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# Comparison of prednisolone with piroxicam in complex regional pain syndrome following stroke: a randomized controlled trial

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# **Summary**

**Background:** Complex regional pain syndrome (CRPS) following stroke aggravates morbidity. CRPS is categorized as CRPSI when no clear nerve injury is defined, and CRPSII when associated with clear nerve injury.

**Aim:** To compare the effect of prednisolone with that of piroxicam in patients with CRPSI following stroke.

Design: Randomized controlled trial.

**Methods:** Patients with CRPSI fulfilling the inclusion criteria (n = 60) underwent a detailed neurological examination, cranial CT scan, radiograph of chest and shoulder joint, blood counts and serum chemistry. Severity of stroke was assessed by the Canadian Neurological Scale (CNS), CRPS by scoring sensory, autonomic and motor symptoms, and activity of daily living by Barthel index (BI) score. Patients were randomly assigned prednisolone 40 mg or piroxicam

20 mg daily, and outcome was assessed at 1 month on the basis of CRPS and BI score.

**Results:** Mean patient age was 56 years and 20 were female. Baseline clinical and radiological parameters were comparable between the two groups. In the prednisolone group, 83.3% patients showed significant improvement, compared to 16.7% in the piroxicam group. The mean change in CRPS score in prednisolone group was 6.47 (95%CI 4.37–7.36), whereas in piroxicam group it was only 0.47. The mean change in BI score was 7.9 (95%CI 0.82–5.98) in the prednisolone group, and 4.5 in the piroxicam group.

**Discussion:** In this patient group, prednisolone resulted in significant improvement in the symptoms and signs of CRPSI following stroke, compared to piroxicam. Both drugs produced an improvement in the BI score.

# Introduction

Complex regional pain syndrome (CRPS) is a relatively recent terminology coined for the syndrome formerly known as reflex sympathetic dystrophy, causalgia, Sudeck's atrophy, shoulder hand syndrome, neuroalgodystrophy and reflex neuromuscular dystrophy. It manifests classically persistent burning pain in a limb, with a region of intense allodynia, hyperalgesia, extreme guarding of the affected limb, reduced range of motion, and objective evidence of local autonomic dysfunction and trophic changes.<sup>1</sup> Currently CRPS is categorized as CRPSI when no clear nerve injury is defined, and CRPSII when associated with clear nerve injury.<sup>2</sup> Stroke is an important cause of CRPSI, and between 1.5% and 61% of patients following stroke have been reported to develop CRPSI.<sup>3–8</sup> CORE

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The pathophysiology of CRPS is complex, and often occurs after a noxious event.<sup>4</sup> During the acute stroke when the patient is comatose, positioning and passive physiotherapy of the patient may result in trauma to the upper limb, including shoulder dislocation. Presence of sensory loss, hemi-neglect and visual inattention may result in improper positioning, rendering the limb vulnerable to frequent trauma, which in turn predisposes to CRPSI. Occurrence of CRPSI is the major limiting factor of good functional outcome, and if insufficient attention is paid, may result in frozen shoulder, with frequent deformity of hand and fingers. The management of CRPSI is controversial: various pharmacological and non-pharmacological treatments have been tried.<sup>9–12</sup> Only two class I trials have evaluated the role of oral corticosteroids in CRPS; both were conducted in smaller patient populations with heterogeneous aetiology and compared the effect of a corticosteroid with placebo.<sup>4,13</sup>

We report the results of a randomized controlled trial evaluating the effect of oral prednisolone over piroxicam in patients with CRPSI following stroke. We did not have a placebo arm, as we included patients with moderately severe CRPS with a score of 8 or more, in whom not offering any treatment may not be ethical. In CRPS, swelling and pain (spontaneous and during movement) are dominant features and histopathology of autopsy specimens reveals inflammatory changes.<sup>4</sup> A role for soluble TNF $\alpha$  has recently been reported in the pathogenesis of CRPS.<sup>14</sup> Piroxicam is a potent analgesic and anti-inflammatory drug, and is efficacious in several inflammatory conditions;<sup>15</sup> it was therefore chosen as an alternate treatment to prednisolone.

