Reappraisal of Methylprednisolone Treatment for Acute Traumatic Cord Injury

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Objective: The value of methylprednisolone (MP) treatment in acute traumatic spinal cord injury (SCI) remains controversial. We attempted to evaluate the utilization of resources, motor function recovery and adverse effect after the use of MP.

Methods: We compared 13 demographic and clinical characteristics between MP and non-MP treatment groups in 110 patients with acute traumatic SCI treated in hospitals between June 1st, 2000 and May 31st, 2001, and analyzed 10 short-term outcome variables. These demographic and clinical characteristics included age, cause of injury, number of associated injuries, Revised Trauma Score, Glasgow Coma Scale, mean blood pressure, level/completeness and pattern of SCI, number and types of spinal surgeries, frequency of rehabilitation therapy and the time interval between trauma and admission.

Results: The MP (64.5%) and non-MP (35.5%) treatment groups showed no significant differences in all characteristics except the time interval between trauma and admission (P=0.024). MP treatment was associated with a higher frequency of infectious complications (P=0.038), but there was no difference between the two treatment groups in other outcome parameters. The results of analysis stratified by dosage of MP showed that the length of ICU stay (P=0.021) and the number of tracheostomies (P=0.005) and pneumonia cases (P=0.004) were increased significantly in the standard dose group.

Conclusions: Although the rate of infection had risen in patients receiving MP, the steroid treatment did not significantly increase utilization of resources during hospitalization and appeared safe in terms of mortality. However, it had not been proven to improve motor function recovery.

Key words: methylprednisolone, spinal cord injury, outcome, infection

The early administration of methylprednisolone (MP) is believed to improve the neurologic recovery of patients sustaining an acute traumatic spinal cord injury (SCI). In the National Acute Spinal Cord Injury Study (NASCIS)-2 Bracken et al. reported that patients who were treated with large dosage of MP (bolus of 30 mg per kilogram of body weight, maintained at 5.4 mg per kilogram per hour for 23 hours) within 8 hours of their injuries had significant neurologic improvement after the periods of 6 weeks, 6 months and one year.[1] In 1997 they even recommended to maintain the treatment for 48 hours if steroid therapy was initiated 3 to 8 hours after injury.[2]

Since the releases of NASCIS-2 and NASCIS-3, there have been several commentaries about the

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methodology of the trials and the risk-benefit of MP treatment.[3,4,5] The results of MP treatment remain controversial. The debate regarding its efficacy ranges between two polarized thoughts. At one end, clinicians, who strongly maintain the convictions of NASCIS-2 and NASCIS-3, use large doses of MP within 8 hours of injury.[6,7] At the other extreme are those who think that large dosage of steroid has no benefit on neurologic recovery, sometimes even harmful for the patient.[8,9,10] The theoretical advantages supporting the early use of MP in the acute phase are prevention of lipid peroxidation, inhibition of free radical injury and early stabilization of the damaged cell membrane, which can maximize the potential for recovery and result in improvement of long-term motor and sensory function.[11]

Owing to their widespread application in North America, the major difficulty in assessing the results of MP treatment is the identification of a suitable control group for statistical analysis. A prospective controlled trial has recently been completed in France and no benefit in neurologic recovery was found; instead, more infectious complications occurred.[12] There were also reports about its septic consequences.[13,14]

We performed a retrospective study to evaluate the utilization of resources, motor function recovery and adverse effect after the use of MP in patients of acute traumatic SCI.

Materials and Methods

Between June 1st, 2000 and May 31st, 2001, we studied 110 patients that were diagnosed to have traumatic SCI and admitted to the medical centers or regional hospitals in the northern and eastern parts of the island, and these medical institutions had the capacity to provide comprehensive care for patients with SCI. To be included in our study, the patients had to be no less than 16 years old and admitted within 30 days after injury without definitive treatment in other hospitals. Patients sustaining spinal column injury without cord involvement or with nerve root injury only or merely the cauda equina syndrome were not included in the study. There was no penetrating injury found in this series.

