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ORIGINAL RESEARCH

The analgesic effect of intravenous methylprednisolone on acute neuropathic pain with allodynia due to central cord syndrome: a retrospective study

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Background: Central cord syndrome (CCS) may be associated with severe neuropathic pain that often resists to conventional pain therapy regimens and affects the patients' quality of life (QoL) seriously. Current treatments for CCS-associated neuropathic pain have limited evidence of efficacy. This retrospective study was performed to present the effects of early treatment with methylprednisolone (MP) on acute neuropathic pain relief and the QoL in CCS patients.

Patients and methods: Data were collected from the medical records of CCS patients who suffered from acute neuropathic pain with allodynia. All the patients received intravenous MP treatment for up to 1 week. Patients were evaluated with standard measures of efficacy: neuropathic pain intensity, the area of allodynia, and the QoL at baseline, daily treatment, and at 1 and 3 months after the end of MP treatment.

Results: Thirty-four eligible patients were enrolled in our study. By the end of MP treatment, the proportion of patients who gained total or major (visual analog scale [VAS] score decreased by 50% or more) allodynia relief from the treatment was 91.18%, and a decrease in spontaneous pain was also observed. Moreover, this study showed MP could significantly improve the QoL of patients based on McGill Pain Questionnaire Short Form and EuroQol Five Dimensions Questionnaire. Four patients (11.76%) during MP treatment experienced mild or moderate side effects. None of the patients manifested CCS-associated neuropathic pain recurrence and MP-associated side effects at follow-up.

Conclusion: The current results suggested that MP offered an effective therapeutic alternative for relieving CCS-associated acute neuropathic pain with allodynia. Given the encouraging results of this study, it would be worthwhile to confirm these results in randomized placebo-controlled clinical trials.

Keywords: spinal cord injury, spontaneous pain, visual analog scale

Introduction

Central cord syndrome (CCS) is the most commonly encountered form of incomplete cervical spinal cord injury (SCI)[1,2] and may be associated with severe neuropathic pain.[2–4] Neuropathic pain is characterized by spontaneous pain, allodynia (pain elicited by a stimulus that normally does not cause pain), and hyperalgesia (an exaggerated response to painful stimuli).[5,6] In addition, CCS-associated neuropathic pain often resists to conventional pain therapy regimens, and more importantly, the possibilities of neuropathic pain relief in such patients are usually low.[7,8] These features not only

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impair patients' mood, quality of life (QoL), and daily activities seriously but also generate higher health care costs.[9,10] However, the management of CCS-associated neuropathic pain usually proves very challenging with unsatisfactory results despite varied traditional and alternative treatments being tried.[11–14]

Previous clinical studies are mostly related to investigating the treatment for chronic neuropathic pain from SCI;[15–18] however, few studies explore the treatment for acute neuropathic pain.[19] In fact, acute neuropathic pain is an important pathophysiological state.[20,21] Once neuropathic pain appears, acute neuropathic pain often does not resolve on its own and resists to conventional analgesia.[19,22,23] Several studies reported that early effective treatment during acute phase of neuropathic pain can prevent neuroplasticity or the physical remodeling of neuronal cytoarchitecture in the central nervous system that often leads to chronic neuropathic pain.[20,22] Therefore, early treatment for acute neuropathic pain may be more preferable, as chronic neuropathic pain is very difficult to treat.[24]

Takeda et al demonstrated that continuous systemic or intrathecal administration of methylprednisolone (MP) inhibited spinal glial activation and relieved neuropathic pain in the spinal nerve ligation model of rats.[25] Moreover, intrathecal MP showed significant effectiveness in postherpetic neuralgia in a clinical study.[26] Although the exact mechanism underlying MP-induced analgesia for neuropathic pain is not well understood yet,[27] their results were consistent with the results observed in this study. Given the absence of other effective pharmacological treatments for CCS-associated neuropathic pain, any medication providing benefit in terms of neuropathic pain relief and QoL improvement in CCS patients has to be evaluated. Therefore, we performed this retrospective study to present the effects of early treatment with MP on acute neuropathic pain relief in CCS patients who suffered from acute neuropathic pain with allodynia.

