Relationship between the interval before high-dose methylprednisolone administration and chronic pain in traumatic spinal cord injury

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ABSTRACT

الأهداف: دراسة العلاقة بين طول الفترة قبل إعطاء الجرعات العالية من عقار ميثيل بريدنيسولون من جهة (methylprednisolone) ومدى شدة الألم لدى المرضى بعد إصابات الحبل الشوكي الرضحية.

الطريقة: استرجعنا في هذه الدراسة سجلات المرضى الذين يشكون من إصابات الحبل الشوكي الرضحية في قسم الطب الفيزيائي والتأهيل بمستشفى تراي العام، كلية الطب، مركز الدفاع الوطني، تايباي، تايوان وذلك خلال الفترة من يناير 2005م إلى يناير 2010م. لقد قمنا بتقييم العلاقة بين طول الفترة قبل إعطاء الجرعات العالية من عقار ميثيل بريدنيسولون من جهة ومدى شدة الألم وظهور الآم العصبية. وقد قسمنا المشاركين في الدراسة إلى مجموعتين: مجموعة المرضى التقليدية (العدد:22) التي تناولت العقار بعد الإصابة بأقل من 8 ساعات، والمجموعة المتأخرة التي تناولت العقار بعد الإصابة بأكثر من أو يساوي 8 ساعات (العدد:10). وبعد ذلك أرسلنا استبيان ماك جيل الموجز إلى المرضى من أجل تقييم الألم، واستبيان دوليور لتقييم الآلام العصبية والمكون من 4 أسئلة.

النتائج: لقد حققت مجموعة المرضى التقليدية (10.4±9.54) درجات عالية في استبيان ماك جيل الموجز وذلك بمقدار الضعف مقارنةً بدرجات مجموعة المرضى المتأخرة(3.5±5.9). وكان هناك علاقة إيجابية بين طول الفترة قبل إعطاء الجرعات العالية من عقار ميثيل بريدنيسولون ودرجات استبيان ماك جيل الموجز واستبيان دوليور لتقييم الآلام العصبية، وعلى الرغم من ذلك لم تكن هذه العلاقة أو هذه الاختلافات بين المجموعتين عالية من الناحية الإحصائية. أشارت نتائج الدراسة إلى أن زيادة طول الفترة قبل إعطاء العقار قد أدت إلى تفاقم الألم وظهور الآلام العصبية.

خاتمة: أظهرت هذه الدراسة بأن التأخر في إعطاء عقار ميثيل بريدنيسولون لا يؤدي إلى زيادة شدة الألم أو ظهور الآلام العصبية وذلك من الناحية الإحصائية، وعلى الرغم من ذلك يجب تجنب مثل هذا التأخير لأن ذلك قد يؤدي إلى زيادة خطر حدوث بعض الآثار الجانبية.

Objective: To examine the relationship between the interval before the administration of high-dose methylprednisolone (MP) and pain in traumatic spinal cord injury (SCI) patients.

Methods: We retrospectively studied the medical records of admitted patients with traumatic SCI at the Department of Physical Medicine and Rehabilitation, Tri-Service General Hospital, School of Medicine, National Defense Medical Center, Taipei, Taiwan from January 2005 to January 2010. We examined the relationship between the interval before the administration of high-dose MP, and the severity of pain and the presence of neuropathic pain (NeP). Patients treated with high-dose MP <8 hours after their injuries were defined as the classical-MP group (n=22), and patients who received high-dose MP ≥8 hours after their injuries were defined as the delayed-MP group (n=10). The patients were mailed questionnaires including the Short-Form McGill Pain Questionnaire (SF-MPQ), and the Douleur Neuropathique 4 Questions questionnaire (DN4Q).

Results: The SF-MPQ score in the classical-MP group (9.54 ± 10.4) was almost 2-fold more than in the delayed-MP group (5.9 ± 3.5). The interval before the administration of high-dose MP was positively correlated with the DN4Q and SF-MPQ scores, although these differences, and associations were not statistically significant. The increased interval in the administration of MP resulted in slightly greater pain and an increased prevalence of NeP.

