Use of methylprednisolone in acute spinal injury

Ahmed M. Alkhani, *MD, FRCS (C),* ***Abdul-Sattar H. Ghomraoui,*** *MD.*

ABSTRACT

Objectives: To obtain an appraisal for the use of methylprednisolone (MP) in the early management of acute spinal cord injury (SCI) in our health system and the attitude to its use.

Methods: A printed questionnaire on MP in acute SCI was distributed to all major spinal and neurosurgical centers in Riyadh, Kingdom of Saudi Arabia between October and November 2001.

Results: A total of 31 replies were collected for statistical analysis. There were 23 replies from doctors (74%) who see 5 or more cases of acute SCI per year. Sixteen doctors (53%) use MP in acute SCI (National Acute Spinal Cord Injury Studies [NASCIS] protocol) regularly, 11 (37%) use it occasionally and 3 (10%) never use it. The use of MP in acute SCI was suggested as a standard of care by 16%, recommended only by 48% and considered optional by 35%. In addition, a review of the literature on the results of the NASCIS I, II and III was conducted.

Conclusion: Our results confirm the diversities in clinical practice regarding the use of MP in acute SCI. They also raise the issue of the need for specialized centers in spinal trauma with a unified protocol for treatment throughout the Kingdom.

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Few, if any injuries result in the physical and psychological devastation as seen with spinal cord injury (SCI) victims. The estimated incidence in the United States of America is 40/1,000,000/year,[1] this can be translated to 640 patients/year in the Kingdom of Saudi Arabia (KSA) where we lack exact figures. Motor vehicle accidents account for 50% of the cases followed by falls (20%).[1] Currently there is no available medical or surgical treatment for this devastating injury. The major volume of published research work in this field was directed toward prevention of secondary injury. Secondary injury is a cascade of events initiated by the primary trauma and results in biochemical and pathological changes that damage spinal axons secondarily when otherwise they should have survived. Possible mechanisms for this secondary injury include ischemia related to vasospasm or thrombosis, electrolyte changes at the cellular level, biochemical changes and accumulation of neurotoxic substances like catecholamine, glutamate, free radicals, prostaglandin and lipid peroxidation.[2-4] The use of systemic steroids like methylprednisolone (MP) was suggested to help prevent secondary injury.[2,5] The proposed mechanism included inhibition of free radicals formation and prevention of lipid peroxidation. This theory was tested clinically by the National Acute Spinal Cord Injury Studies (NASCIS) I, II and III.[6-8] The National Acute Spinal Cord Injury Study II and III concluded neurological improvement after using a mega dose of MP. Soon after, MP became a suggested standard of care in the treatment of acute SCI injury.[3,9-12] However, many recent publications started to question the benefits of this drug based on revisiting the statistical methodology used in the NASCIS or the observed

From the Division of Neurosurgery, (Alkhani, Ghomraoui) Department of Neurosciences, King Faisal Specialist Hospital and Research Centre and the Department of Surgery (Alkhani), College of Medicine, King Saud University, Riyadh, *Kingdom of Saudi Arabia*.

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Address correspondence and reprint request to: Dr. Ahmed Alkhani, Division of Neurosurgery, Department of Neurosciences, King Faisal Specialist Hospital and Research Centre, MBC - 76, PO Box 3354, Riyadh 11211, *Kingdom of Saudi Arabia*. Tel. +966 (1) 4647272 Ext. 32772 or 32773. Fax. +966 (1) 4424763. E-mail: alkhani@yahoo.com

adverse reactions in patients treated with the NASCIS recommended dose of MP.[13-20] In this study we elected to distribute a questionnaire to medical specialists treating patients with acute SCI in the city of Riyadh, KSA to obtain an appraisal on the use of this drug in our health system and the attitude toward its use. We also included a general review of the topic in our discussion.

Methods. A printed questionnaire was distributed to all major spinal and neurosurgical centers in the city of Riyadh, KSA between October and November 2001. The forms were distributed by mail, fax and personal delivery. It was consisted of 4 sections: data on the physician and his institution, the use of MP in acute SCI in their center and the use of MP in elective intradural spinal surgery. The fourth section contained open questions on recommendations to improve the current practiced management of spinal cord injuries in our society.