Moreover, patients with incomplete records about the treatment method or in-hospital course were not included. Using a chart review, we recorded the patients' data on demographic and admission characteristics, treatment methods, clinical course of hospitalization, complications and outcome parameters by predetermined form.

Ten parameters of short-term outcome were used in this study for the evaluation of the utilization of resources, neurologic recovery and adverse effects after the use of MP. Because the adverse effects on the patient after steroid treatment would be apparent shortly after administration, we only chose the in-hospital parameters of short-term outcome for evaluation in this study. To evaluate the utilization of resources, we looked at the length of hospitalization, ICU stay, number of ventilated days, number of tracheostomy cases and duration between admission and start of rehabilitation; for the neurologic recovery, the scores of motor function change during hospitalization and 6 weeks after admission were used; and for the evaluation of adverse effects, the number and types of complications and in-hospital mortality were used.

In this study, the patients received MP treatment only once and no additional peri-operative prophylactic use. Halos or skull tongs were rarely applied and were not included as spinal surgery.

Only motor function was analyzed for neurologic recovery. In a previous study of cord injury, the patients who were treated with high-dose MP had significant motor functional improvement after 6 weeks.[1] Therefore; this shorter follow-up interval (6 weeks) was used in the present study.

The 5-point scale of muscle power of each extremity was used for motor function assessment. A score of 0 indicated no contraction, 1 indicated reduced contraction, 2 indicated active movement without antigravity, 3 indicated active movement with antigravity, 4 indicated reduced function but active movement against resistance, and 5 indicated normal motor function. A normal motor scale was described as 20 and the lowest was 0. The change in motor scale was calculated between admission and examination done at discharge and 6 weeks after admission.

The pattern of SCI was classified as quadriplegic, paraplegic, quadriparetic, and paraparetic. The classification is as follows: quadriplegic, if most cephalad muscle with no contraction was the first dorsal interosseous (C-8 to T-1) or higher with no contraction in any distal muscle; paraplegic, if most cephalad muscle with no contraction was below the first dorsal interosseous with no contraction in any distal muscle; quadriparetic, if most cephalad muscle with a trace of contraction or active movement without antigravity was the first dorsal interosseous or higher; and paraparetic, if most cephalad muscle with a trace of contraction or active movement without antigravity was below the first dorsal interosseous. The completeness of SCI was recorded according to the description of the admission diagnosis.

We hypothesized that the effect of treatment would be influenced by how fast and in how large dosage MP

was given to the patient. Hence, stratified analysis was done by timing ($\leqq$8 hours or $>$8 hours) and dosage (standard or lesser dose) according to the NASCIS-2 protocol. At present, the NASCIS-3 protocol is rarely applied in Taiwan.

Details of 13 demographic and clinical characteristics, including age, cause of injury, time interval between trauma and admission, number of associated injuries, Revised Trauma Score (RTS), Glasgow Coma Scale (GCS) and mean blood pressure (MBP) at the emergency room (ER), level/completeness and pattern of SCI, number and types of spinal surgeries, and frequency of rehabilitation therapy were recorded to compare the entrance features between the two groups and to minimize the opportunity of confounding.

The information was entered into the computer for processing by 8.0 SPSS. Standard statistical methods, such as the Chi-square test and Fisher test, were utilized properly for data analysis. $P<0.05$ was considered significant.

Results

Of the 110 patients, 71 patients received MP treatment (MP group), and 39 patients had no such treatment (non-MP group). There was no significant difference between the two treatment groups concerning the level of hospitals providing treatment, either medical centers or regional hospitals.

Table 1 compares the 13 characteristics of patients at entry between the two groups. There was no difference in age, cause of injury and associated non-spinal injuries. The severity of trauma, represented by the MBP, RTS and GCS at ER, was not significantly different between the two groups, nor the severity of the SCI, including level, completeness and pattern.

Approximately 82% of the patients had spinal surgery, which was performed mainly for neural decompression, and no significant difference was noted in the number or types of surgeries between the two groups. Frequency of rehabilitation therapy also showed the same results.