Patients and methods

Patients

This study was approved by the Medical Ethics Committee of Tianjin Medical University General Hospital and conducted in accordance with the ethical standards of the Declaration of Helsinki. After obtaining approval from the institutional review board and written informed consent from each patient, medical records of CCS patients who suffered severe acute neuropathic pain with allodynia and received MP treatment from July 2016 to November 2017 were retrospectively examined. At our institute, the medical records for CCS patients suffering from acute neuropathic pain with allodynia were documented, and all patients received a 3-month follow-up period after the end point of MP treatment.

The inclusion criteria for this study were patients presented with CCS (diagnosed by appropriate clinical examination and spinal CT scan and MRI[2]); patients who suffered from severe acute neuropathic pain with allodynia or acute neuropathic pain intensity visual analog scale (VAS) score ≥6 caused by CCS;[15] and patients who received intravenous MP treatment for the CCS-associated acute neuropathic pain.

The exclusion criteria were patients with malignant tumor or with a history of malignant tumor; patients who were previously diagnosed with psychiatric diseases or had a history of chronic pain before onset of CCS; patients with mild to moderate CCS-associated acute neuropathic pain (VAS <6); and patients without available follow-up data after MP treatment.

Treatments

Before treatment, the patients were asked to fill out two QoL questionnaires (see below), and the following baseline measurements were measured: 1) neuropathic pain (spontaneous pain and allodynia) VAS scores; 2) the area of allodynia; 3) temperature; 4) heart rate; 5) blood pressure; 6) electrocardiograph; and 7) blood glucose. After the baseline measurements, we first treated acute neuropathic pain for 2 days with conventional treatments, such as parecoxib and flurbiprofen axetil, which are non-steroidal anti-inflammatory drugs commonly prescribed for patients with neuropathic pain.[28,29] However, none of the patients responded to conventional treatments with satisfactory results in this study (Table 1). Then, all the patients were started on MP (Pfizer Inc., New York, NY, USA) treatment with the following dosing schedule: patients received an intravenous MP infusion of 80 mg once per day for up to 1 week. The therapeutic regimen would be stopped if severe side effects occurred, such as nausea, severe hypertension, obvious infection, femoral head necrosis, psychosis, and oxygen saturation of 75% or less. On each day of the MP treatment, and then at 1 month and 3 months after the end of MP treatment, the following tests were performed: 1) neuropathic pain (spontaneous pain and allodynia) VAS scores; 2) the area of allodynia; 3) QoL questionnaires; 4) temperature; 5) heart rate; 6) blood pressure; 7) electrocardiograph; 8) blood glucose; and 9) side effects.

Assessments

Spontaneous pain

Because of neuropathic pain patients mostly suffer from spontaneous pain,[30] we firstly assessed spontaneous pain intensity using a 10 cm VAS. This consists of a 10 cm line

Table 1 Summary of the results of acute neuropathic pain VAS scores and allodynic areas after the conventional treatments

Group	Baseline	After conventional treatments	*P*-value
Parecoxib (N=17)			
Pain intensity (VAS 0–10)			
Spontaneous pain	7.25±0.68	7.22±0.73	0.79
Allodynia	8.23±0.52	8.19±0.59	0.72
Allodynic area, cm^2	2726.28±664.74	2714.65±649.76	0.53
Flurbiprofen axetil (N=17)			
Pain intensity (VAS 0–10)			
Spontaneous pain	7.41±0.70	7.46±0.52	0.75
Allodynia	8.22±0.69	8.23±0.50	0.90
Allodynic area, cm^2	2856.17±596.09	2871.71±530.33	0.73

Notes: Compared with the baseline, there were no significant effects on acute neuropathic pain VAS scores and allodynic areas after the conventional treatments (all $P>0.05$). Data are expressed as mean ± SD.
Abbreviation: VAS, visual analog scale.

with "no pain" written at one end and the "worst imaginable pain" written at the other end. The patient was asked to place a mark along the line that corresponds with their pain. The distance from the no pain end to the location of the mark gives a measurement of the pain.[31,32] Two ratings of baseline pain intensity were recorded with a 15-minute interval. And then, the patients were divided into those gaining total relief (100% decrease in VAS score), major relief (a decrease of at least 50% in VAS score), and poor relief or worse pain (VAS score decreased by less than 50% or increased).[33]

