Intravenous regional guanethidine blockade in the treatment of post-traumatic complex regional pain syndrome type 1 (algodystrophy) of the hand

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A total of 57 patients, aged between 23 and 86 years, with complex regional pain syndrome (CRPS) type 1 nine weeks after an isolated closed fracture of the distal radius, was randomised to receive either serial intravenous regional blockade (IVRB) with 15 mg of guanethidine in 30 ml of 0.5% prilocaine or serial IVRB with 30 ml of normal saline at weekly intervals until the tenderness in their fingers had resolved or they had received a maximum of four IVRBs.

The analgesic efficacy was assessed at 24 hours, 48 hours and one week after each procedure by the dolorimetry ratio and verbal pain scores, and at intervals up to six months after the fracture.

There was no significant difference in the number of IVRBs administered or in finger tenderness, stiffness or grip strength between the two groups. The guanethidine group experienced more pain in the affected hand (p = 0.025) and at six months had more vasomotor instability (p < 0.0001) compared with the control group.

IVRB using guanethidine offers no significant analgesic advantage over a normal saline placebo in the treatment of early CRPS type 1 of the hand after fracture of the distal radius. It does not improve the outcome of this condition and may delay the resolution of vasomotor instability when compared with the placebo.

The term complex regional pain syndrome (CRPS) type 1 was promulgated by the International Association for the Study of Pain (IASP) in 1994 to establish uniform terminology and diagnostic criteria among research groups. CRPS type 1 is defined as a syndrome which usually develops after an inciting noxious event, and results in pain and tenderness which are disproportionate to the injury and not limited to the territory of a single peripheral nerve. Features of vasomotor instability occur and no other condition is present which could account for the degree of pain and dysfunction. CRPS type 1 is a preferable alternative term to reflex sympathetic dystrophy in the absence of evidence to support the role of reflex sympathetic activity in this condition. The new definition does not include the trophic changes or joint stiffness which contribute to the long-term morbidity. During the last two decades the term algodystrophy has been used in the orthopaedic and rheumatology literature to include all the features described above.

Abnormalities of sympathetic nervous function have been considered to be a central feature of the condition, a view based on both the clinical findings of CRPS type 1 and on the reported relief from pain after manipulation of the sympathetic nervous system which has taken a major place in treatment. Intravenous regional sympathetic blockade (IVRB) using guanethidine was first described by Hannington-Kiff. Guanethidine is an adrenergic neuromuscular blocking drug which acts on the peripheral nervous system to inhibit the presynaptic release and subsequent re-uptake of noradrenaline from post-ganglionic sympathetic nerve endings. It may also have some direct vasodilator action.

The role of guanethidine blockade in the treatment of CRPS type 1 or algodystrophy was investigated extensively before the IASP definition, yet there are few well-designed studies to support its continued use, since their conclusions are weakened by inadequate power, lack of control groups and a heterogeneous case mix with varying aetiology and stage of disease. In 1995, a systematic review of the use of IVRBs in the treatment of reflex sympathetic dystrophy found no evidence to support their use and emphasised the need for well-designed randomised controlled trials to evaluate this treatment. The Cochrane database lists no such studies.

Previous investigations have shown an incidence of CRPS type 1 after Colles’ fracture of between 19% and 28%. We have therefore tested the hypothesis that...
intravenous regional guanethidine blockade produces a measurable decrease in pain in CRPS type 1 of the hand after Colles’ fracture and alters the outcome.

**Patients and Methods**

Over a period of 21 months, all adult patients presenting to the Bristol Royal Infirmary with a closed unilateral Colles’ fracture, were examined after nine weeks for evidence of CRPS type 1. All patients gave informed consent and prior approval of the Ethics Committee was obtained. Exclusion criteria were: 1) surgical fixation of the fracture; 2) the presence of another injury of the upper limb; 3) inability to co-operate with the assessment; 4) pre-existing abnormality of the hand which would affect the measurements; 5) medication with known or possible antisympathetic effects; 6) contraindication to sympathetic blockade; and 7) inability to receive an IRVB within two weeks of the initial assessment.