However, the two groups showed significant differences in the time interval between trauma and admission. The patients in the MP group arrived at the hospital for definitive treatment on an average of 4 days sooner than those without. These differences were due to treatment policy recommended by the NASCIS protocol, which selected only patients arriving at the hospital in less than 8 hours after injury.

The outcome evaluated for in-hospital utilization of resources including length of hospitalization, length of intensive care, number of ventilated days, number of

Table 1. Demographic and Clinical Characteristics of the 110 Patients

Characteristics	MP (N=71)	Non-MP (N=39)	P-value
Age			0.247
16-20	4.2%	0	
21-30	25.4%	10.3%	
31-40	9.9%	23.1%	
41-50	15.5%	17.9%	
51-60	15.5%	10.3%	
61-70	14.1%	23.1%	
71-80	9.9%	12.8%	
81-90	4.2%	2.6%	
91-100	1.4%	0	
Cause of injury			0.476
Traffic accident	56.3%	59.0%	
Fall	36.6%	28.2%	

Time between injury to admission (average day)	0.4366%	4.3889%	0.024
Mean Blood Pressure at ER (average)	91.8584%	96.4017%	0.263
Glasgow Coma Scale at ER (average)	14.4789%	13.9231%	0.234
Revised Trauma Score at ER (average)	7.6445%	7.5857%	0.604
Level of SCI			0.354
C-spine	76.1%	82.1%	
T-spine	9.9%	2.6%	
L-spine	18.3%	33.3%	
Completeness of SCI			0.179
Complete	18.8%	18.8%	
Incomplete	81.3%	81.3%	
Pattern of SCI			0.408
Quadriparetic	53.5%	56.4%	
Quadriplegic	7.0%	5.1%	
Paraparetic	16.9%	5.1%	
Paraplegic	9.9%	10.3%	
Number of associated injury*			0.857
0	36.6%	38.5%	
1	38.0%	30.8%	
2	15.5%	20.5%	
≧3	9.9%	0.3%	
Spinal surgery following injury			0.289
Yes	63.4%	69.2%	
No	36.6%	28.2%	
Type of spinal surgery			0.588
Ant. Decompression	48.9%	45.7%	
Post. Decompression	33.3%	17.1%	
Rehabilitation therapy before discharge			0.289
Yes	69.0%	59.0%	
No	31.0%	41.0%	

*Associated injury included head injury, facial fracture, bony fracture of limb, thoracic injury, abdominal injury, pelvic fracture and severe burn injury.

tracheostomy cases and length between admission and start of rehabilitation. There was no significant difference in these parameters between the two treatment groups (Table 2).

With the previously mentioned method of neurologic assessment, the MP group showed no significant motor recovery at discharge. Only 37 patients were admitted for more than 6 weeks, an average motor-function change of 2.769 and 0.200 was found respectively in the MP and non-MP groups and that only approached significant difference (Table 2).

As seen in Table 3, only three patients died during hospitalization with a mortality rate of 2.7%. When the mortality rate was examined in relation to treatment regimen, no difference was noted. We also found no difference in frequency of complications between the two groups. Sepsis was rare (1.8%) and no thrombo-embolic complication (deep vein thrombosis or pulmonary embolism) was noted in the study. Seven categories of complications were analyzed: pneumonia, respiratory failure, upper gastro-intestinal bleeding (UGIB), urinary tract infection (UTI), pressure sores, neurogenic bladder and "other infections". The category of "other infections" was defined as all in-hospital infections other than

Table 2. In-Hospital Utilization of Resource and Motor Function Change

Outcome parameter	MP (N=71)	Non-MP (N=39)	P value
Mean length of hospitalization (day)	45.28	31.94	0.144
Mean length of stay in ICU (day)	4.99	3.39	0.37
Mean length of ventilated day	18.87	8.36	0.071
Case number of tracheostomy	9	3	0.532
Mean duration from admission to the start of rehabilitation (day)*	25.82	25.13	0.922
Mean score of in-hospital motor function change	2.18	1.45	0.764
Mean score of motor function change six weeks after treatment**	2.76	0.20	0.057

