Complex regional pain syndrome related movement disorders : studies on pathophysiology and therapy.

Munts, A.G.

Chapter 9

Efficacy and safety of a single intrathecal methylprednisolone bolus in chronic complex regional pain syndrome

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Abstract

Activated immune cells in the spinal cord may play an important role in the development and maintenance of neuropathic pain, such as occurs in response to peripheral inflammation or tissue injury. Immune activation may therefore serve as a therapeutic target for immune modulating drugs like corticosteroids. This double-blind randomised placebo-controlled parallel-group trial aimed to investigate the efficacy and safety of a single intrathecal administration of 60 mg methylprednisolone (ITM) in chronic patients with complex regional pain syndrome (CRPS). The primary outcome measure was change in pain (pain intensity numeric rating scale; range 0-10) after 6 weeks. With 21 subjects per group the study had a 90% power to detect a clinically relevant difference (≥2 points). After 21 patients (10 on ITM) were included, the trial was stopped prematurely after the interim analysis had shown that ITM had no effect on pain (difference in mean pain intensity numeric rating scale at 6 weeks 0.3, 95% CI -0.7 to 1.3) or any other outcome measure. We did not find any difference in treatment-emergent adverse events between the ITM and placebo group. We conclude that a single bolus administration of ITM is not efficacious in chronic CRPS patients, which may indicate that spinal immune activation does not play an important role in this phase of the syndrome.

Introduction

Complex regional pain syndrome type 1 (CRPS) is usually preceded by tissue injury and characterized by pain, oedema, skin discoloration, altered temperature, hyperhidrosis, and movement disorders.[1,2] The initial symptoms of CRPS have been attributed to aberrant inflammation in which both C and Aδ sensory nerve fibers and the immune system of the skin contribute.[3-5] This peripheral inflammation may lead to profound changes in spinal processing resulting in allodynia, hyperalgesia, and the chronification of pain (central sensitisation).[6,7] In turn this process may corrupt sensorimotor network function causing motor dysfunction.[8,9]

The mechanisms underlying central sensitisation in CRPS are still largely unknown. Activation of spinal microglia has been implicated in the development and maintenance of neuropathic pain states.[5,10,11] In this process, a range of immune mediators is released, among which prostaglandin E_2 (PGE_2) plays a crucial role.[12] Cyclooxygenase-2 (COX-2), induced by spinal interleukin-1β (IL-1β), is the major limiting factor in the production or release of PGE_2.[13]

Glucocorticoids have powerful anti-inflammatory effects throughout the whole body with COX-2 repression as one of the mechanisms of action.[14] In CRPS, glucocorticoids may be beneficial early in the course of the syndrome,[15] which most likely is explained by the suppression of peripheral inflammation. Because of the poor spinal bioavailability,[16] oral corticosteroids may lack efficacy with respect to the chronic features of CRPS caused by central sensitisation. A possible method to circumvent this problem is intrathecal administration. In chronic postherpetic neuralgia, another neuropathic pain syndrome, intrathecal methylprednisolone (ITM) was shown to be effective.[17]

The aim of this study was therefore to evaluate the efficacy and safety of a single administration of ITM in chronic patients with CRPS.

Methods

Subjects were male or female outpatients, with a clinical diagnosis of CRPS type 1 who were referred to the Movement Disorders outpatients clinic of the Department of Neurology. In all cases patients were referred by neurologists and anesthesiologists throughout the Netherlands. Patients had to fulfill the diagnostic criteria of the consensus report of CRPS 1,[18] had to be 18-75 years old, have experienced symptoms for more than 6 months and less than 6 years, and report spontaneous pain of at least five on a pain

intensity numeric rating scale (PI-NRS; on which 0 represents no pain, and 10 the worst imaginable pain). Patients were excluded if they had experienced satisfactory relief of symptoms with conventional treatments, had contraindications for steroid therapy or lumbar puncture, were pregnant or breast-feeding women or women of childbearing potential not using effective contraception, had clinically significant psychiatric illness, were suspected of poor compliance, or were involved in legal proceedings claiming compensation for their CRPS.