CRPS type 1 was defined according to the IASP criteria. All patients were assessed for vasomotor instability with or without sudomotor involvement, pain and tenderness in the fingers and digital stiffness. These features were considered to be categorical variables (normal or abnormal). Using a saturated log linear model the association between these three features was analysed using backward elimination of variables. Vasomotor and sudomotor instability was determined using a verbal questionnaire and examination to identify alteration in hand swelling, colour, temperature and sweating. Each of these features was scored as 0 (absent) or 1 (present) to give a semiquantitative assessment of instability. A score of three or more was arbitrarily considered to be evidence of instability.

The pain threshold was assessed using a dolorimeter to give a ratio of finger tenderness on the affected/unaffected hand. The lower 95% confidence interval (CI) of the reference range for the dolorimetry ratio in an age-matched
control group was 0.85. The coefficient of variation for the measurement was 3.6%. Patients were asked about pain at rest and on exercise and these features were recorded as present or absent.

Stiffness was assessed by calculating the total range of flexion at three joints in all four fingers using a goniometer. The value for stiffness was obtained by subtracting one hand from the other. The upper 95% CI of the reference range in the age-matched control group was 62° with a coefficient of variation for the measurement of 16.8%. Grip strength was measured using a Jamar grip dynamometer and the value expressed as a ratio of the normal to the abnormal hand. The swelling ratio in the index finger was measured using an arthrocircameter at the proximal interphalangeal joint and that of the hand by a water displacement test. The reference ranges for all measurements were obtained from an age- and gender-matched population by the principal investigator (JL) before the study began.

A consecutive series of 377 adults was assessed for features of CRPS type 1 at a mean of 9.21 weeks (95% CI 9.06 to 9.35) after sustaining a Colles’ fracture. The association between vasomotor instability, dolorimetric finger tenderness and finger stiffness was significant (p = 0.013) and these measurements were used to define CRPS type 1 qualitatively and quantitatively. A total of 82 patients (21.8%) had algodystrophy. These patients had been immobilised in plaster casts for a mean 39 days (38 to 41) and 52% had been referred for physiotherapy.

Of the 82 patients identified, 57 were entered into the study (Fig. 1); 15 refused to participate, six could not be admitted for an IVRB within 14 days of their initial assessment and in four there were contraindications to IVRB. There were no significant differences between the groups as regards age, dolorimetry ratio, finger stiffness, vasomotor instability score, grip ratio and index finger or hand swelling (Table I).

Patients who had CRPS type 1 were randomly assigned by the toss of a coin to receive IVRB with either 15 mg of guanethidine monosulphate (Ismelin Ciba) in 30 ml of 0.5% prilocaine hydrochloride (Citanest, Astra) (n = 27) or 30 ml of normal saline (n = 30), respectively. Assignment was carried out by an independent clinician who took no further part in the study. The treatment was drawn up immediately before injection by an independent clinician in a separate theatre suite. Both injections were of equal volume and colourless. All IVRBs were administered by one investigator (JL).

Each block was injected in an anaesthetic suite with monitoring of the blood pressure and pulse and pulse oximetry. A padded double-cuff tourniquet was applied to the upper arm, which was elevated for two minutes before inflation of the proximal cuff to 250 mmHg and administration of the test solution. The total tourniquet time was 20 minutes (10 for the proximal cuff and 10 for the distal cuff).

Assessments were carried out before each block and at 24 hours, 48 hours and one week after. Further blocks were administered, up to a maximum of four, at weekly intervals until the dolorimetry ratio was ≥0.85.

According to the protocol 22 patients had one block, 20 had two, eight had three and seven had four. After breaking the code it was found that 53 guanethidine blocks and 61 placebos had been administered.

The patients started physiotherapy, with simple active and passive exercises only, within 48 hours of each block.

