

POSITION PAPER

NATIONAL ASSOCIATION OF EMS PHYSICIANS

HIGH-DOSE STEROIDS FOR ACUTE SPINAL CORD INJURY IN EMERGENCY MEDICAL SERVICES

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POSITION STATEMENT

It is the position of the National Association of EMS Physicians (NAEMSP) that:

1. The evidence on use of high-dose steroids for acute spinal cord injury remains inconclusive.
2. No research exists demonstrating any value of out-of-hospital treatment for acute spinal injury with high-dose steroids.
3. The potential for serious side effects from high-dose steroid administration is significant and must be considered against any proposed benefit.
4. The use of high-dose steroids for the treatment of acute spi-

nal cord injury should not be considered the standard of care for out-of-hospital emergency medical care.

INTRODUCTION

Acute spinal cord injury (ASCI) is a potentially disabling condition that has been extremely resistant to treatment. Emergency medical services (EMS) providers are often among the first members of the health care team to treat victims of ASCI. Although initial human and animal studies indicated that high-dose corticosteroid therapy might be an effective therapy for ASCI, subsequent human and animal studies have not been able to reproduce the beneficial effects described in the earlier research. High-dose corticosteroid therapy for the treatment of ASCI was introduced to prehospital care in the 1980s. It was postulated that early administration of corticosteroids could limit the severity of neurologic deficit associated with ASCI by stabilizing neuronal membranes and reducing inflammation and swelling. The recommended corticosteroid for acute spinal cord injury was methylprednisolone (MP), and the doses were large. Prior to this recommendation, many EMS services carried standard doses, typically 125 mg, of MP for use in severe allergic

reactions, for anaphylaxis, and for difficult cases of asthma and chronic obstructive pulmonary disease. Few carried enough MP (30 mg/kg) to treat ASCI as recommended by early studies. Thus, some EMS systems prepared a special "spinal cord injury kit" that contained adequate quantities of the drug.

REVIEW

The use of potent anti-inflammatory drugs, such as corticosteroids, in the management of neurologic trauma has always been intriguing. In the 1970s and 1980s, researchers began to look at the use of these drugs for the treatment of ASCI. Initially, the studies were limited to laboratory animals. Later, several human trials were completed.

The first important publication of this work was the first National Acute Spinal Cord Injury Study (NASCIS 1). In that study, patients received either a 1,000-mg infusion of MP followed by a bolus of 250 mg every six hours for 10 days, or they received a 100-mg infusion of MP followed by 250 mg every six hours for 10 days. No significant improvements were noted in either group.^{1,2} Following that study, new data from ongoing animal studies suggested that the MP dose used in NASCIS 1 was too low. Instead, a dose of 30 mg/kg of body weight

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was felt to be the therapeutic threshold.^{3,4} Based on this finding, researchers embarked on a second study, termed NASCIS 2.

In NASCIS 2, patients were divided into three treatment groups. One group received high-dose MP (30-mg/kg bolus followed by an infusion of 5.4 mg/kg per hour for 24 hours), the second group received a high dose of the narcotic antagonist naloxone (5.4-mg/kg bolus followed by an infusion of 4.0 mg/kg per hour for 23 hours), and the third group received a placebo as a control. Naloxone was included in the study, as some earlier studies had found that it improved systemic hypotension, spinal cord blood flow, and neurologic recovery in laboratory animals.⁵⁻⁸ In the NASCIS 2 study, patients, physicians, and researchers were blinded as to which patients were receiving which therapy. They found that patients who received high-dose MP had "significant improvement" compared with those in the other two study groups.⁹ When they further analyzed the data, they found that patients who received high-dose MP within eight hours of injury had the best outcomes.¹⁰ The findings were felt to be highly significant, and both the media and practitioners were notified of the findings by fax and express mail before they were published in peer-reviewed journals.¹¹ In a one-year follow-up study to the NASCIS 2 study, the same researchers reported that the treatment group who had received MP within eight hours of injury had increased recovery of neurologic function at six weeks, at six months, and one year after their injury.¹⁰ Further, reporting of a highly selected data subset (right-sided motor function) indicating statistically significant improvement was not correlated with any significant clinical or functional improvement.

In a follow-up study, subsequently termed NASCIS 3, researchers looked at extended

dosing regimens of high-dose MP (following the NASCIS 2 schedule) for a period of either 24 or 48 hours. In addition, they compared MP therapy with a drug (tirilazad mesylate) thought to enhance spinal cord recovery. They concluded that patients who received high-dose MP within three hours of injury should be maintained on the treatment regimen for 24 hours, whereas patients who received the first bolus between three to eight hours after injury should be maintained on steroid therapy for 48 hours.¹²⁻¹⁴ However, this study clearly exposed the significantly increased occurrence of adverse events such as infection, gastrointestinal bleeding, and death due to respiratory compromise.