Conclusion: Although the delayed administration of high-dose MP did not significantly increase the severity of pain or prevalence of NeP, it should still be avoided due to the increased risk of serious side effects.

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Pain is a significant problem in spinal cord injury (SCI) patients, and has been widely studied. Pain affects 70% of SCI patients, and one-third of these patients describe it as a serious pain.[1,2] Three major types of pain have been identified in SCI: 1) nociceptive pain is described as a dull or cramping pain, and is a result of damage or inflammation in bones, ligaments, or muscles; 2) visceral pain is a vague, dull, or diffuse abdominal pain that is difficult to localize, and is a result of problems with internal organs; and 3) neuropathic pain (NeP) is frequently described as a burning, stabbing, or shooting pain with an abnormal sensation, and is induced by injury to the nervous system. Neuropathic pain affects more than 40% of patients with SCI, and is refractory and chronic.[3] The onset of NeP occurs within the first 6 months after injury in 43-63% patients, and during the first year in 80-95% of patients.[4,5] Methylprednisolone (MP) is the only neuroprotective drug in widespread use for the treatment of SCI. The National Acute Spinal Cord Injury Study 2 (NASCIS 2) concluded that high-dose MP should be prescribed in SCI patients seen less than 8 hours after injury.[6] However, a subgroup of patients with incomplete injuries who were treated with MP more than 8 hours after injury had poorer neurological outcomes than the placebo group when functional improvement was evaluated after 6 months and one year.[6] Therefore, we considered it likely that high-dose MP may be harmful to some SCI patients, although no motor scores were reported, and the difference between these 2 groups was not statistically significant. Furthermore, the series of NASCI studies focused on motor and sensory recovery without discussing the subsequent SCI-related pain. We previously reported a patient with spontaneous spinal epidural hematoma (SSEH) who received high-dose MP 16 hours after the symptoms began.[7] Although the patient had a good functional recovery after emergency surgical decompression, we observed intractable NeP 5 weeks later. We speculated that the delay in the initiation of high-dose MP may be the primary cause of the intractable NeP; therefore, our aim in this study was to examine whether a delay in the initiation of high-dose MP may cause more serious pain or not, especially SCI-related NeP.

Methods. The Ethics Committee of the Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan approved this retrospective study. We collected the following details from the medical records of patients aged between 18-65 years with traumatic SCI: age, gender, onset time, level of injury, cause, completeness of SCI, interval before the administration of high-dose MP, and surgical intervention. We included patients from our hospital who received high-dose MP according to the NASCIS 2 and 3 guidelines from January 2005 to January 2010.[6,8] Patients were able to communicate, and willing to participate in the study by undergoing telephone interviews and completing questionnaires. We excluded patients with complicated brain injuries, multiple organ damage, SSEH, mental illness, psychotic history, and impaired communication. Prior to data collection, the patients were informed of the purpose of this study and given a description of SCI-related chronic pain by a specific nurse over the telephone. After a patient agreed to enroll in the study, the questionnaires (the Short-Form McGill Pain questionnaire [SF-MPQ], and the Douleur Neuropathique 4 Questions questionnaire [DN4Q]), a consent form, and a cover letter, including a number of questions assessing education level and marital status, were mailed to the patient. Patients were given a gift of $5 for completing and returning the consent form and questionnaires. If the survey were not returned after 3 weeks, we called the patients up to 3 times to remind them. Patients treated with high-dose MP <8 hours after their injuries were defined as the classical-MP group, and patients who received high-dose MP ≥8 hours after their injuries were defined as the delayed-MP group. The SF-MPQ was used to score the pain experience.[9] It contains 2 subscale scores (4 affective words such as tiring-exhausting and sickening; 11 sensory words such as throbbing and shooting) that were computed by separately summing ratings. The intensity of that pain is then evaluated as 0 (none), 1 (mild), 2 (moderate), or 3 (severe). The total score of all 15 items is summed, and higher scores indicate higher levels of pain severity. The correlation coefficients between the short and long forms of the MPQ are high and significant (r = 0.62-0.90). The DN4 uses interview questions and physical tests to identify the presence of NeP with 83% sensitivity and 90% specificity. The DN4Q has only 7 self-reported questions (burning, painful cold, electric shocks, tingling, pins and needles, numbness, and itching) and slightly less sensitivity (78%) and specificity (81%) was previously reported. The DN4Q score ranges from 0-7, and scores ≥3 are considered indicative of NeP.[10]

Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 13.0 for Windows. Significant differences between groups were assessed by student's t-test for continuous variables and chi-square test for categorical

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variables. Comparisons were made with the chi-square test between the classical- and delayed-MP groups in the presence of NeP and the SF-MPQ scores. Correlations between the interval before the administration of high-dose MP and the DN4Q and SF-MPQ scores were made with Spearman's rank invariant analysis. A *p*-value <0.05 was taken to indicate statistical significance.

Results. Of the 60 questionnaires mailed, 35 (59%) were returned. Of them, 3 were returned with incomplete data. The demographic data and characteristics of the patients are shown in **Table 1**. There were 22 patients in the classical-MP group (19 men, 3 women; mean age 42.9±12.9 years; range 23-64 years), and 10 patients in the delayed-MP group (8 men, 2 women; mean age 39.3±12.4 years; range 24-59 years). The period since SCI ranged from 4-68 months (mean 30.9±18.5 months) in the classical-MP group, and 3-69 months (mean 37.3±22.1 months) in the delayed-MP group. Motor vehicle accidents were the most common cause of SCI in both groups, and their incidence in the classical-MP group was higher than in the delayed-MP group. Injuries from falling and others were the remaining causes of SCI in the respective groups. There was a similar percentage of cervical level SCI in both groups. The rare incidence of thoracic level SCI in the classical-MP group was noted, but the delayed-MP group contained no patients with this injury. The incidence of lumbar level SCI in the delayed-MP group was higher than in the classical-MP group. The injury was categorized as either complete or incomplete based on the presence of motor and sensory function below the level of the lesion. Most injuries in the classical-MP group were incomplete, and 100% of the injuries in the delayed-MP group were incomplete. Operations such as decompression or fixation were performed in 68.2% of the classical-MP patients, and in 70% of the delayed-MP patients. No significant differences were observed between the classical-MP and delayed-MP groups for gender, age, time since injury, marital status, education, causes, level of injury, completeness, and surgical intervention.

Table 2 shows the mean SF-MPQ scores and the presence of NeP in the classical- and delayed-MP

Table 1 - Demographic data and characteristics of patients with spinal cord injury (SCI) in the National Defense Medical Center in Taiwan.

Variables	All patients (n = 32)	Classical-MP group (n = 22)	Delayed-MP group (n = 10)	*P*-value	95% CI
Gender (%) (M/F)	(84.3)/(15.7)	(86.4)/(13.6)	(80)/(20)	0.706	0.118 - 23.374
Age (years), mean ± SD	(23-64) 41.7 ± 12.7	(23-64) 42.9 ± 12.9	(24-59) 39.3 ± 12.4	0.466	-6.378 - 13.596
Months since SCI (mean ± SD)	(3-69) 32.9 ± 19.62	(4-68) 30.9 ± 18.5	(3-69) 37.3 ± 22.1	0.402	-21.742 - 8.961
Marital status, n (%)				0.787	0.185 - 9.267
Married	21 (65.6)	16 (72.8)	5 (50.0)		
Single	10 (31.2)	6 (27.2)	4 (40.0)		
Divorced	1 (3.2)	0 (0.0)	1 (10.0)		
Education, high level, n (%)				0.856	0.355 - 3.479
Elementary school	1 (3.1)	1 (4.5)	0 (0.0)		
Junior high school	2 (6.2)	1 (4.5)	1 (10.0)		
Senior high school	15 (46.8)	11 (50.0)	4 (40.0)		
University	14 (43.9)	9 (41.0)	5 (50.0)		
Causes of SCI, n (%)				0.313	0.54 - 6.861
Motor vehicle accident	17 (53.1)	13 (59.1)	4 (40.0)		
Fall	7 (21.8)	4 (18.2)	3 (30.0)		
Sport	1 (3.1)	0 (0.0)	1 (10.0)		
Violence	2 (6.2)	1 (4.5)	1 (10.0)		
Other	5 (15.8)	4 (18.2)	1 (10.0)		
Level of injury, n (%)				0.650	0.008 - 20.384
Cervical	25 (78.1)	17 (77.3)	8 (80.0)		
Thoracic	2 (6.3)	2 (9.1)	0 (0.0)		
Lumbar	5 (15.6)	3 (13.6)	2 (20.0)		
Completeness, n (%)				0.999	
Incomplete	29 (89.7)	19 (86.4)	10 (100.0)		
Complete	3 (10.3)	3 (13.6)	0 (0.0)		
Surgery, n (%)				0.596	0.046 - 5.839
Yes	22 (68.7)	15 (68.2)	7 (70.0)		
No	10 (31.3)	7 (31.8)	3 (30.0)		