Allodynia

All of the patients in this study suffered from acute neuropathic pain with a prominent allodynia. To our knowledge, three types of mechanical allodynia are usually described: dynamic mechanical allodynia evoked by light touch; punctate allodynia evoked by punctate skin stimulation with a pin or monofilament (400 mN); and static allodynia provoked by pressure to skin or deep tissue.[6] However, dynamic mechanical allodynia to a brush or cotton swab is the outcome most often assessed.[6] In order to reduce the suffering of patients, we only selected to assess the dynamic mechanical allodynia. The dynamic mechanical allodynia was assessed by stroking the most painfully sensitive area of the skin three times gently with a standardized brush (Senselab Brush-05; Somedic, Horby, Sweden) at ≥5 second intervals, and all strokes were of the same length, minimum 2 cm. The intensity of allodynia within the area of maximal pain was marked on a VAS score (as the highest score of three consecutive VAS scores).[34]

Mapping of the allodynic area

The clinical assessment of allodynia should include mapping of the area of allodynia.[6] The edge of the region of dynamic mechanical allodynia was evaluated with a standardized brush gently stroked on the skin. These stimuli were started away from outside the allodynia area where no pain sensation was experienced and repeated tangentially to the area of pain at a progressively closer radius until the subject reports pain. That site was marked on the skin with a felt tip pen.[35] This process produced a plot of the area of allodynia, and the surface area was calculated using a vector algorithm.[36]

Questionnaires

Two questionnaires were used to evaluate the QoL of our patients and took ~20 minutes to complete. These questionnaires included: McGill Pain Questionnaire Short Form (MPQSF)[37,38] and EuroQol Five Dimensions Questionnaire (EQ-5D).[15]

The main component of the MPQSF consists of 15 descriptors (11 sensory, 4 affective) which are rated on an intensity scale as 0= none, 1= mild, 2= moderate, or 3= severe. From the MPQSF, the total, sensory, and affective scores were derived, along with the VAS and the present pain intensity index.

The EQ-5D consists of two sections. The first section (EQ-5D health status description) measures health status in terms of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Patients indicate for each dimension whether they experience no, some, or serious health problems. Then each health status description is converted into a single available score using the time trade-off elicitation technique during interviews with non-institutionalized adults from the general UK population. The second section (EQ-5D VAS) indicates the perception by the patient of his overall health on a 100 mm VAS (zero corresponds to the imaginable health state and 100 corresponds to the best imaginable health state).

Side effects

Side effects were collected using open-ended questions during and after MP treatment and by presenting the patients a list of possible side effects after infusion. The possible side effects include infection, femoral head necrosis, hyperglycemia, psychosis, headache, dizziness, blurred vision, arrhythmia, hypertension, nausea and edema.[39,40]

Data analysis

The statistical calculation was based on data collected by our group in CCS patients suffering from acute neuropathic pain with a prominent allodynia. All results are expressed as mean ± SD. A pain reduction of 50% or more in VAS score compared with baseline was considered a clinically relevant effect during MP treatment.[15,41,42] Pain (spontaneous pain and allodynia) VAS scores, allodynic areas, and the data collected from the QoL questionnaires were analyzed by a paired Student's *t*-test through the correction method of Bonferroni. Analyses were performed using SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA) and *P*-values <0.05 were considered to be statistically significant.

Results

Patients

Thirty-four eligible patients were enrolled in our retrospective study. All the patients received MP treatment for 1 week. The general characteristics of these patients are shown in Table 2. Patients had an average age of 59.74 years (range 50–71) and were predominantly men (58.82%). Patients were likely to have been injured in a motor vehicle collision (55.88%) as by fall (26.47%). In this study, each patient suffered from acute neuropathic pain with a prominent allodynia, and also with spontaneous pain simultaneously. The CCS-associated acute neuropathic pain affected bilateral upper limbs in 26 patients (bilateral C5–T2: 12 patients, bilateral C6–T2: 8 patients, and bilateral C5–T1: 6 patients) and bilateral forearms in 8 patients (bilateral C6–T1: 8 patients).