# **Methods**

Of 106 patients with CRPSI following stroke managed by us from 2002 to 2004, 46 were excluded, because of diabetes mellitus (n=20), uncontrolled hypertension (n=21), ischaemic heart disease (n=6), heart failure (n=2), previous history of peptic ulcer (n=5) and CRPS score <8 (n=10). We therefore studied 60 patients with CRPSI following stroke (Figure 1). All patients gave

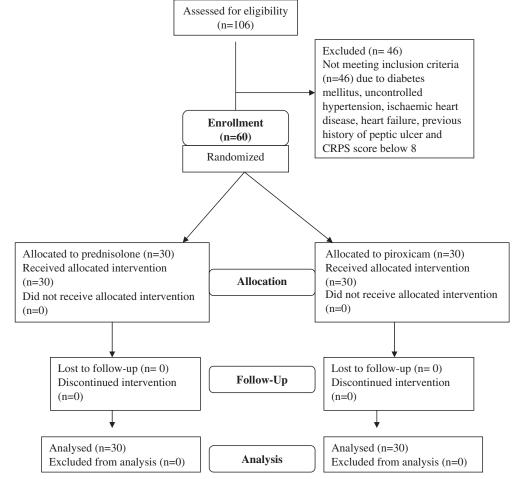


Figure 1. CONSORT flowchart.

informed consent, and the study was approved by the local ethics committee.

Patients underwent a detailed clinical evaluation. During the acute stage of stroke, consciousness was assessed by Glasgow coma scale (GCS) and severity of stroke by Canadian Neurological Scale (CNS). The time period taken for the development of CRPSI after stroke and onset of CRPSI to recruitment for the trial was also noted. Activity of daily living was assessed by the Barthel index (BI), which has a 0-20 point range, 0 being the lowest and 20 the highest.<sup>16</sup> The diagnosis of CRPSI was based on the presence of pain and tenderness during humeral abduction, flexion and extension; pain and dorsal swelling over carpal bones; moderate fusiform oedema of metacarpophalangeal and interphalangeal joints; change in temperature, colour and dryness; and loss of dorsal line and change in nails. The severity of CRPSI was scored on a 0-14 scale (Table 1).<sup>4</sup> Patients with a CRPS score of  $\geq 8$  were included in the trial. Complete haemogram, serum chemistry, electrocardiogram, and radiograph of chest and shoulder joint were done. Cranial CT scan was done within 24 h of stroke using a spiral CT scanner; 8 mm axial cuts were obtained parallel to the orbitomeatal line. Strokes were classified into ischaemic and haemorrhagic, and these were further categorized according to location and size.<sup>17,18</sup>

 Table 1
 Variables used for scoring complex regional pain syndrome I

Variable	Score
Sensory: pain, hyperalgesia	
No	0
Mild	1
Moderate	2
Distinct	3
Severe	4
Spontaneous	5
Autonomic: distal oedema	
No	0
Mild	1
Distinct	2
Severe	3
Motoric: painless passive range of motion	
Humeral abduction	
>120°	0
<120°	1
$< 90^{\circ}$	2
$<45^{\circ}$	3
Humeral external rotation	
$>30^{\circ}$	0
$< 30^{\circ}$	1
$<20^{\circ}$	2
<10°	3

#### **Exclusion criteria**

Patients with diabetes mellitus, uncontrolled hypertension (BP 180/110 mmHg), hemiplegia due to other than stroke, history of earlier shoulder dysfunction and deformity, rheumatoid disease, brachial plexus injury, gastrointestinal bleeding, septicaemia and CRPS score <8 were excluded.

#### Sample size calculation

Considering the improvement of therapy if CRPS score reduced by  $\ge 2$ , 27 patients were required in each group for a 95% power of test, using the 5% level of significance.

#### Randomization and outcome measures

Patients with CRPSI fulfilling the inclusion criteria were randomized into study and control groups using random table numbers. The study group received oral prednisolone 40 mg/day for 14 days, followed by 10 mg/week taper. The control group received oral piroxicam 20 mg/day. The drugs were provided to the patients in identical packets. Randomization was done by one investigator (JK) and evaluation by another (AB). Both the groups continued physiotherapy. The effect of treatment was assessed at the end of 1 month. The primary end-point was improvement in CRPS score, with improvement considered significant if the score was reduced by 2 or more. The secondary end-point was improvement in Barthel Index (BI), to obviate bias. In patients who improved completely, drugs were withdrawn; the remaining patients were prescribed prednisolone and/or analgesics.

