

Original Article

High-dose methylprednisolone may cause myopathy in acute spinal cord injury patients

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Study design: Prospective cohort study.

Objective: Although Bracken *et al* have demonstrated a significant neuroprotective effect of high-dose intravenous (i.v.) methylprednisolone (MP) within 8 h post spinal cord injury (SCI), this practice has recently been challenged. We hypothesized it is possible that acute corticosteroid myopathy (ACM) may occur secondary to the MP. This pilot study was performed to test this hypothesis.

Setting: University of Miami School of Medicine/Jackson Memorial Hospital, Miami VA Medical Center, FL, USA.

Methods: Subjects included five nonpenetrating traumatic SCI patients, who received 24 h MP according to National Acute Spinal Cord Injury Studies (NASCIS) protocol, and three traumatic patients who suffered SCI and did not receive MP. Muscle biopsies and electromyography (EMG) were performed to determine if myopathic changes existed in these patients.

Results: Muscle biopsies from the SCI patients who received 24 h of MP showed muscle damage consistent with ACM in four out of five cases. EMG studies demonstrated myopathic changes in the MP-treated patients. In the three patients who had SCI but did not receive MP, muscle biopsies were normal and EMGs did not reveal evidence of myopathy.

Conclusion: Our data suggest that MP in the dose recommended by the NASCIS may cause ACM. If this is true, part of the improvement of neurological recovery showed in NASCIS may be only a recording of the natural recovery of ACM, instead of any protection that MP offers to the injured spinal cord.

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Introduction

Since the National Acute Spinal Cord Injury Studies (NASCIS), high-dose methylprednisolone (MP) has been used worldwide for the treatment of the acute spinal cord injury (SCI) patients.^{1,2} Since this time however, considerable controversy has questioned the validity of the results of these original studies because of their scientific limitations.^{3–9} Another issue that may have gone overlooked in the NASCIS is the possibility

of acute corticosteroid myopathy (ACM) that MP may cause.^{10,11} The dosage of MP recommended by the NASCIS is the highest dose of steroids to be recommended for use during a 24- or 48-h period for any clinical condition.^{1,2} Based on this information, we chose to study traumatic SCI patients who had and had not received MP according to NASCIS standards for histologic and electromyographic evidence of ACM. We hypothesized that those subjects who received MP would show evidence of myopathy whereas those who did not receive MP would not.

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Methods

Subjects

The Institutional Review Board approval was obtained prior to the study. Five cases presented as the MP treatment group are males, 22–65 years of age, with acute nonpenetrating traumatic SCI treated with 24 h high-dose intravenous (i.v.) MP, according to the NASCIS protocol (i.v. MP 30 mg/kg in the first hour and maintained on 5.4 mg/kg/h for 23 h). Three acute SCI patients who did not receive i.v. MP serve as controls. (Two patients sustained gunshot wounds, and one was involved in a motor vehicle accident and came to the hospital after 8 h.) Exclusion criteria include patients age younger than 18 years and more than 65 years of age, already receiving maintenance steroids at the time of injury, pregnant women, those with a history of myopathy or neuropathy, and those who have received medication that could cause either acute rhabdomyolysis (amphetamines, heroin, diazepam, barbiturates, amphotericin B, isoniazid) or inflammatory myopathy (D-penicillamine, procainamide, levodopa, phenytoin).¹²

Procedure and measures

Muscle biopsy and electromyography (EMG) were performed for the diagnosis of ACM.^{13–19} Muscle biopsy shows direct evidence of muscle damage from ACM.²⁰ EMG is an electrodiagnostic study and is performed to confirm ACM from a functional point of view.¹² To increase the accuracy of the diagnosis of ACM, both measurements were applied in the cases reported.

All the SCI cases reported underwent surgical internal fixation and spinal fusion to stabilize the spine. Muscle biopsies were performed during the surgery by the neurosurgeons. The timing of the spinal surgery and muscle biopsy was decided by the surgeons according to the patient's clinical condition. Muscle biopsy samples (1 cm³) were obtained from the paraspinal muscles at the surgical incision, above the SCI level. The tissues were handled in a manner similar to that used for diagnostic muscle biopsies. A portion of the specimen was snap frozen in isopentane cooled with liquid nitrogen for histochemistry. Another portion was fixed in formalin for paraffin embedding. Cryostat sections were processed for myofibrillar adenosine triphosphatase (AT-Pase) at three pH levels (4.3, 4.4, 9.4), to identify fiber types. Other histochemical studies were also performed, including nicotinamide adenine dinucleotide-tetrazolium reductase (NADH-TR), succinic dehydrogenase (SDH), alkaline phosphatase, esterase, periodic acid-Schiff reaction (PAS) and Gomori Trichrome.²⁰ Changes in muscle fibers were assessed by a neuropathologist, blinded to the case history.