Table 2 Patient demographics and baseline characteristics

Characteristics	Study population
Number	34
Age (years), mean (range)	59.74 (50–71)
Gender, M/F	20/14
Cause of injury, n (%)	
Vehicular	19 (55.88)
Fall	9 (26.47)
Other	6 (17.65)
Localization of allodynia, n (%)	
C5–T2, bilateral	12 (35.29)
C6–T2, bilateral	8 (23.53)
C5–T1, bilateral	6 (17.65)
C6–T1, bilateral	8 (23.53)

Abbreviations: M, male; F, female; C, cervical vertebrae; T, thoracic vertebrae.

Effects on spontaneous pain

The time course of the mean spontaneous pain scores is shown in Figure 1A and 1B respectively. The mean spontaneous pain intensity VAS scores ± SD before and after 1 week of MP treatment changed from 7.33±0.69 to 0.93±1.32. A statistically significant decrease in mean pain score at end point was observed for MP treatment ($P<0.001$), and the effects were maintained during the subsequent follow-up period, all $P<0.001$ compared to the VAS scores at the baseline.

The proportion of patients who gained total or major (VAS score decreased by 50% or more) spontaneous pain relief from the treatment was 91.18% at the end of treatment. Eighteen patients were totally relieved by MP at the end of treatment (Figure 2), and no patient was aggravated during the MP treatment. At the 1 month follow-up point, a total of 10 patients (29.41%) still suffered from CCS-associated spontaneous pain, including 2 patients (5.88%) presenting with mild spontaneous pain (VAS =3, VAS =3.5, respectively). At the 3-month follow-up point, all the patients achieved excellent pain relief (VAS ≤2).[43]

Effects on dynamic mechanical allodynia and allodynic areas

All patients enrolled in this study showed severe dynamic mechanical allodynia. The mean allodynia scores at baseline, end point of MP treatment, and subsequent follow-up period are displayed in Figure 1B. After the treatment, the mean dynamic allodynia intensity VAS scores ± SD decreased significantly compared with the baseline values (8.18±0.64 vs 1.70±1.43, $P<0.001$). The proportion of patients with a ≥50% reduction in mean dynamic allodynia scores from baseline to end point was 91.18%. At the end point of MP treatment, seven patients were totally relieved from dynamic mechanical allodynia (Figure 2), and no patient became aggravated in the MP group. At the 1-month follow-up point, we did not observe severe allodynia in any of the followed up patients (34 patients), although three patients (8.82%) presented with moderate allodynia (VAS =4.0, VAS =4.5, VAS =4.2, respectively). Moreover, at the end of the follow-up period (3 months), we observed that the efficacy of MP did not decrease, since a total of 31 patients (91.18%) achieved excellent allodynia relief (VAS ≤2) and none of the patients manifested symptom recurrence.