MP - methylprednisolone, classical-MP group - patients treated with high-dose MP <8 hours after their injury, delayed-MP group - patients who received high-dose MP ≥8 hours after their injury, CI - confidence interval

Table 2 - Means and standard deviation of the scores of SF-MPQ and presence of neuropathic pain in the classical- and delayed-MP group patients with spinal cord injury in the National Defense Medical Center in Taiwan.

Measures	Classical-MP (n=22)	Delayed-MP (n=10)	*P*-value	Odds ratio	95% CI
SF-MPQ (mean ± SD)	9.54 ± 10.4	5.9 ± 3.5	0.155	3.645	-1.460 - 8.750
Neuropathic pain			0.141	0.25	0.043 - 1.454
DN4Q ≥3 (n, %)	10 (45.4)	2 (20.0)			
DN4Q <3 (n, %)	12 (54.6)	8 (80.0)			

SF-MPQ - short-form McGill Pain Questionnaire, MP - methylprednisolone, SD - standard deviation, DN4Q - Douleur Neuropathique 4 Questions questionnaire, CI - confidence intervals

groups. The SF-MPQ score in the classical-MP group was almost 2-fold more than in the delayed-MP group, but this difference was not significant. A total of 10 patients (45.4%) presented with NeP in the classical-MP group compared with 2 patients (20%) in the delayed-MP group; however, this was not a significant difference. The Spearman rank order correlation test revealed a correlation between the interval before the administration of high-dose MP with the DN4Q (r=0.008, p=0.965), and the SF-MPQ (r=0.137, p=0.452) scores, although these correlations were not statistically significant.

Discussion. Many studies have examined the predictive risk factors for SCI-related chronic pain because of its profound negative impact on patients' mood, daily activities, quality of life, and rehabilitation outcomes. Most studies agree that the level of injury, complete or incomplete injury, the existence of initial surgery, and gender are not predictive factors of NeP in SCI patients. The negative prognostic factors include old age at the time of injury, bullet injury as the cause of trauma, early onset of pain in the weeks following the injury, their initial nature, and continuous pain.[11] Unfortunately, there is limited information on the relationship between the interval before the administration of high-dose MP and the severity of chronic pain, and the presence of NeP in patients with traumatic SCI. In addition, there is a lack of studies assessing whether the initiation of high-dose MP at more than 8 hours after SCI induces severe posttraumatic pain.