EMG was performed on the study patients. Bilateral biceps, deltoid and quadriceps muscles were tested twice in 1 month (at 2 weeks and 4 weeks after the SCI). Any abnormal spontaneous activity (including positive sharp

waves and fibrillations) was recorded. Recruitment patterns were also recorded, as well as measuring the amplitude of the motor unit potentials. Nerve conduction studies (NCS) were performed bilaterally on the ulnar and tibial nerves. EMG and NCS were performed by a physiatrist, not blinded to the case history.

Results

Case 1

This 25-year-old man suffered a C4 ASIA B SCI from a motor vehicle accident. The subject received 24 h of MP according to the NASCIS protocol. A C4 corpectomy, cord decompression and spinal fusion with fibula autograft were performed 5 days after his SCI due to cord compression and instability of the spine. Muscle sample was obtained from the cervical paraspinal muscles during the surgery. Muscle biopsy showed clear evidence of acute myofiber necrosis (Figure 1) and severe type II muscle atrophy (Figure 2). EMG performed at 2 and 4 weeks after SCI and MP treatment demonstrated positive sharp waves and fibrillations in all the muscles tested (at bilateral biceps, deltoid and quadriceps). Recruitment pattern was not tested because of his high level of injury. NCS were normal. This patient was ventilated for 9 weeks and was still ventilator dependent at the time of discharge. He also had a left femoral fracture.

Case 2

This 29-year-old man suffered a C5 ASIA A SCI from a motor vehicle accident. The subject received 24 h of MP according to the NASCIS protocol. A C5 corpectomy, cord decompression and spinal fusion were performed 7 days after his SCI. Muscle sample was obtained from the cervical paraspinal muscles during the surgery.

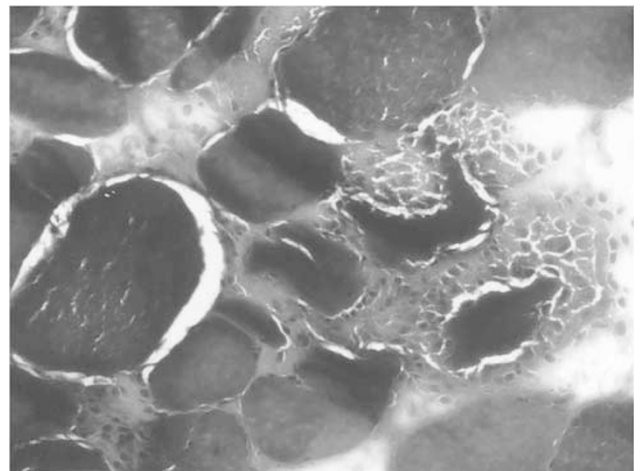


Figure 1 Gomori Trichrome staining of the cervical paraspinal muscle from case 1. It shows invasive myophagocytosis in myofibers with relatively preserved sarcoplasmic contents. Magnification: $\times 40$



Figure 2 ATPase staining of the cervical paraspinal muscle from case 1 (at pH 9.4, type II muscle fibers stain darker). It shows moderate to severe type II myofiber atrophy. Magnification: $\times 20$

Muscle biopsy also showed evidence of acute myofiber necrosis and severe type II muscle atrophy. EMG was performed on the patient at 2 and 4 weeks after his SCI. Positive sharp waves and fibrillations were noted in all the muscles tested (at bilateral biceps, deltoid and bilateral quadriceps). Increased recruitment and decreased amplitudes of the motor unit potentials were noted in the muscles above the SCI level (at bilateral biceps and deltoid). Recruitment could not be tested below the SCI level (at bilateral quadriceps) because of the lack of muscle movement. NCS were normal. He was ventilated for 8 weeks and was still ventilator dependent at the time of discharge. This patient had a left forearm fracture.

Case 3

A 22-year-old man with C5 ASIA A SCI from diving accident. He was treated with 24 h of MP. The patient underwent a C5 corpectomy, cord decompression and spinal fusion with allograft about 72 h after injury. Muscle biopsy was obtained during the surgery at the cervical paraspinal muscles and showed mild myofiber necrosis and type II muscle atrophy. This patient refused EMG. He was also ventilated for 8 weeks and was still ventilator dependent by the time of discharge.