The power of the study was calculated with a significance level of 0.05, to detect a difference in the mean dolorimetry ratio of 0.15 with 26 patients in each group. This sample size had a power of 80% with α = 0.05 to detect a difference of at least 40% in the proportion of patients expected to have abnormal finger tenderness at 15, 20 and 30 weeks based on the studies of the natural history described by Bickerstaff.

### Statistical analysis

We used SPSS 7.0 for Windows (SPSS Inc, Chicago, Illinois). The means were compared using Student’s t-test or the Mann-Whitney U test. For categorical variables, 2x2 tables with Yates’ correction were used for comparison of proportions. If the results were significant (p < 0.05), comparisons between individual groups were determined using the chi-squared or Fisher’s exact test. Ranked data were analysed by Wilcoxon or McNemar tests. Kaplan-Meier life tables were constructed for the resolution of features of CRPS type 1. For comparison between treatment groups, we used log-rank analysis.

Data were analysed on an intention-to-treat basis and all patients who received a block were included.

### Results

#### Short-term

There was no significant difference between the two groups in terms of the number of IVRBs required (p = 0.68). Analysis of dolorimetry ratio and verbal pain scores showed no difference between the groups before receiving a block. There was a significant improvement in the mean dolorimetry ratio after the blocks in both groups, but there was no significant difference between the two groups up to one week (Fig. 2).
At 24 hours after the block there was a significant reduction in the proportion of patients complaining of pain at rest in both groups. This improvement was still evident in the normal saline group at one week, but not in the guanethidine group. Similarly, pain on exercise was significantly reduced in both groups at 24 hours, but by one week there was a significant difference between the two groups (p = 0.035), and only the normal saline group had significant improvement compared with their pre-block value.

Analysis of assessments at 24 hours, 48 hours and one week after IVRB showed a significant improvement in dolorimetry ratios, verbal pain scores, finger stiffness, grip strength and swelling in both groups compared with baseline values, but no significant therapeutic advantage was associated with the use of guanethidine compared with placebo (Table II).

After the first block 31 patients showed a therapeutic response which lasted for more than a week. At assessment one month after the first block, four patients in the normal saline group and three in the guanethidine group had relapsed. Another three in the guanethidine group had relapsed by two months. All these patients required further IVRBs. Further analysis of the first, second, third and fourth blocks suggested that those who responded after each block had a higher dolorimetry ratio (i.e., less tender fingers) than those who did not respond (Table II). Although the proportion of guanethidine patients responding to each block was greater than the saline group the numbers did not differ significantly. The dolorimetry ratios in responders and non-responders were similar for both groups before all the blocks.

**Long-term.** Analysis of the change in the mean dolorimetry ratio in the two groups revealed a similar response pattern in each group (Fig. 3). By 15 weeks, the mean dolorimetry ratio had returned to within the reference range, and there was no significant difference between the groups. There was a moderate improvement in both groups up to 30 weeks with a slightly lower mean dolorimetry ratio in the guanethidine group, although the values for both groups were within the normal reference range with a mean dolorimetry ratio of 0.99 for the normal saline group and 0.95 for the guanethidine group (p = 0.07). No significant difference was observed between groups in the proportion of patients complaining of pain at rest or on exercise. There was no difference in the improvement of finger stiffness or grip strength during the period of the study, but swelling of the index finger and hand was greater in the guanethidine group at 30 weeks (Fig. 4).

In the saline group, there was a probability of 74.3% that the dolorimetry ratio returned to within the reference range by 15 to 18 weeks compared with 63% in the guanethidine group. Formal comparison of survival curves revealed no significant difference (log-rank test p > 0.2) between the two groups up to 30 weeks from the time of fracture (Fig. 5).

Symptoms of vasomotor instability were significantly slower to resolve in the guanethidine group, which had higher mean vasomotor instability scores at 15, 20 and 30 weeks compared with the saline group. At 15 weeks, patients in the guanethidine group were significantly more likely to have persistent alteration in hand colour

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**Table II.** Analysis of the effects of IVRBs on the median (range) dolorimetry ratio in the guanethidine and normal saline groups. Responder or non-responder indicates that the dolorimetry ratio did or did not return to the normal range (>0.85) after the index block.