#### Statistical analysis

Statistical analysis used SPSS software. The various clinical and radiological parameters were compared by non-parametric tests ( $\chi^2$ , Fisher's exact and Mann-Whitney U tests). To evaluate the effect of therapy, the total CRPS score and its components within the group were compared by Wilcoxon signed ranked test. The effect of therapy between the prednisolone and piroxicam groups was compared by Mann-Whitney U test. The risk factor was evaluated using descriptive statistics (cross table).

### Results

Of 60 patients fulfilling the inclusion criteria, 20 were female. Mean age was 56 years, range 40–70. CRPSI symptoms developed after a median 28

(7–100) days post stroke. During the acute stage of stroke, 59 patients had altered sensorium and four had deep coma (GCS score  $\leq 6$ ). Mean CNS score was 2.9; 35 patients scored  $\leq 3$  and 25 >3. Hemiplegia was severe (Grades 0-I) in 19 patients, moderate (Grades II-III) in four, and mild (Grade IV) in 20. Hemisensory loss to pin prick and joint position was present in eight, and cortical sensory loss in nine. CT scan revealed infarctions in 25 and intracerebral haematoma in 35. Infarctions were located in the middle cerebral arterial territory in 17, anterior cerebral in six and posterior cerebral in two patients. Haematomas were putaminal in 18, thalamic in nine, lobar in five and infratentorial in three patients. The size of infarcts was small in nine, medium in 15 and large in one patient. Haematomas were large in eight, medium in 20 and small in seven. Mean BI score was 2.06 (0-20) and CRPS score 10.3 (8–14). Baseline clinical, radiological and CRPS parameters were not significantly different between the prednisolone and piroxicam groups (Table 2).

**Table 2** Comparison of various clinical and radiologicalvariables in patients with CRPSI following stroke betweenprednisolone and piroxicam groups

Variable	Prednisolone	Piroxicam		
Gender				
Male	20	20		
Female	10	10		
Stroke				
Infarct	13	12		
Haematoma	17	18		
Haematoma size				
Small	2	6		
Medium	10	10		
Large	5	2		
Infarct size				
Small	5	4		
Medium	8	7		
Large	0	1		
Primary sensory loss				
Present	2	6		
Absent	28	24		
Cortical sensory loss				
Present	5	4		
Absent	25	26		
BI score mean $\pm$ SD	$1.97 \pm 4.94$	$2.57 \pm 4.32$		
CNS score mean $\pm$ SD	$3.07 \pm 1.77$	$2.53 \pm 1.44$		
Side-effects				
None	25	28		
Present	5	2		
CRPS score mean $\pm$ SD	$10.73\pm1.95$	$9.83 \pm 2.34$		

BI, Barthel index; CNS, Canadian neurological scale; CRPS, complex regional pain syndrome.

### **Effect of therapy**

Following therapy, improvement in CRPS was observed in 25 (83.3%) patients in the prednisolone group, but 5 (16.7%) in the piroxicam group. In the prednisolone group, mean CRPS score reduced from  $10.73 \pm 1.95$  to  $4.27 \pm 2.83$  at the end of the 1 month (Z = -4.47; p < 0.0001). In the piroxicam group, however, CRPS score reduced from  $9.83 \pm 2.34$  to  $9.37 \pm 2.89$ , which is not significant (Z = -1.64, p = 0.24).

The response to prednisolone was observed in all the components of the CRPS scale; i.e. sensory (Z=-4.33, p < 0.0001), autonomic (Z=-4.26, p < 0.0001) and motor functions (humeral abduction Z=-3.96, p < 0.0001; humeral external rotation Z=-4.34, p < 0.0001). In the piroxicam group, a significant response was seen in autonomic (Z=-2.50, p=0.01) but not in sensory (Z=-1.31, p=0.19) or motor (humeral abduction Z=-0.82, p=0.41; humeral external rotation Z=0.00, p= 1.00) functions. Barthel index score, however, improved in both prednisolone (Z=-4.48, p < 0.0001) and piroxicam (Z=-4.21, p < 0.0001) groups (Table 3).