A review of the literature showed that methylprednisolone acetate (Depo-Medrol) was administrated intrathecally in patients in more than 5,900 occasions (see the discussions in The Medical Journal of Australia,[19-27] Archives of Neurology[28-35] and The Clinical Journal of Pain[36-38]). Serious adverse events were reported in 31 of these occasions and involved cerebral hemorrhage,[39] meningitis,[39-47] conus syndrome,[48] progressive weakness,[49] reversible bladder dysfunction,[39] paresthesia,[22] adrenal insufficiency[50] and hypercortisonism[39]. Most of these side effects were reported in patients with multiple sclerosis who received repeated administrations.
Patients in our study were orally and written informed about these facts. Patient consent was obtained according to the Declaration of Helsinki and the study was approved by the medical ethics committee of the Leiden University Medical Centre.

Study design
We used a double-blind randomised placebo-controlled parallel-group design. Randomization was done with a computer-generated list and took place at the Department of Pharmacy. Treatment allocation remained concealed from patients and investigators (including those who performed the assessments) throughout the study. Lumbar puncture (20 or 22 gauge needle) was performed by physicians experienced in performing lumbar punctures (A.M. or A.P.). Subjects received 60 mg methylprednisolone acetate (Depo-Medrol 40 mg/ml) or 1.5 ml sodium chloride 0.9% (placebo). Study medication was distributed in opaque syringes, which made unblinding impossible. Clinical assessments were scheduled at baseline (1 week before administration of study treatment), at 6 weeks and 12 weeks follow-up.
An independent data monitoring committee was instituted to monitor safety and to perform an interim analysis on efficacy halfway during the study. At the interim analysis, this committee assessed the probability that efficacy of ITM could be demonstrated at the end of the study. The study is registered with the Netherlands Trial Register, number NTR61.

Outcome measures

Pain was evaluated with the PI-NRS,[51] and the McGill pain questionnaire[52] and were computed as the means of the scores at 09:00, 13:00, 17:00 and 21:00 h at one day. The effect of ITM on movement disorders was studied with the Burke-Fahn-Marsden dystonia rating scale (BFM),[53] unified myoclonus rating scale (UMRS; sections 2-4)[54] and tremor research group rating scale (TRGRS; items 1-8)[55]. Change of CRPS signs and symptoms was rated on a global impression scale: both the investigator and the patient assessed the change from baseline at the end of the study period on a scale ranging from -3 (very much worse) to +3 (very much improved).[51,56]

The integrity of the blinding procedure was investigated by asking both the patient and investigator to indicate which treatment they thought had been administered.

Safety assessments included history taking and physical examination at each follow-up visit.

Statistical analysis

The primary outcome measure was the change in pain on the PI-NRS at six weeks. It was estimated that 21 patients in each treatment group would provide a 90% power to detect a mean difference in the mean PI-NRS of ≥2 points between the two groups, which was considered clinically relevant,[51] with a type I error rate of 5%. Based on previous studies,[51,57] an SD of 2 was assumed. Independent-samples *t*-tests were used to compare the PI-NRS change between the two groups after 1, 6 and 12 weeks. Mann-Whitney *U* tests were used to compare the patient's and investigator's global impression scores between both groups. One-way between groups analyses of covariance (ANCOVA) with the baseline scores of the various outcome measures entered as covariates, were used to compare the efficacy of ITM to placebo while adjusting for baseline differences between the two groups. For the ANCOVA, preliminary checks were conducted to ensure that there was no violation of the assumptions of normality, linearity, homogeneity of variances, homogeneity of regression slopes, and reliable measurement of the covariate. The relation between the patient's and investigator's global impression score was investigated using Spearman rank correlation coefficient. Significance was assumed at the 0.05 level. For all tests, the SPSS software package version 14.0 (SPSS Inc., Chicago, IL) was used.

Results

Participant characteristics

Twenty-eight patients were screened for enrollment, seven of whom were ineligible: two did not meet the inclusion criteria, and five refused to participate (in whom clinical characteristics were not different from the remaining patients; Figure 9.1). The other 21 patients (16 females, 5 males) were randomised; their mean (SD) age was 46 (11) years and their mean (SD) duration of CRPS 4.5 (2.2) years. One randomised patient (who had received placebo) withdrew from the study because she developed severe post-dural puncture headache as well as a major depressive disorder. All male patients (*n*=5) received placebo. Twelve patients had two or more affected extremities, of which eight received ITM. Other baseline characteristics were similarly distributed between treatment groups (Table 9.1).

Efficacy

The study was ended prematurely because the interim analysis showed that the chance of reaching efficacy on the pre-established primary outcome measure was <1%.