* 72 patients had in-hospital rehabilitation therapy. (MP= 49, Non-MP=23)
** 37 patients were admitted more than 6 weeks. (MP= 30, Non-MP=7)

Table 3. In-Hospital Mortality and Complications

Outcome parameter	MP (N=71)	Non-MP (N=39)	P value
In-hospital mortality	2	1	0.714
Frequency of in-hospital complications	1.29	0.87	0.099
Neurogenic bladder	25	10	0.303
Urinary tract infection	20	5	0.066
Pneumonia	12	4	0.344
Pressure ulcer	9	3	0.534
Respiratory failure	9	4	0.483
UGI bleeding	6	1	0.418
“Other infections”	8	5	0.517
Infectious complication*	42	14	0.038

* Infectious complications included pneumonia, UTI, sepsis and "other infections"

pneumonia, UTI, sepsis and wound infection after surgery. This category included cellulitis, epididymitis, vaginitis, empyema, etc. No significant difference was noted concerning these seven categories between the two groups. UTI was the most common infectious complication in this study and showed a difference barely approaching the significant level (P=0.066). However, if we compared infectious complications between the two groups, which included pneumonia, UTI, sepsis and "other infections", 42 instances were found in the former and 14 instances in the later group, and the difference was significant (P=0.038). The types of infectious complications in both groups were shown in Table 4.

Forty-nine patients had spinal surgery (MP=32, Non-MP=17), mainly for spinal cord decompression, and no significant difference was found concerning post-operative complications, which included wound infection (P=0.664) and re-operation (P=0.583).

The dosages of MP administration could be traced clearly in all 71 patients of the MP group. Fifty-three patients (74.6%) received the standard dose of NASCIS-2 and 18 patients (25.4%) received an MP dose less than that assigned in the NASCIC-2 protocol. The results of the analysis stratified by doses are shown in Table 5. Owing to the lack of accurate data about the timing of MP administration in more than half of the patients (59%), no analysis stratified by timing was attempted.

Table 4. Frequency and Content of Infectious Complications in Table 3

	MP (N=71)	Non-MP (N=39)
Pneumonia	12	4
Urinary tract infection	20	5
sepsis	2	0
“Other infections”		
Cellulitis	*2*	*0*
Wound infection	*2*	*1*
Empyema	*1*	*0*
Epididymitis	*1*	*0*
Vaginitis	*1*	*1*
Hepatitis	*0*	*1*
Mastitis	*1*	*0*
Brain abscess	*0*	*1*
Osteomyelitis	*0*	*1*
Total	42	14

Table 5. Stratified Analysis of 71 Patients by dose of MP

Outcome measure	Dose*		
	STD (N=53)	Non STD (N=18)	P value
Mean length of hospitalization (day)	47.07	26.18	0.093
Mean length of stay in ICU (day)	4.74	1.38	0.021
Mean length of ventilated day	17.54	13.06	0.646
Case number of tracheostomy	6	1	0.005
Mean duration from admission to the start of rehabilitation (day)	23.76	14.57	0.281
Mean score of in-hospital motor function change	2.87	-0.21	0.066
Mean score of motor function change six weeks after treatment	3.13	-1.00	0.389
In-hospital mortality	2	0	0.438
Frequency of in-hospital complications	1.33	0.87	0.280
Pneumonia	9	1	0.004
Infectious complication	21	3	0.053

*dose of MP as NASCIC-2 protocol
STD: standard treatment dose as NASCIC-2 protocol
Non STD: treatment dose less than NASCIC-2 protocol

Discussion

Objective measurement of the results of different treatment regimens in acute SCI is difficult due to the complexity of the nature of injury and the lack of randomized and prospective controlled studies. It was not until the release of the NASCIC -2 results in 1990 that the medical treatment of acute SCI was standardized.[1] At present, large dosage of MP is widely accepted in North America as the routine treatment in emergency care and neurosurgical practice. Failure of administration after cord injury may become a medico-legal problem.[10] Although the NASCIC reports strongly recommend that large dosage of steroids has been useful for neurologic recovery, there is still considerable controversy regarding this topic.[7,15,16]