Comparing the response to therapy between prednisolone and piroxicam groups at 1 month revealed significant improvement in the study group, both in total CRPS score (Z = -5.09), p < 0.0001) and in its various components (sensory Z = -5.43, p < 0.0001; autonomic Z = -4.32, p < 0.0001; humeral abduction Z = -2.72, p <0.006; humeral external rotation Z = -3.56, p < 0.0001). BI score was also higher, although not significantly so, in the prednisolone vs. the piroxicam group (Z = -1.88, p = 0.06) (Table 4). Considering the criterion of 2 or more points improvement in CRPS score, 25 (83.3%) patients showed improvement in the prednisolone and 5 (16.7%) patients in the piroxicam group, giving an odds ratio for prednisolone therapy of 25 (95%CI 6.43-97.2).

Severity of stroke (p=1.00) and BI score (p=0.25) at baseline were not related to response to therapy. Of the 35 patients with CNS score  $\leq$  3.5, 17 improved, and of the 25 patients with CNS score >3.5, 12 improved. Similarly, 11/17 patients with BI score >0 improved and 19/43 with BI score of 0. None of the patients deteriorated in the prednisolone group but four of the piroxicam group had a deterioration in CRPS score (mean 3.3, range 1–8). Mild side-effects in the form of gastritis were seen in four patients in the prednisolone and one in the piroxicam group, and one patient in each group developed upper respiratory tract infection. In none of these patients, however, did drugs need to be

discontinued. The occurrence of side-effects was not significantly different between the two groups (p=0.39).

### Discussion

In this randomized controlled trial, improvement in the symptoms and signs of CRPSI following stroke was observed in 83.3% patients in the prednisolone group, but in only 16.7% of the piroxicam group. Benefits from corticosteroid in complex regional pain syndrome have previously been reported in two class I trials.<sup>4</sup> In one study, 23 patients were randomly allocated to oral prednisolone 10 mg three times daily or placebo, and medication was continued until clinical remission or up to 12 weeks. All the patients receiving prednisolone therapy improved, but only 20% of those on placebo.<sup>13</sup> In another study on CRPSI following stroke, methylprednisolone 32 mg/day in four divided doses was given for 2 weeks, followed by a tapered dose over 2 weeks, showing improvement in symptoms in 91% of patients.<sup>4</sup>

We used a fixed protocol of single-dose oral prednisolone in a homogenous and relatively larger group of patients, and compared it with piroxicam, a non-steroidal anti-inflammatory drug. The chief limitation of our study is the lack of a placebo control group, making it difficult to

 Table 3
 Primary and secondary outcome of patients with complex regional pain syndrome (CRPS) following stroke receiving prednisolone and piroxicam

Parameters	ameters Initial (mean $\pm$ SD)		Z
Prednisolone group			
Total CRPS score	$10.73 \pm 1.95$	$4.27 \pm 2.83$	-4.47**
Sensory	$3.97 \pm 0.85$	$1.13 \pm 1.31$	-4.33**
Autonomic	$2.17 \pm 0.70$	$0.77 \pm 0.73$	-4.26**
Humeral abduction $2.30 \pm 0.70$		$1.27 \pm 0.87$	-3.96**
Humeral ext rotation	$2.37 \pm 0.72$	$1.13 \pm 0.94$	-4.34**
BI score $1.97 \pm 4.94$		$9.87 \pm 4.43$	-4.48**
Piroxicam group			
Total CRPS score	$9.83 \pm 2.34$	$9.37 \pm 2.89$	-1.16
Sensory	$4.00 \pm 0.87$	$3.67 \pm 1.35$	-1.31
Autonomic	$2.00 \pm 0.53$	$1.70 \pm 0.65$	$-2.50^{*}$
Humeral abduction	$2.03 \pm 0.85$	$1.97 \pm 0.93$	-0.82
Humeral ext rotation	$2.07 \pm 0.87$	$2.07 \pm 0.91$	0.00
BI score	$2.57 \pm 4.32$	$7.07 \pm 5.56$	-4.21**

p < 0.01; p < 0.001; BI, Barthel index; ext, external.