Results. Thirty-one replies were collected and used for statistical analysis. One response was incomplete and only the completed part was used. There were 26 forms (84%) completed by neurosurgeons and 5 forms (16%) by orthopedics specialized in spinal surgery. There were 23 forms (77%) completed by doctors in consultant positions and 7 forms (23%) by assistant consultant or senior registrar/registrar. Twenty-three doctors (74%) from those who completed the form do see patients with acute SCI, more than 5 cases per year. Regarding the use of MP in acute SCI (NASCIS protocol); 16 doctors (53%) use it all the time, 11 doctors (37%) use it occasionally and 3 doctors (10%) never use it. Based on their readings and clinical practice, 22 doctors (71%) believe that the use of MP is beneficial, 5 doctors (16%) believe it is not and 4 doctors (13%) are not sure. Only 5 doctors (16%) recommend MP to be a standard of care, 15 doctors (48%) elected MP to be recommended and 11 doctors (35%) elected it to be optional only. For 21 doctors who perform elective intradural surgery; 11 doctors (53%) use MP (NASCIS protocol) occasionally and 4 doctors (19%) use it all the time and 6 doctors (29%) never use it. The open ended questions on recommendations to improve the management of patients with acute SCI in our society showed anonymous agreement on the need for specialized trauma centers for the treatment of acute SCI. In addition, improving public awareness, traffic safety and paramedic standards was also suggested.

Discussion. The use of corticosteroids in the treatment of SCI was first evaluated in a clinical trial on humans in 1984 by Bracken et al.[6] This was the first of 3 NASCIS - I, II and III.[6-8] The 3 NASCIS are multicenteric double-blind randomized trials examining the efficacy of high dose MP in improving patients with acute SCI. Corticosteroids were advocated earlier in the treatment of acute SCI based on animal experiments.[21]

In NASCIS I (1984),[6] 330 patients with acute SCI were divided into 2 groups. The first group received a high dose of MP (1,000 mg as a bolus followed by 250 mg every 6 hours for 10 days) and the second group received low dose MP (100 mg as a bolus followed by 25 mg every 6 hours for 10 days). There was no control placebo group in this trial. The trial results illustrated no significant differences in motor or sensory outcomes observed between the 2 groups. The high dose group had increased mortalities and morbidities such as infections and gastrointestinal bleeding.

In NASCIS II (1990),[7] 487 patients with acute SCI were divided into 3 groups. The first group received MP at 30 mg/kg as a bolus then maintenance of 5.4 mg/kg/hr for 23 hours. This very high dose MP was suggested in animal studies to result in a more favorable outcome. Methylprednisolone doses studied in NASCIS I were below this therapeutic threshold. The second group received naloxone hydrochloride, an opiate receptor blocker suggested to improve neurological recovery in animal studies. The third group received placebo. National Acute Spinal Cord Injury Study II was the only NASCIS that compared MP to placebo. Inclusion criteria in this study included patients with acute SCI treated within 12 hours and exclusion criteria included; nerve root injury, cauda equina injury, gun-shot wounds, life threatening morbidity, use of narcotics and steroids, pregnancy and age under 13 years. National Acute Spinal Cord Injury Study II results at 6 weeks after the injury reported naloxone to be not effective. In the MP group, counting all patients (162) there was no motor or sensory improvement observed. A sub-group of patients treated within 8 hours from injury (66) had a favorable (statistically significant motor ($p = 0.048$) and sensory ($p = 0.034$) improvement) outcome as compared to a placebo group. National Acute Spinal Cord Injury Study II results at 6 months showed that naloxone is not effective, in the case of MP for all patients ($n = 162$) there were no motor, but sensory improvements. For the group of patients treated within 8 hours (66) there were again statistically significant motor ($p = 0.033$) and sensory improvements ($p = 0.016$-0.030) as compared to placebo. The study also reported complications related to the use of MP including wound infections (7.1%) and gastrointestinal bleeding (4.5%). National Acute Spinal Cord Injury Study II results at 12 months were published subsequently and continue to show the significant motor improvement ($p = 0.03$) but only to patients treated within 8 hours from injury.[22] Since the publication of NASCIS II many trauma centers have started to adapt this protocol and MP became recommended as a standard of care in treating patients with acute SCI. This had major influences on clinical as well as medico-legal aspects in the management of acute SCI.[9,10]