<table>
<thead>
<tr>
<th></th>
<th>1st IVRB</th>
<th>2nd IVRB</th>
<th>3rd IVRB</th>
<th>4th IVRB</th>
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<tr>
<td></td>
<td>Number</td>
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<td></td>
<td>of patients</td>
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</tr>
<tr>
<td>Guanethidine</td>
<td>Dolorimetry</td>
<td>Dolorimetry</td>
<td>Dolorimetry</td>
<td>Dolorimetry</td>
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<tr>
<td>Responders</td>
<td>0.75 (0.46 to 0.85)</td>
<td>0.79 (0.69 to 0.84)</td>
<td>0.78 (0.75 to 0.83)</td>
<td>0.68 (0.59 to 0.78)</td>
</tr>
<tr>
<td>Non-responders</td>
<td>0.70 (0.25 to 0.82)</td>
<td>0.73 (0.53 to 0.82)</td>
<td>0.66 (0.5 to 0.76)</td>
<td>0.16</td>
</tr>
<tr>
<td>p value</td>
<td>0.1</td>
<td>0.04</td>
<td>0.0</td>
<td>0.16</td>
</tr>
<tr>
<td>Normal saline</td>
<td>0.73 (0.37 to 0.85)</td>
<td>0.70 (0.69 to 0.84)</td>
<td>0.82 (0.76 to 0.84)</td>
<td>0.74 (0.68 to 0.84)</td>
</tr>
<tr>
<td>Responders</td>
<td>0.68 (0.38 to 0.83)</td>
<td>0.69 (0.53 to 0.83)</td>
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<tr>
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(p = 0.015) with 55.6% complaining that the hand was red, 7.4% blue and 18.5% red and blue at different times. There was no difference in the proportion of patients complaining of alteration of temperature, but the guanethidine group reported that the colour and temperature of their hands were more sensitive to changes in ambient temperature (p = 0.003). Both groups noticed a similar frequency of sweating of the affected hand. At 30 weeks there was no difference between the groups with regard to change in colour, sweating or sensitivity to change in environmental temperature, but there was a greater proportion of patients complaining of altered hand temperature in the guanethidine group (69%) compared with the saline group (14%) and this was significant (Fig. 6).

**Discussion**

The study was designed to assess the efficacy of regional sympathetic blockade compared with a placebo in the treatment of CRPS type 1 of the upper limb. Prospective screening of patients, nine weeks after sustaining a fracture of the distal radius, provided a well-matched population with early untreated symptoms. The incidence of CRPS type 1 was similar to that reported by previous studies which have used these methods of assessment, and a prospective association between vasomotor instability, finger tenderness and finger stiffness was demonstrated.²,¹⁹,²¹

Analysis of the short-term effects of IVRB with guanethidine and normal saline showed a significant improvement in tenderness of the fingers (Fig. 3) and swelling of the hand (Fig. 4) compared with pre-block values, but no significant difference between groups at any time. There was a significant difference between the groups at 30 weeks (p = 0.04).

![Graph showing the changes in tenderness of the fingers (dolorimetry ratio expressed as mean ± SEM) after IVRB with guanethidine and normal saline. There is a significant improvement compared with pre-block values, but no significant difference between groups at any time.](image)

**Fig. 3**

![Graph showing the changes in swelling of the hand, expressed as mean ± SEM after IVRB with guanethidine and normal saline. Both groups show a significant reduction in swelling from nine weeks. There is a significant difference between guanethidine and normal saline groups at 30 weeks (p = 0.04).](image)

**Fig. 4**

**Fig. 5**

Survival curve for resolution of abnormal finger tenderness in the guanethidine and normal saline groups. There is no significant difference between the two groups (log rank p > 0.2).