Table 4	Comparison of complex regional pain syndrome (CRPS) and Barthel Index (BI) score between prednisolone and
piroxicar	groups at 1 month

	Treatment	п	Mean rank	Sum of ranks	Z	р
CRPS total score	Prednisolone	30	19.07	572.00	-5.09	< 0.0001
	Piroxicam	30	41.93	1258.00		
Components of CRPS score						
Sensory	Prednisolone	30	18.50	555.00	-5.43	< 0.0001
	Piroxicam	30	42.50	1275.00		
Autonomic	Prednisolone	30	21.35	640.50	-4.32	< 0.0001
	Piroxicam	30	39.65	1189.50		
Humeral abduction	Prednisolone	30	24.63	739.00	-2.72	0.006
	Piroxicam	30	36.37	1091.00		
Humeral ext rotation	Prednisolone	30	22.97	689.00	-3.56	< 0.0001
	Piroxicam	30	38.03	1141.00		
BI score	Prednisolone	30	34.70	1041.00	-1.88	0.06
	Piroxicam	30	26.30	789.00		

ext, external. p values are by Mann–Whitney U test.

assess fully the significance of the improvement with either prednisolone or piroxicam. A placebo arm was considered unethical, as we have included relatively severe CRPS patients with a score of 8 or more.

Autopsy study of CRPS reveals evidences of perivenous micro-bleeding in the periarticular soft tissues in the affected shoulder joints, which is more prominent in the suprahumeral area. Perivascular lymphocytic infiltration in the synovium and granulation tissues are also seen.<sup>4</sup> Significant reduction in distal swelling following piroxicam may be due to its anti-inflammatory mechanism, as it inhibits arachidonic acid, resulting in reduced pro-inflammatory substances. The pain and motor function symptoms, however, are not relieved by piroxicam, suggesting that these symptoms in CRPS may be due to some other additional mechanisms.

Suprahumeral structures are highly innervated with autonomic and sensory nerve fibres.<sup>19</sup> These nerve endings may be injured during upward gliding of the head of the humerus during abduction.<sup>20,21</sup> In stroke patients, this injury is likely to be due to severe hemiplegia, spasticity, sensory deficit and physiotherapy.<sup>22-25</sup> Damage to peripheral nerves and tissues releases various chemical mediators, and the resulting continuous stimulation of A-delta and polymodal C fibres produces initially localized sharp, followed by continuous, pain.<sup>26</sup> The nociceptor barrage may alter the dorsal horn cell processing mechanisms, allowing for the expression of the A beta mechanoallodynia and triggering aberrant noradrenergic sprouting within the dorsal root ganglia.<sup>27</sup> Corticosteroids not only inhibit arachidonic acid metabolism resulting in reduced production of leukotrines but also inhibit substance P, CGRP, and regulates neuropeptides in sensory neurons of dorsal root ganglia.<sup>13,25</sup> The lack of benefit from piroxicam to the sensory and motor components suggest a dominant neural mechanism in the pathophysiology of CRPSI. In a stroke patient, pain in the affected side may also be due to deafferentation of spinothalamic projection neurons, which is characterized by hyperpathia and burning or deep boring pain, and usually follows a small thalamic stroke. This is unlikely in our patients, as pain was predominantly restricted around the shoulder joint, with limitation of movement due to pain and associated autonomic dysfunction. Moreover we have followed a stringent diagnostic definition of CRPS.<sup>1,2</sup>

In our study, none of the patients developed uncontrolled hypertension or diabetes mellitus, and all complied with the treatment, which may be due to a relatively small single morning dose for shorter duration, and stringent exclusion criteria. Gastrointestinal upsets and respiratory infections were comparable between the two groups, and none had to discontinue therapy due to side-effects. In an earlier study on CRPS, following oral methyl prednisolone therapy for similar duration, minor side-effects were reported, including transient increase in blood sugar in 15, sleeping problems in 7, acne in 5 and slight increase in blood pressure in two out of 34 patients.<sup>4</sup>

Bias was unlikely in our study, as randomization and evaluation were done by different individuals. Both the groups were given identical packets of drug and advised to take one after breakfast. Although the size and shape of the tablets were different, as the patients were only given one modality of treatment, this factor is unlikely to influence our results. Several other drugs have been tried in CRPS, but the results were no closer to corticosteroid.<sup>28</sup>

The change in BI scores was also higher in prednisolone group than in the piroxicam group. This may be due to the contribution of shoulder joint functions in performing various activities of daily living. None of our patient had fixed deformities of fingers and shoulder joint that limited joint function.

In conclusion, a short course of oral prednisolone significantly reduces the symptoms and signs of CRPSI following stroke compared to piroxicam, and both drugs improve the activity of daily living as assessed by BI score.

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