There was no significant difference in PI-NRS change score between the ITM and the placebo group after 6 weeks (t = 0.65, df = 18, P=0.53; difference in means 0.3, 95% CI -0.7-1.3). PI-NRS change scores in the ITM group were in the range between -0.75 and +1.75, thus indicating that none of the patients met the predefined criteria of clinically significant improvement. Additionally, adjusting for baseline PI-NRS scores did not yield a significant difference (F (1,17) = 0.33, P=0.57, partial eta squared = 0.02) (Table 9.2). There was a strong relation between the PI-NRS at baseline and 6 weeks (partial eta squared value = 0.73). Contrary to the placebo group, myoclonus deteriorated in the ITM group, leading to a significant difference between the groups (F (1,17) = 6.17, P=0.02, partial eta squared = 0.27) (Table 9.2). There were no significant differences between ITM and placebo treatment in any of the remaining outcome measures. In the ITM group, two patients reported improvement (global impression score +1), and three reported worsening (-3, -2, and -1), whereas the other 5 remained unchanged. The investigator's global impression score showed improvement in one patient in the ITM group (+2) and worsening in two (-3, and -1), whereas the other seven remained unchanged. In the placebo group, one patient reported improvement (+2), and six reported worsening (-3 in one patient, -2 in three, and -1 in two), the investigator's global impression score showed improvement in one patient (+2), and worsening in three (-2 in one, and -1 in two). There

was a strong positive correlation between patient's and investigator's global impression scores (Spearman rho = 0.75, *P*<0.0005).