**Fig. 6**

Survival curves for resolution of vasomotor instability in the guanethidine and normal saline groups. There is a significant difference between the two groups (log rank p < 0.0001).
GUANETHIDINE BLOCKADE IN THE TREATMENT OF POST-TRAUMATIC COMPLEX REGIONAL PAIN SYNDROME OF THE HAND

thidine showed no significant analgesic advantage compared with a normal saline placebo block at up to one week after the block. Both groups showed a significant therapeutic response to treatment. The dose of guanethidine used in our study was 15 mg, which is that described for blocks in the upper limb by Hannington-Kiff in his original series. Higher doses may be given, but have an unacceptable incidence of side-effects. There has been considerable debate regarding the nature and extent of the response to placebo in sympathetically maintained pain syndromes; it may be as high as 40%. Ischaemia of peripheral nerves during the administration of a Biers block may also have an analgesic effect. In the absence of an untreated control group, however, we can make no comment regarding the placebo effect of the treatments.

At long-term follow-up, both groups showed continuing improvement with no difference in terms of pain, finger tenderness, finger stiffness or grip strength six months after fracture. The symptoms of vasomotor instability were significantly prolonged in the group receiving guanethidine, and this was accompanied by a relative increase in swelling of the hand and index finger compared with the normal saline group. Little attention has been paid to the effect of sympathetic blockade on symptomatic vasomotor instability in CRPS type 1. Microcirculatory disturbances evolve from stage 1 with an increase in total skin blood flow, which may reflect a decrease in sympathetic efferent activity, to a decrease in stages 2 and 3 which may reflect increased sensitivity to circulating catecholamines. In normal volunteers, guanethidine sympathectomy lasts for three to four days. In patients with CRPS type 1, blood flow in the hand remains elevated at one week after IVRB with guanethidine. The persistent vasomotor instability and swelling seen in our study suggest a more prolonged effect of guanethidine, perhaps because of increased peripheral sensitivity to α blockade in CRPS type 1, or to a ‘staircase’ effect with repeated blocks.

There are several published randomised clinical trials investigating the effect of IVRB in reflex sympathetic dystrophy. Jadad et al in a systematic review, identified only two studies which compared guanethidine with a control intravenous block which had been published in peer-reviewed literature. Both had serious methodological flaws including poorly-defined diagnostic criteria and incomplete cross-over. The second part of the study by Jadad et al was a randomised, double-blind cross-over trial which had to be halted prematurely because of the high incidence of side-effects with IVRBs containing 30 mg of guanethidine. Of 16 patients entered into this investigation, only nine reached the double-blind phase. The authors indicated that a minimum of ten patients with α = 0.05 and β = 0.2 would be required to detect a difference of 40% in the primary outcome measure. Only eight patients completed the cross-over part of the study and thus it had inadequate power.

Most authors agree that early identification and treatment of CRPS type 1 improve the outcome, regardless of the method of treatment. Studies of the natural history of CRPS type 1 suggest that spontaneous resolution is the usual outcome and failure to account for this in uncontrolled studies may exaggerate the efficacy of treatment. This tendency to resolution may explain the apparent therapeutic response in patients with mild disease in both control and treatment groups. There are no data in the literature which identify those patients with CRPS type 1 who will benefit most from treatment. At the end of our study only six of the 57 patients continued to have an abnormally low dolorimetry ratio and four of these had initial dolorimetry ratios which placed them among the 25% most severely affected. As many as 37% of the study group had objective evidence of persistent finger stiffness at six months, a feature which is related to the CRPS type 1 syndrome, although not expressly included in the new definition. It could be argued that future studies should identify and enrol only those patients who are the most severely affected, and that both functional impairment and pain scores should be assessed.

There is no evidence to support the use of intravenous guanethidine blockade in CRPS type 1 in the literature. Our randomised, controlled study indicates that there is no benefit in using such blocks in early CRPS type 1 of the hand and also suggests that its use may delay the resolution of some features of the condition.

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References