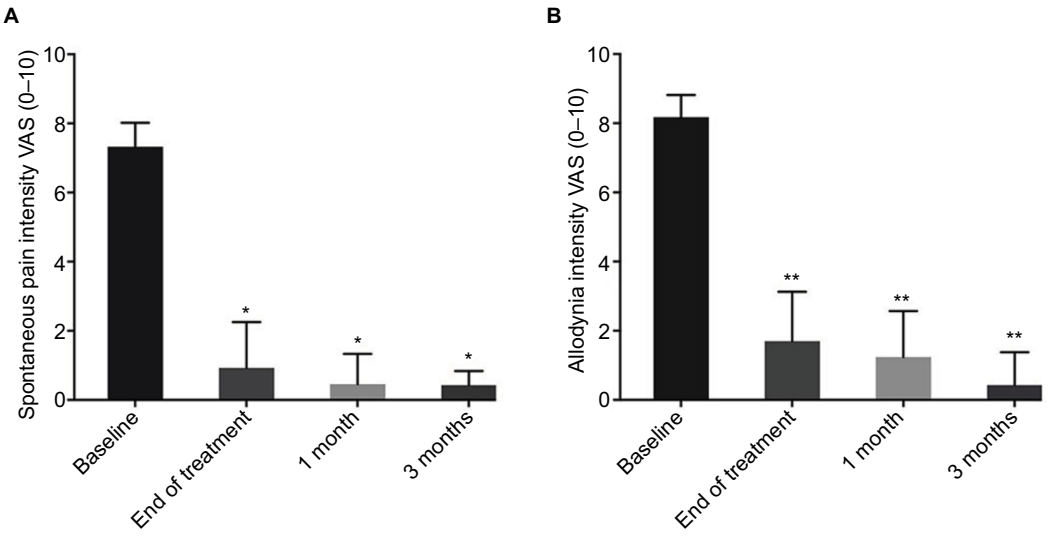

Figure 1 Time course of mean spontaneous pain (**A**) and allodynia (**B**) VAS scores during study.
Notes: The baseline, end of treatment, and the follow-up scores obtained after 1 month and 3 months of MP treatment are presented in the graph. Compared with the baseline, spontaneous pain and allodynia VAS scores decreased significantly over the whole period (*P<0.001 [**A**]; **P<0.001 [**B**]). Data are expressed as mean ± SD.
Abbreviations: VAS, visual analog scale; MP, methylprednisolone.

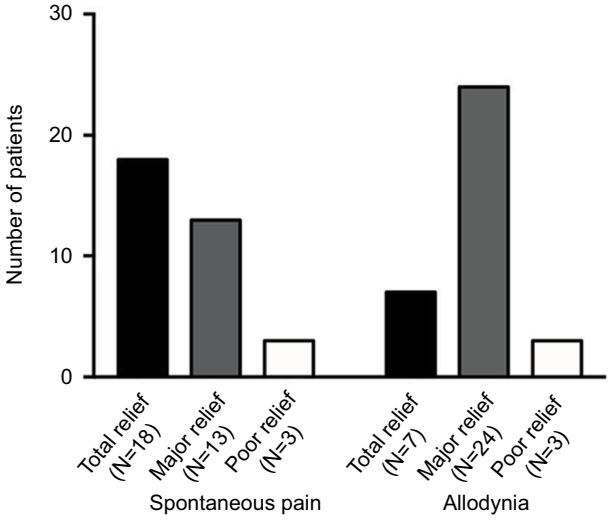

Figure 2 The number of patients reporting total (100%), major (≥50%), and poor (<50%) spontaneous pain and allodynia relief compared with baseline, as measured by VAS scores, at the end of MP treatment.
Abbreviations: VAS, visual analog scale; MP, methylprednisolone.

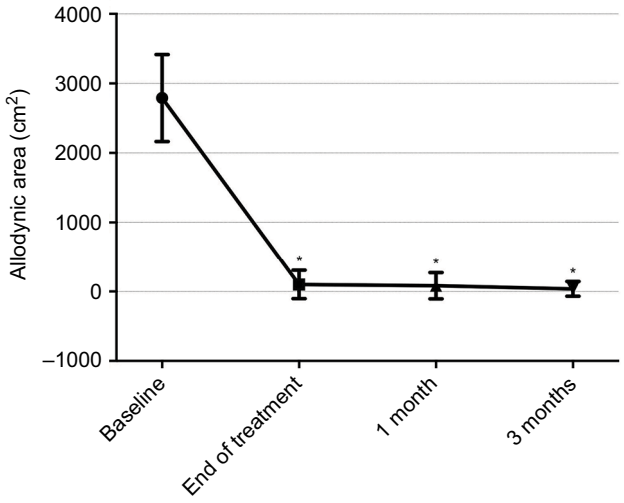

Figure 3 The time course of mean allodynic areas (cm^2) during study.
Notes: Comparison of the effects of intravenous MP and baseline on allodynic areas measured at baseline, end of MP treatment, and then at 1 month and 3 months after the MP treatment. Compared with the baseline, MP induced a significant reduction of allodynic areas over the whole period (*P<0.001). Data are expressed as mean ± SD.
Abbreviation: MP, methylprednisolone.