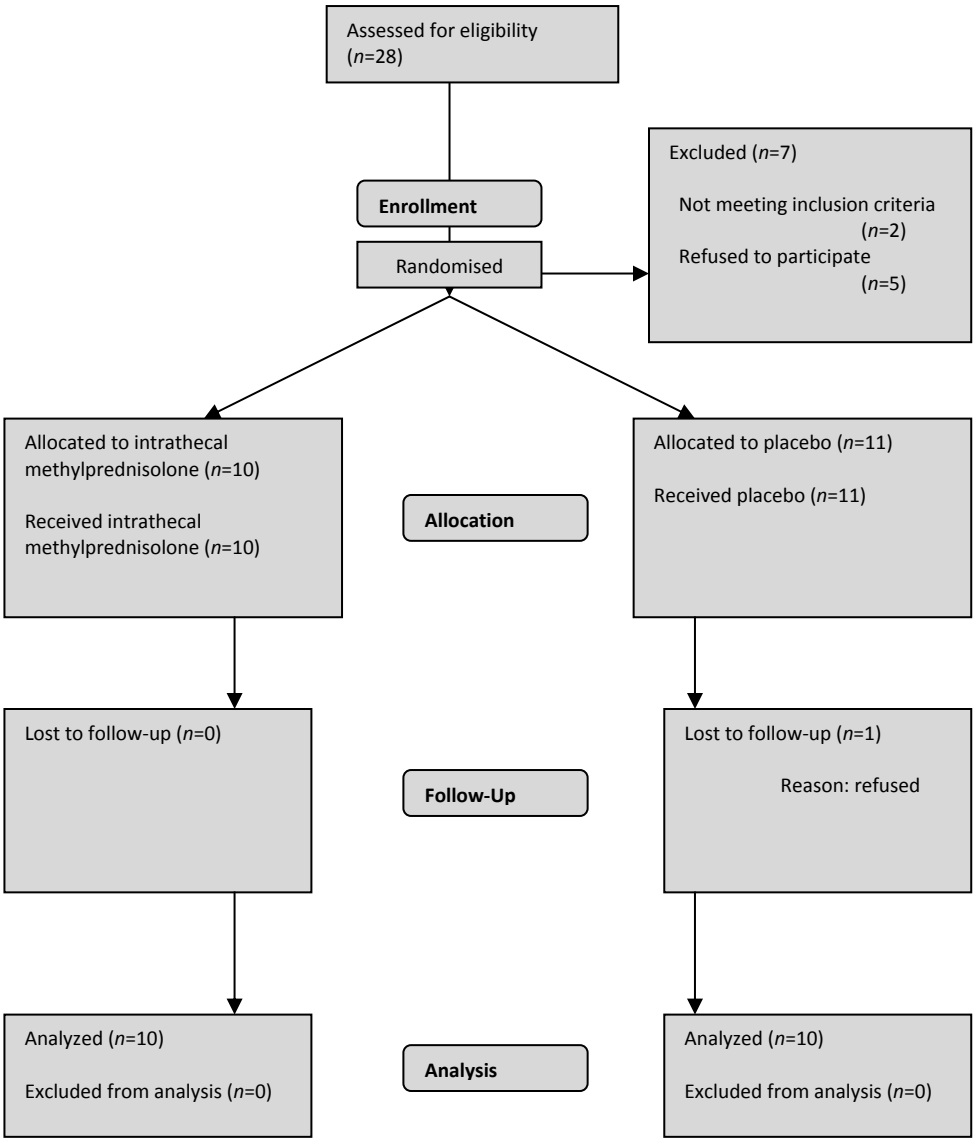

Figure 9.1. Patient disposition.

Table 9.1. Baseline characteristics of the 21 patients

Characteristic	Methylprednisolone (*n*=10)	Placebo (*n*=11)
Gender (F/M)	10/0	6/5
Age (yr; mean, SD)	45 (7)	46 (15)
Duration of CRPS (yr, mean, SD)	5 (2)	4 (2)
Preceding trauma, *n*		
Contusion	5	5
Fracture	1	2
Surgery	0	4
Other	4	0
Affected extremity		
Right/left arm	6/7	5/7
Right/left leg	7/8	5/4
Mean PI-NRS (SD)	6.9 (2.1)	7.3 (1.7)
McGill Pain Questionnaire (SD)		
NWC	12.2 (6.3)	11.5 (6.0)
PRI	24.2 (17.7)	25.5 (18.4)
Autonomic abnormalities, *n*	9	10
Oedema	9	7
Skin discoloration	8	7
Altered temperature	9	10
Hyperhidrosis	7	7
Sensory abnormalities, neurological examination, *n*	9	11
Tactile hypesthesia or hypalgesia	5	7
Tactile hyperesthesia, hyperalgesia or allodynia	9	7
Movement disorders, *n*	10	11
Dystonia	9	9
Myoclonus	5	6
Tremor	5	5

CRPS = complex regional pain syndrome; NWC = number of words chosen; PI-NRS = pain intensity numeric rating scale; PRI = pain rating index.

Data at 1 and 12 weeks follow-up showed no significant differences compared to baseline (data not presented). Both patient's and investigator's guesses of which treatment was administered, were correct in 52%.

Table 9.2. Summary of outcome measures at six weeks

Outcome measures means, (SD)	Range scale[a]	Methylprednisolone		Placebo		*P* value[b]
		Baseline	Follow up	Baseline	Follow up	
PI-NRS (SD)	0-10	6.9 (2.1)	6.9 (2.0)	7.3 (1.7)	6.8 (1.9)	0.57
McGill pain questionnaire (SD)						
NWC	0-20	12.2 (6.3)	11.9 (5.7)	11.5 (6.0)	9.7 (6.1)	0.35
PRI	0-63	24.2 (17.7)	22.3 (17.2)	25.5 (18.4)	19.5 (18.4)	0.53
BFM (SD)	0-120	15.7 (17.5)	14.6 (16.5)	7.3 (7.6)	9.3 (12.4)	0.28
UMRS (SD)	0-305	9.3 (17.3)	15.5 (21.0)	2.7 (3.6)	2.3 (3.5)	0.02
TRGRS, items 1-8 (SD)	0-76	2.9 (4.2)	2.5 (3.4)	1.4 (2.1)	1.7 (2.1)	0.89
PGI	-3-+3	-0.4		-0.9		0.42[c]
CGI	-3-+3	-0.3		-0.2		0.83[c]

BFM = Burke-Fahn-Marsden dystonia rating scale; CGI = clinician's global impression; NWC = number of words chosen; PGI = patient's global impression; PI-NRS = pain intensity numeric rating scale; PRI = pain rating index; TRGRS = tremor research group rating scale; UMRS = unified myoclonus rating scale.

[a]Best score is underlined.

[b]Analysis of covariance (with adjustment for baseline value).

[c]Independent-samples *t*-test.