About 30 years ago, the patho-physiology of SCI was evaluated and the role of glucocorticoids for SCI treatment was emphasized. Several reports on animal trial in laboratory were published.[17] The mechanism of cord damage after injury involves activation of membrane lipases, which results in disturbance of the cell membrane. Since lipid peroxidation is considered as a major factor in cord damage and deterioration of the function of the central nervous system, it seems rational to apply MP because of its strong capacity of antioxidant effect and its activities as a free-radical scavenger. Braughler and Hall et al. reported using corticosteroids as a means of inhibiting free radical injury in experimental spinal cord injury, and post-injury neurologic condition was improved.[18] The NASCIC-2 trial was the first prospective, randomized, placebo-controlled trial that confirmed the efficacy of MP and justified its use as the first medication proved to improve the neurologic outcome for victims of SCI. Since then, its utility has grown rapidly and immediate administration has become the rule of care.[19,20]

Gerndt et al. analyzed 140 patient records with acute SCI admitted to a Level I trauma center, and compared different outcome parameters. The MP group had an increase in number of ventilated days and length of ICU stay; but also a shorter duration of rehabilitation. They concluded that a large-dose steroid increased utilization of resources during hospitalization.[21] According to the results of our study; MP did not increase utilization of resources, which was represented by the length of hospitalization, ICU stay and the number of ventilated days, as well as the number of tracheostomy cases. Large dosage of steroids did not prolong in-hospital rehabilitation. No evidence showing an increased utilization of medical resources after MP treatment was found in our analysis.

The evolution of neurologic function not only parallels biological changes in the spinal cord; it is also essential for the following rehabilitation therapy that can help the patient regain social activity. Recovery of neurologic status is not only the motive but also the cornerstone of the MP treatment. In-hospital and six-week changes in motor function were the measures of neurologic gain in this study. Although there were some improvements in these parameters, no significant difference in recovery was found between the two treatment groups.

Despite the results of NASCIC-2 and NASCIC-3, large-dose steroid treatment is still of concern to many physicians due to its well-known immunosuppressive action and its adverse effects in old-aged and trauma patients, particularly septic and gastro-intestinal complications.[13,22,23] Gerndt et al. reported an increase in pneumonia in the MP group. Although large-dose steroids induced early infection, they concluded that the steroid usage was safe and had no adverse impact on mortality.[21]

No significant increase in mortality and frequency of complications was noted between the two treatment groups in our study. When we divided the complications into seven categories (neurogenic bladder, UTI, pneumonia, pressure ulcer, respiratory failure, UGI bleeding, and other infections), again no significant differences were found, except UTI that appeared to occur more frequently in the MP group. When we measured infectious complications as a single parameter which included pneumonia, UTI, sepsis and "other infections", we indeed found a significant difference between the two groups. (P=0.038) The result strongly indicated that the patients were more likely to have infectious complications when receiving MP.

In France, Pointillart et al. prospectively evaluated 106 patients with SCI, addressed the controversy by analyzing the results of MP versus non-MP management in concurrently treated patients. They found no difference in neurologic recovery; instead, more infectious complications occurred.[12] Our finding was consistent with the observation of Pointillart et al.

There were some surprising results disclosed after analysis stratified by dosage of MP as the NASCIC-2 protocol, thus separating the 71 patients into two groups: standard dose and non-standard dose. The group of non-standard dosage included patients that received a smaller dosage of MP. The length of ICU stay and the number of tracheostomy cases increased significantly in the standard dose group, as well as the number of septic complications, particularly pneumonia. Interestingly both parameters of motor function change deteriorated in the non-standard dose group compared with the recovery gain in the other

group, although the difference was not significant. Owing to the small number in some sub-groups after stratification, the data should be verified carefully by further studies with a larger sample size. However, the stratified results might imply that the dosage of MP is crucial for its clinical consequence and impact in the patient's outcome, either positively or negatively.