Our study demonstrated that the intensity of pain and the prevalence of NeP in the classical-MP group was higher than in the delayed-MP group. In addition, the interval before the administration of high-dose MP was positively correlated with pain severity and DN4Q score, but not statistically significant. In other words, the administration of high-dose MP at more than 8 hours after onset did not significantly produce severer pain or increase the prevalence of NeP. However, the increased interval administration of MP resulted in slightly greater pain and increased prevalence of NeP. The underlying reasons for these results are unclear because there is no previous research that can be used as a reference. In our opinion, it may be that the patients in the classical-MP group had more serious initial accidents than the delayed-MP patients, and were treated quickly with high-dose MP. In contrast, most patients in the delayed-MP group had no obvious initial neurological deficit, resulting in a delayed diagnosis and administration of high-dose MP. As a result, the pain intensity, and incidence of NeP in the classical-MP group were higher than in the delayed-MP group under severe traumatic SCI. In addition, the sample size was too small with limited statistical analysis, especially in the delayed-MP group (n=10). This was due to the declining use of high-dose MP in SCI patients, especially at more than 8 hours after injury. This may be a factor in the lack of significant differences. Despite the small sample size, the prevalence of NeP in our study (12/32, 37.5%) was within the range of previous reports. The severity of SCI-related pain could be modulated by affective distress such as depressed mood, anxiety, sadness, and perceptions of excessive fatigue;[12,13] therefore, it is difficult to explain the results of this study simply by the interval before the administration of high-dose MP.

Methylprednisolone has been used extensively to attenuate the secondary effects of SCI via its anti-inflammatory properties, which have been ascribed to the alleviation of spinal cord edema. The NASCIS3 study concluded that intravenous MP (30 mg/kg) should be initiated within an hour of injury, and that the infusion should be maintained at 5.4 mg/kg/h for 24 hours if MP treatment is initiated within 3 hours of injury. For patients whose treatment was initiated 3-8 hours after injury, the maintenance dose should be administered for 48 hours.[8,14] The high-dose MP protocol has become the standard of care for acute SCI since the publication of the NASCIS 2 and 3 in 1990 and 1997, respectively;[6,8] however, an increasing number of authors argue against the validity of these studies. For example, Hurlbert[15] and Hall et al[16] questioned the validity of the NASCI studies on the basis of their randomization method, statistical analysis, clinical endpoints, and overall clinical outcome. Further, they warned that the use of MP is associated with serious side effects, including wound infection, pneumonia,

sepsis, gastrointestinal hemorrhage, steroid-induced myopathy, and so forth.

In a study of MP therapy on regional spinal cord blood flow before and after cord compression, Carlson et al[17] found that, unlike the control group treated with saline, the group treated with MP after decompression failed to return to baseline function. Therefore, they hypothesized that MP did not satisfactorily improve neurological recovery after acute SCI.

Due to these negative effects of high-dose MP in SCI patients, an increasing number of countries do not recommend high-dose MP as the standard protocol. Therefore, the need to take into account the exact time of the injury should be considered when making a decision on whether or not to treat SCI patients with high-dose MP. Although the delayed administration of high-dose MP did not significantly increase the severity of pain and prevalence of NeP in our study, the initiation of high-dose MP therapy after more than 8 hours should still be avoided due to the increased risk of serious side effects. The results of this study do not support our previous hypothesis that delayed initiation of high-dose MP might cause more serious pain, especially SCI-related NeP in non-traumatic SCI patients.[7] Because of the limited numbers of patients with non-traumatic SCI, we studied traumatic SCI patients instead in this study. Even so, a further study is needed to investigate the relationship between the delayed high-dose MP and pain in patients with non-traumatic SC, especially SSEH, in the future.

This study has several methodological limitations. First, the response rate (59%) to the primary survey was low; therefore, this sample may be not representative of all patients with traumatic SCI. Second, our study cannot distinguish the true incidence and severity of nociceptive or visceral pain from common pain and NeP as the survey forms here are not specific for these types of pain. Finally, the retrospective survey and reported data from the postal survey may present certain limitations because the onset and duration of pain after SCI are variables in the studied patients, and the patients' level of comprehension cannot be determined with any certainty. In the future, a large prospective study is recommended.

In conclusion, although our study showed the administration of high-dose MP at more than 8 hours did not significantly increase the severity of pain and prevalence of NeP, the administration of delayed high-dose MP in patients with traumatic SCI should be avoided due to its severe side effects.

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