Bracken, the lead investigator of the NASCIS studies, performed a meta-analysis of five studies that included the three NASCIS trials, a Japanese study, and a French study. He reported that the methodologic quality was high for the NASCIS studies and moderate to low for the Japanese and French studies. Based on his meta-analysis, Bracken concluded, "High-dose MP given within 8 hours of acute spinal cord injury is a safe and modestly effective therapy that may result in important clinical recovery for some patients."¹⁵ In a similar review for *The Cochrane Library*, Bracken analyzed data from the same five studies and reported, "This analysis indicates significant recovery in motor function after MP therapy when administration commences within 8 hours of injury." He further reported that high-dose MP therapy was also effective for whiplash injuries and for improving recovery after surgery for lumbar disc disease.¹⁶

Following publication of the NASCIS studies, clinicians began to take a closer look at the data. Nesathurai critically reviewed the NASCIS 2 and NASCIS 3 trials and found that the positive results claimed by researchers in NASCIS 2

and NASCIS 3 had not been reproduced. The Japanese study that was asserted to replicate the NASCIS 2 study (and was included in Bracken's meta-analysis¹⁷) was found to be from a journal not indexed on Medline, which had used dubious methodology.¹⁷ Furthermore, when Nesathurai analyzed the NASCIS 2 study in detail, he found that the reported improvements in neurologic function secondary to high-dose MP were relatively modest and might not warrant the risks of treatment.¹⁸

The French study included in Bracken's meta-analysis compared neurologic outcomes of ASCI patients who received nimodipine, MP, or both with a nontreatment control group. One hundred six patients were enrolled in the study, and the investigators found no benefit from any of the pharmacologic regimens studied.¹⁹

Coleman et al. similarly analyzed the NASCIS 2 and 3 studies. They concluded that there were inadequacies in both the statistical methodology and reporting used in the NASCIS trials. Their list of concerns included questionable interpretations, choice of methodologies, poorly explained and unjustified scales of measurement, and an excessive number of statistical tests performed. More importantly, they concluded that the statistical procedures were poorly documented, and they were concerned that the preliminary data were never made available.²⁰

Short et al. undertook a narrative review of the literature related to high-dose MP for ASCI. They included three clinical trials and six cohort studies and concluded, "The evidence produced by this systematic review does not appear to support the use of high-dose MP in ASCI to improve neurological mortality. A deleterious effect on early mortality and morbidity cannot be excluded by this evidence."²¹

Hurlbert completed an evidence-based analysis of the role of steroids

for ASCI and found nine studies that had attempted to evaluate the role of steroids in nonpenetrating ACSI. All of the studies failed to demonstrate improvements secondary to steroid administration.¹¹

Merola et al. studied microscopic tissue changes following high-dose MP therapy. They administered high-dose MP followed by a 23-hour human-dose-equivalent infusion of MP to rats. They found that the MP reduced the development of severe edema and preserved spinal cord structure adjacent to the zone of injury, but did not alter the development of spinal cord necrosis or astrocytic response at the zone of injury.²² Similarly, when Rabchevsky et al. evaluated the efficacy of MP therapy for rats with surgically induced ACSI, they found no improvement. Their conclusion was that "the results of our study add to the growing evidence that the use of MP as a standard therapy or a positive control may not be justified."²³

Galandiuk et al. studied 32 patients with cervical or upper thoracic spinal cord injuries, 22 of whom had complete spinal cord injuries. Of these, 14 patients had received steroids after injury. They found that the length of hospital stay was longer (44.4 vs. 27.7 days) for the patients who had received steroids, and that the rate of infectious complications was higher. They concluded that vital immune responses were adversely affected in the patients who had received steroids.²⁴ Later studies detailed numerous reports of significant complications associated with high-dose MP administration. These complications tended to fall into three categories: infectious (severe pneumonia, septicemia), delayed wound healing, and hyperglycemia. The literature has clearly indicated that the incidence of complications is increased in patients who receive high-dose MP.^{19,25}

Qian et al. postulated that the improvement in motor function seen following high-dose MP ther-

apy may actually have been due to recovery from steroid-induced myopathy rather than any improvement in neurologic function resulting from spinal cord healing.²⁶

Spencer and Bazarian published a systematic review abstract from the *Cochrane Database of Systematic Reviews*. They questioned some methodologic issues in the core trials that had been analyzed in the Cochrane Library review.¹⁶ In these studies, neurologic improvement was measured by calculating the difference between two neurologic exam scores taken on admission and at each follow-up time interval. Motor function over 14 motor segments was evaluated by two examiners using a six-point scale between 0 and 5, yielding a total score between 0 and 70. Sensory function was measured over 29 dermatomal segments on a three-point scale, ranging from 1 to 3, with a total score between 29 and 97. Using such a large range of variables increases the likelihood of error, as there is no evaluation of interrater reliability. Thus, when scoring motor function, a one-point difference over each motor segment would result in a 14-point fluctuation in the final score. Overall, high-dose MP was associated with only a four-point improvement in motor function score. Although this finding was statistically significant, a four-point improvement distributed over 14 motor segments might not indicate clinically significant improvement.²⁷

Based on these studies, as well as their own review of the NASCIS studies, Hurlbert et al. concluded that high-dose MP for ACSI is an inappropriate standard of care.^{28,29} Short concluded, "High-dose MP cannot be justified as a standard treatment in ACSI within current medical practice."³⁰

As a result of the premature promulgation of the value of high-dose MP use in ACSI, it appears that its use in the out-of-hospital

arena was a foregone conclusion. However, no research exists indicating the value of high-dose MP for the treatment of ACSI by out-of-hospital emergency medical services.

CONCLUSIONS

The findings reported in the NASCIS 2 and NASCIS 3 studies have not been duplicated. Furthermore, the methodology used in the NASCIS studies was questionable, making its conclusions suspect. Existing publications advocating the use of high-dose MP for ACSI as efficacious used the same data and were published by the same group of investigators. Despite attempts to refine the data through republication and meta-analysis, the final conclusions remain weak. Consequently, there is no indication that high-dose MP is effective for ACSI. Furthermore, the side effects of high-dose MP therapy, which were minimized in the NASCIS studies, were found to be significant in several subsequent studies.

Until the true value of high-dose steroids for the treatment of acute spinal cord injury is determined—as well as what, if any, benefit may exist for out-of-hospital administration—NAESMP does not support their routine use in EMS.

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