Shortly after the release of NASCIC-1,[24] DeMaria et al. reported an increase in septic complications, not only in frequency but also severity, after use of corticosteroids for CNS trauma.[25] Since then, the contention around the risk and benefit of large-dose steroids persisted and many reports or reviews have been published.[10,26,27] Nasathurai et al. reported more sepsis and pneumonia in the MP group in NASCIS-3.[3] Gerndt et al. also reported that the incidence of pneumonia would increase after MP treatment.[21] The association between steroids and some adverse consequences, such as infection, delayed healing, gastro-intestinal complications, are widely accepted[14,22,23] The reason for use of large dosage steroids is only justified by the fact that neurologic recovery is the supreme priority for the SCI patient and there is currently no alternative medication. The consequences caused by large dosage of steroids should be emphasized and evaluated seriously if the results of such treatment are still in question.

Although we reviewed the charts of each patient extensively, this observation has its limitations because of the potential shortcomings of a retrospective study and the relatively small size of the sample. The results of this study should be interpreted with caution.

Conclusions

The present study could not confirm that the use of steroid would increase the utilization of resources during hospitalization, including length of hospitalization and ICU stays and number of ventilated days, and it would not delay the rehabilitation therapy that was essential for functional recovery. Although the use of MP treatment appeared safe in terms of mortality, the MP treatment did not show beneficial effects in motor function recovery in our observation. We found that patients receiving MP were more likely to have infectious complications. On the contrary, large-dosage therapy could increase the opportunity of serious complications such as pneumonia and the utilization of medical resources such as the ICU care and the number of tracheostomy cases. Controversy still exists; the value of MP in the treatment of acute SCI remains unconfirmed. Further rigorously controlled, randomized, prospective study, particularly a well-prepared stratification by the dosage and timing of MP administration, is essential for solving this puzzle.

Abbreviations

Abbreviations used in this paper: MP=methylprednisolone; SCI=spinal cord injury; MBP=mean blood pressure; RTS=Revised Trauma Score; GCS=Glasgow Coma Scale; ER=emergency room; NASCIS=the National Acute Spinal Cord Injury Study; UTI=urinary tract infection; UGIB=upper gastro-intestinal bleeding; ICU=intensive care unit; CNS=central nervous system

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以甲基去氫氧化可體松治療急性外傷性脊髓傷害病人的再評估

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使用甲基去氫氧化可體松（methylprednisolone）來治療急性外傷性脊髓損傷，仍然是充滿爭論的方法。本研究的目的是探討此種治療方法的醫療資源消耗、運動機能改變和併發症發生的情形。

研究對象是選擇自公元2000年6月至2001年5月共12個月間，首次住院的新發生急性外傷性脊髓損傷共110名病患，首先比較使用及未使用甲基去氫氧化可體松兩組間共13項人口學及臨床特徵（自變項），然後再比較並分析兩組間共10項預後指標（依變項）的差異。

此13項人口學及臨床特徵包括年齡、受傷原因、合併傷害數、修正後外傷分數、格拉斯哥昏迷指數、平均血壓、脊髓傷害的節數、完全性及形態、脊椎手術的數目及方式、接受復健治療的人數及受傷至住院間天數。

研究結果顯示，上述兩組間13項人口學及臨床特徵中，僅受傷至住院間天數此自變項呈現明顯差異（P=0.024）。使用甲基去氫氧化可體松會有較多的感染併發症發生（P=0.038），但在其他與醫療資源消耗和運動機能改變有關的預後指標上，兩組間並無明顯差異。以使用劑量來進行分層分析，結果顯示高劑量甲基去氫氧化可體松不但會增加加護病房住院天數（P=0.021）和接受氣管切開術人數（P=0.005），同時會增加肺炎（P=0.004）的發生機會。

所以我們認為，雖然使用甲基去氫氧化可體松會增加感染併發症的機會，但不會明顯增加住院中的醫療資源消耗。由於兩組間的死亡率並無明顯差異，所以使用甲基去氫氧化可體松應是安全的治療方法。但對於運動機能的改善則並未呈現明顯的改變。

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