious adverse events in the blinded phase. One patient on placebo developed severe headaches and vomiting, and another patient in the IVIG group developed severe headaches. Both required hospitalization, but were discharged the next day and quickly recovered. Open phase events are detailed in the Appendix (Table 3 near here).

Table 3. *Harm reported during the blinded phase of the study**

Adverse Event	**IVIg (n = 52)**	**Placebo (n = 56)**
Death	-	-
Withdrawal from study medication due to adverse event	3 (6)	3 (5)
≥ 1 adverse event	39 (75)	40 (71)
Serious adverse event	1 (2)	2 (4)
- Headache	1 (2)	1 (2)
- Vomiting	-	1 (2)

* Values are numbers (percentages)

Conclusions

In this phase III randomized controlled trial, treatment with two, low doses (0·5g/kg/dose) of intravenous immunoglobulin, over 6 weeks had no significant effect on patients' pain intensities. In the active group, no patient reported substantial pain reduction contrasting results from previous smaller studies.

We had conducted this trial to obtain definite evidence for the low-dose IVIg treatment, based on preliminary data indicating efficacy. Immunoglobulin treatment did not reduce pain, nor improve any of the secondary or exploratory outcomes. We found no predictive marker for a better treatment response

amongst pre-specified parameters. The small pain reduction of 7·8% in the placebo group is consistent with recent meta-analysis data indicating that patients with persistent CRPS have a relatively stable natural course and only a small placebo effect in clinical trials (18).

English-language MEDLINE search about intravenous immunoglobulin treatment for CRPS returned 4 primary reports (two case reports, of which one is with high-dose treatment in acute CRPS (19, 20)), our case series (9), our prior randomized controlled trial (RCT) (8), and our report on maintenance therapy in two patients (21), overall n=25 cases). Each report indicated IVIg efficacy in CRPS. Additionally, other authors have highlighted that they have successfully been using IVIg in their patients (22, 23), without providing details. It is not known why the results in the current RCT differ so markedly from these prior studies. Small trials, particularly when associated with only few primary events, are subject to biases, including selection and exaggeration. The importance of responder analysis to identify predictive factors for a response is evident, however our results suggest that responders to low-dose IVIg will be rare.

Our findings add to negative evidence for the efficacy of anti-inflammatory treatments in persistent CRPS including lenalidomide, infliximab, intrathecal steroids, and oral steroids (24-27). Recent *in vivo* and *in vitro* studies have suggested a role for functionally active, non-inflammatory autoantibodies (28-30), indicating that patients might respond to immune therapies which either directly reduce autoantibody plasma levels, or target lymphocytes (23, 31-34).

Study *strengths* include its multicenter-nature, size for a rare disorder – the largest academic trial in persistent CRPS to date, recruitment over the pre-specified, relatively short time-period, successful blinding, and high patient adherence; the latter resulted in high data quality minimizing uncertainty (Appendix Table 1). The patient demographics are typical for this group and active and comparator groups are well balanced. The consistently negative primary, and pre-defined secondary endpoints provide clear, definite evidence that this intervention is not effective in this group.

Limitations include that our data are not applicable to the groups of patients with either >5 years, or <1 year disease duration, which had been excluded.
Our results do not extend to treatment with full-dose IVIg, e.g. 2g/kg/infusion. The use of albumin as control treatment might have confounded treatment effects because of its possible activity in immune-mediated disorders (35). We chose a very low albumin concentration (0.1%), and the overall placebo response in this trial was low. We infer that our results are not substantially confounded by the use of albumin placebo. Our study was not powered to detect any subgroup effects.

In *conclusion*, in this randomized controlled trial in 108 patients, once-repeated treatment with low-dose (0·5g/kg) intravenous immunoglobulin over 6 weeks did not reduce pain in patients with Complex Regional Pain Syndrome of between 1-5 years' duration. No patient experienced >50% pain relief on drug contrasting results from earlier studies. Alternative analgesic technologies are required to allow treatment of this often-devastating condition.

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Reproducible Research Statement

Study Protocol: freely available through open access publication (Goebel et al., Trials, 2014 Oct), including all substantial amendments to the protocol. There were no additional substantial amendments between publication and the end of the trial.

Computer Code: the computer code will be available on demand from the CI, Dr. Andreas Goebel, andreasgoebel@rocketmail.com

Analytic Dataset: the analytic dataset will be available on demand from the CI, Dr. Andreas Goebel, andreasgoebel@rocketmail.com

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