In NASCIS III (1997),[8] 499 patients with acute SCI treated within 8 hours were randomized into 3 groups. The first group received MP for 24 hours (NASCIS II protocol). The second group had also NASCIS II protocol but the MP maintenance dose was extended to

48 hours. The third group had also NASCIS II protocol in addition to tirilazad mesylate, a potent lipid peroxidation inhibitor with potentially fewer complications than anticipated with MP. There was no placebo group in this study. National Acute Spinal Cord Injury Study III results illustrated that tirilazad adds no benefits. When MP (NASCIS II protocol) started less than 3 hours after injury; 48 hours extension of MP maintenance had no advantages. But when it was started 3-8 hours after injury; 48 hours of MP improved neurological outcome ($p = 0.03$).[23]

National Acute Spinal Cord Injury Study II & III results were taken initially as good evidence to recommend the use of MP as an accepted standard of care in treating patients with acute SCI.[3,9,12] Failure to deliver this medication was counted as a case of medical negligence in an United States of America court in Southern California even before 1990.[17] However, recent criticism of the data analysis results and conclusions of NASCIS II raised a big question mark on the indications and safety of the drug. In addition, the clinical experiences of many trauma centers with MP in terms of complications resulted in uncertainty about MP as a standard treatment in acute SCI.[13-17,19,24-27] More recently, a published comprehensive review of the topic recommended MP for acute SCI as an option knowing the risks and benefits.[28]

For this uncertainty regarding MP to resolve, we will need another large prospective randomized multicenteric study comparing MP to placebo. Obviously such a study is not that simple and may face many ethical concerns. Recently, some medical association started to define their own protocol and standards based on recommendations of an elected committee.[18,28] In our study we aimed at exploring the opinions and current practice of medical specialists treating acute SCI in our community through this simple questionnaire survey. The results came back as expected, variation in the clinical practice indicating that the use of MP is not widely accepted as a standard of care. In light of these results, the authors do recommend the use of MP in acute SCI (NASCIS protocol) in younger patients with a relatively low risk in using mega dose steroid.

In conclusion, our results confirm the diversities in the clinical practice regarding the use of MP in acute SCI. Spinal surgeons in our health system do not consider MP a standard of care in these cases. The study raised an issue regarding the need for specialized committees to define certain standards in the medical practice as acceptable to our local needs and available facilities. It also demonstrates the need for specialized centers in spinal trauma and improving the paramedics' services with special focus on handling patients with acute SCI.

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Title: The use of intrathecal baclofen for the management of spasticity

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Abstract

Spasticity is a common complication of neurologic disorders like spinal cord injury, multiple sclerosis, traumatic brain injury and cerebral palsy. lntrathecal administration of baclofen is a useful new adjunctive treatment for spasticity in patients who have not responded to local treatment or oral agents. Baclofen is a gamma-aminobutyric acid analogue that binds to gamma-aminobutyric acid "B" receptors and likely acts at both the spinal and supraspinal levels. lntrathecal administration requires lower doses to produce therapeutic effect and blood levels may be 1/100 of those when the drug is taken orally. A test dose of baclofen produces effects within 30 to 60 minutes, peaks at 4 hours and lasts up to 8 hours. The baclofen pump provides drug delivery in precisely regulated doses adjusted to the needs of the patient. Side effects may include sedation, leg weakness and nausea. Infection is an uncommon complication. Potentially fatal overdose associated with respiratory and cardiovascular depression has been reported in less than 2% of patients. Over time, tolerance may develop and the dose must be increased. Patients successfully treated with baclofen report dramatic reduction in their spasticity with corresponding improvement in their quality of life and function. The literature suggests baclofen is cost effective because it reduces hospitalizations from spasticity related medical complications.