Meanwhile, we calculated the areas of dynamic allodynia, and the time course of the mean allodynic areas are displayed in Figure 3. The baseline mean allodynic areas (± SD) were 2791.23±625.20 cm^2 and after 1 week of MP treatment, the mean areas of allodynia (± SD) became 101.65±205.55 cm^2. Moreover, during the entire follow-up period, we also observed that allodynic areas of each patient showed a significant decrease at the end point of MP treatment. Taken together, MP effectively relieved the patients' dynamic mechanical allodynia and decreased the allodynic areas.

Effects on QoL

The five MPQSF domain scores, the EQ-5D utility scores, and EQ-5D VAS scores are shown in Table 3. MPQSF results indicated that MP treatment significantly reduced each domain score compared with baseline (all P<0.001). Also, MP treatment achieved a significant improvement in each of the EQ-5D domains compared with baseline (all P<0.001). Moreover, these effects were maintained during the follow-up

Table 3 Mean values (± SD) of quality of life assessments

Patients' health status scores	Baseline	End of treatment	*P*-value
MPQSF			
Sensory	17.14±2.54	3.43±1.72	*P*<0.001
Affective	9.14±2.12	1.86±1.68	*P*<0.001
PRI-Total	26.29±4.46	5.29±3.30	*P*<0.001
VAS	7.60±0.72	1.21±1.19	*P*<0.001
PPI	3.86±0.69	0.86±0.69	*P*<0.001
EQ-5D utility	–0.19±0.3	0.8±0.16	*P*<0.001
EQ-5D VAS	24.29±11.70	85.71±7.41	*P*<0.001

Notes: The MPQSF comprises five domains including sensory, affective, PRI-Total, VAS, and PPI. Responses are summed and then transformed onto a scale for each domain. Lower scores in each domain indicate improved health status. The EQ-5D is composed of two sections including EQ-5D utility and EQ-5D VAS. Higher scores indicate improved health status. Compared with the baseline, MP induced a significant improvement in quality of life after the MP treatment (all *P*<0.001). Data are expressed as mean ± SD.

Abbreviations: MPQSF, McGill Pain Questionnaire Short Form; EQ-5D, EuroQol Five Dimensions Questionnaire; PRI-Total, the total pain rating index as the sum of rank values; VAS, visual analog scale; PPI, pain intensity index; MP, methylprednisolone.

period. Taken together, MP could significantly improve the QoL of most CCS patients suffering from acute neuropathic pain with allodynia.

Side effects

Treatment with intravenous MP was well tolerated. No patient had severe side effects necessitating specific treatment during or after the infusion. Table 4 shows the frequency of side effects during and after the administration of MP in all the patients. MP produced side effects in four patients (11.76%). The most frequent MP-induced side effects were dizziness and nausea. Side effects were generally of mild or moderate intensity, and no MP-associated side effect was found in all patients during the entire follow-up period.

Discussion

In this retrospective study, intravenous MP seems to be effective for acute neuropathic pain with allodynia caused by CCS. We have shown that treatment with MP significantly decreased dynamic mechanical allodynia and allodynic areas as well as spontaneous pain in all the patients. Additionally, MP was efficacious in improving QoL in our patients. Furthermore, the acute neuropathic pain relief and QoL improvement in our patients lasted throughout the 3-month follow-up period and none of the patients was associated with any side effects. All our patients in this study were suffering from acute neuropathic pain with allodynia caused by CCS and resistant to conventional analgesic treatments.

Table 4 Summary of side effects

Side effects	Number of patients experiencing side effects (%)	
	During MP treatment (N=34)	During the entire follow-up period (N=34)
None	30 (88.24)	0 (0)
Dizziness	2 (5.88)	0 (0)
Nausea	2 (5.88)	0 (0)
Hyperglycemia	1 (2.94)	0 (0)
Hypertension	1 (2.94)	0 (0)
Other	0 (0)	0 (0)

Abbreviation: MP, methylprednisolone.