Table 9.3. Treatment-emergent adverse events

Adverse event	Methylprednisolone (*n*=10)	Placebo (*n*=11)
Post-dural puncture headache	5	3
Tension-type headache	-	1
Backache	5	4
Major depressive disorder	-	1
Constipation	1	-
Diarrhea	-	1
Flushing	1	-
Oedema	-	2
Vasovagal syncope	-	1
Decubitus	-	1
Abnormal skin odor	1	-
CRPS exacerbation[a]	-	1
Total	**13**	**15**

CRPS = complex regional pain syndrome.

[a]In this patient, worsening of CRPS-related pain occurred.

Safety

Serious AEs did not occur. Non-serious AEs occurred in 16 patients: 13 events in 8 patients who received ITM and 15 events in 8 patients who received placebo (Table 9.3). Post-dural puncture headache occurred in eight patients (38%), with durations ranging from 2 days to the complete study period of 84 days (median 9 days, persistent in three patients). Three epidural blood patches were administered in two patients, though, without effect. Backache occurred in nine patients (43%), the duration of which ranged from 2 days to the whole study period (median 14 days, persistent in four patients).

Discussion

Despite the extensive evidence for a role of the immune system in chronic pain disorders,[5,10,12,13] and the favourable findings of ITM in postherpetic neuralgia,[17] we did not find a positive effect of ITM in chronic CRPS patients. Moreover, none of the patients met the predefined criteria of clinically significant improvement. There may be several explanations for this lack of efficacy. Firstly, the role of the immune system in pain in CRPS may be different from other chronic pain disorders. The evidence suggesting increased levels of inflammatory mediators in CSF of chronic CRPS patients is inconsistent.[58,59] Secondly, the lack of effect of ITM in chronic CRPS may indicate that it is much too late to expect effects on glia cell activation mechanisms since these occur early in the process of chronification of pain. Patients in Kotani *et al.*'s study[17] had a mean (SD) duration of postherpetic neuralgia of 3 (2) years. Thirdly, one administration of ITM may have been insufficient since Kotani *et al.*[17] applied four intrathecal administrations. However, since after a single intrathecal administration of methylprednisolone acetate, CSF levels of the drug remain measurable for at least 2 weeks, some improvement of symptoms can be expected.[60] In view of the risks associated with repeated ITM administrations (see above), a study with repeated intrathecal administrations would only be appropriate if some improvement had occurred after a single administration. Finally, it is possible that the efficacy of ITM in postherpetic neuralgia is overestimated. Until now, replication of the results from Kotani *et al.*[17] have not been reported.

We did not find any difference in treatment-emergent AEs between the ITM and placebo group, which is in line with the earlier study on ITM[17]. Post-dural puncture headache developed in 38% of patients (*n*=8), and no relation with the administered treatment was found. Additionally, post-dural puncture headache extended beyond the follow-up period of 12 weeks in 14% (*n*=3), which is unusual as compared to published findings in other

diseases.[61] Indeed, we used fairly wide-bore needles (20 or 22 Gauge) which is common at neurology departments, at least in The Netherlands. Although the use of small-bore needles may have led to lower rates of post-dural puncture headache, recent observations suggest that other mechanisms besides intracranial hypotension may contribute to the development of post-dural puncture headache in CRPS.[62]

We cannot rule out that patient selection may have influenced the findings. This partly results from the fact that this study was performed at a neurology department, where the majority of the randomised patients had movement disorders. However, all patients had typical features of CRPS including prominent chronic pain. Since there are no indications for a different pain pathophysiology in CRPS patients with or without movement disorders, there is no clear reason to assume that patient selection negatively influenced our findings. Because all men in this study received placebo, the efficacy of ITM in male patients remains unknown, although there are no arguments to assume gender specificity. Furthermore, since the mean duration of symptoms in our patients was five years, we cannot exclude that ITM may have been efficacious in an earlier phase of the condition. The meaning of the significant deterioration of myoclonus in the ITM group is uncertain.
In conclusion, a single bolus administration of ITM is not efficacious in chronic CRPS patients, which may indicate that spinal immune activation does not play an important role in this phase of the syndrome.

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Appendix

The data monitoring committee consisted of Prof.dr. A. Dahan (Department of Anesthesiology, Leiden University Medical Centre), Prof.dr. A.F. Cohen (Centre for Human Drug Research, Leiden) and Prof.dr. R. Brand (Department of Medical Statistics and Bioinformatics, Leiden University Medical Centre).

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