CCS-associated neuropathic pain is a clinically debilitating problem and resists to conventional pain therapy regimens.[7,8] Previous randomized controlled clinical trials have demonstrated gabapentin, pregabalin, lidocaine, duloxetine, lamotrigine, and morphine could cause relief from the chronic neuropathic pain following SCI partially;[9,15–18,33,44] however, the analgesic effects of these treatments usually are inadequate and side effects limiting patient compliance are common. So far, none of the treatment modalities for coping with the neuropathic pain following SCI was proven to have satisfactory results in all cases. Therefore, the treatment for this kind of pain remains a major clinical challenge.[7,28,45]

In this study, the current results suggested that intravenous MP offered an effective therapeutic alternative for the alleviation of acute neuropathic pain with allodynia caused by CCS, and no patients experienced symptom recurrence during the 3-month follow-up period. In fact, acute phase of neuropathic pain is an important pathophysiological state. Current theories indicate that the physical remodeling of neuronal cytoarchitecture and neuroplasticity changes occur after the onset of persistent acute neuropathic pain and then lead to the transition from acute neuropathic pain to a chronic neuropathic pain state. Therefore, early treatment for acute neuropathic pain may be more preferable and effective.

By the end of MP treatment, 76.47% of the patients (26/34) achieved excellent allodynia relief (VAS ≤2),[43] and this proportion increased to 91.18% (31/34) at 3-month post-MP treatment, which was higher than that reported in several studies on allodynia.[9,15-18,33,44,46] Importantly, there were 18 (52.94%) and 7 (20.59%) patients gaining total spontaneous pain and allodynia relief, respectively, at the end of MP treatment, which might suggest that MP is the specific drug for the CCS-associated acute neuropathic pain. In this study, we also calculated the allodynic areas of our patients. We observed the areas of dynamic allodynia decreased significantly at the

end of the study. This effect was consistent with the result that showed a decrease in VAS scores of allodynia. These improvements indicated that MP was significantly effective in relieving severe acute neuropathic pain in CCS patients.

Neuropathic pain after SCI is a complicated condition with physical, emotional, and environmental factors often playing an essential role.[13] Therefore, the efficacy of treatment for neuropathic pain can be measured not only in terms of the amount of pain the patients experience but also in terms of their overall physical and emotional well-being (QoL). This study used validated instruments, MPQSF and EQ-5D, to measure the patients' QoL which corroborated the efficacy of MP observed in the aforementioned analyses. Patients scored significantly better after MP treatment for every domain of the MPQSF and EQ-5D questionnaires. Considering the refractory nature of allodynia and the possibilities of acute neuropathic pain relief in such patients are usually low,[19] the improvement of the acute neuropathic pain observed in this study is encouraging.

In addition, treatment with intravenous MP was well tolerated. The side effects in this study were consistent with those reported for the clinical studies in SCI,[39,40] with dizziness and nausea being most common. The mild to moderate intensity of these side effects, along with their apparent transient nature, may be the reason behind the fact that all patients opted to remain on treatment. Moreover, no MP-associated side effect was found in all patients during the entire follow-up period.

Taken together, the persistent existence of long-term acute neuropathic pain relief and improvement in QoL indicated that intravenous MP is an effective and safe treatment for acute neuropathic pain with allodynia following CCS, although the involved mechanisms are not clear.

This study has several important limitations that must be pointed out. Firstly, pain relief was evaluated using the VAS, which is a relatively subjective tool and may be affected by multiple unknown factors. Secondly, because pain management was our first aim, the current study did not investigate the motor function outcomes in our CCS patients during and after administration of MP. Given that motor function problems also characterize CCS, outcomes focused on changes in motor function would need to be included in the future research. Thirdly, although we demonstrated MP was effective in relieving acute neuropathic pain and also improved patients' global status in CCS patients by current retrospective study, randomized placebo-controlled trials are needed to confirm these results.

Conclusion

In summary, intravenous MP could provide persistent long-term pain relief and improvement in the QoL and prevent the transition from acute neuropathic pain into a chronic neuropathic pain state in CCS patients with acute neuropathic pain. The current results suggested that intravenous MP might be useful as a new effective therapy for acute neuropathic pain following CCS. Given the encouraging results of this study, it would be worthwhile to confirm these results in randomized placebo-controlled clinical trials.

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Disclosure

The authors report no conflicts of interest in this study.

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