Case 4

A 65-year-old man with T2 ASIA B SCI from a fall. He was treated with 24 h of MP. A T2 and T3 corpectomy, decompression and spinal fusion with allograft was performed about 72 h after injury. Muscle biopsy was obtained during the surgery from the thoracic paraspinal muscles and showed mild myofiber necrosis and type II muscle atrophy. EMG was performed on the patient at 2 and 4 weeks after his SCI. Positive sharp waves and fibrillations were noted in all the muscles

tested (at bilateral biceps, deltoid and bilateral quadriceps). Increased recruitment and decreased amplitudes of the motor unit potentials were noted in the muscles above the SCI level (at bilateral biceps and deltoid). Recruitment could not be tested below the SCI level (at bilateral quadriceps) because of the lack of voluntary muscle movement. NCS were normal.

Case 5

This 34-year-old man presented with a T7 ASIA B SCI after motor vehicle accident. He received 24 h of MP. Immediately prior to completion of the IV MP, the patient was pushed to the operating room with the MP drip and underwent spinal surgery. A T7 and T8 corpectomy, cord decompression and spinal fusion with allograft was performed for cord compression and instability of the spine. Muscle sample was obtained from the thoracic paraspinal muscles. Muscle biopsy failed to show any muscle damage. However, EMG at 2 and 4 weeks demonstrated positive sharp waves and fibrillations in all the muscles tested (at bilateral biceps, deltoid and bilateral quadriceps). Increased recruitment and decreased amplitudes of the motor unit potentials were noted at above the SCI level (at bilateral biceps and deltoid). Recruitment could not be tested below the SCI level (at bilateral quadriceps) because of the lack of voluntary muscle movement. NCS were normal.

Cases 6, 7 and 8 (no MP treatment)

Case 6 is a 27-year-old man with C8 ASIA D SCI. Case 7 is a 19-year-old man with C4 ASIA A SCI. Case 8 is a 38-year-old man with T12 ASIA A SCI. Patients in cases 6 and 7 were injured from gun shot wounds and did not receive MP.²¹ Both patients underwent spinal surgery within 24 h after SCI for leaking of spinal fluid and instability of the cervical spine. Muscle biopsies were performed during the surgery from the cervical paraspinal muscles. Patient in case 7 was ventilator dependent for over a year before he died from respiratory failure. Patient in case 8 was injured from a motor vehicle accident overseas and also did not receive MP. He was transferred to our center and underwent spinal surgery for cord compression and spine instability 5 days after his injury. A T12 and L1 decompression, fracture reduction and T11/T12, L2/L3 pedicle screw instrumentation was performed. Muscle biopsy was obtained from the thoracic paraspinal muscles during the surgery. Muscle histologies from all three patients who did not receive MP were normal. EMGs were performed at 2 and 4 weeks after injury in all three patients who did not receive MP, and were normal.

Discussion

Subsequent to the reports of NASCIS in 1990 and 1997,^{1,2} high-dose i.v. MP protocol has been widely used for the care of patients with nonpenetrating acute SCI.

However, there have been some disagreements as to whether the NASCIS actually showed the benefits of this high-dose MP.^{3–9} Currently, MP is recommended as an option in the treatment of acute SCI patients that should be undertaken only with the knowledge that the evidence suggesting harmful side effects is more consistent than any suggestion of clinical benefit.^{5,6} One issue, not mentioned in the NASCIS studies and has not been received much attention in the literature to date, is the possibility of ACM that the high-dose i.v. MP may cause.^{10,11}

Several animal and clinical studies have attributed the occurrence of ACM to the use of high doses of corticosteroids in a short period of time.^{13–19,22–24} Nava *et al.*,²² in their rat model, showed that i.v. MP 80 mg/kg/day for 5 days could induce severe limb and respiratory muscle wasting and predominantly type IIb muscle atrophy. Afifi and Bergman²³ in their rabbit model, showed that cortisone acetate 10 mg/kg could cause muscle damage as early as 4 h after given the medication. In human clinical studies, high doses of steroids (up to 3 g/day) are often administered for patients in status asthmaticus or rejection after organ transplantation.¹⁸ ACM has been reported with increased frequency,^{13–19} in patients who have been treated with high-dose corticosteroids since its first description by MacFalane and Rosenthal²⁴ in 1977. ACM differs from the slowly progressive steroid myopathy described by Cushing²⁵ in 1932. In ACM, the process is general weakness involving both distal and proximal muscle groups with degeneration of type I as well as type II muscle fibers. Considerable muscle fiber necrosis occurs, resulting in marked elevation of creatine phosphokinase and release of myoglobin.¹⁸

The protocol recommended by NASCIS 3 trial is that patients receive i.v. MP treatment 30 mg/kg in the first hour and if the initiating MP treatment is within 3 h of injury, the patient will be maintained on 5.4 mg/kg/h for 24 h. For the patients initiating treatment 3 to 8 h after injury, their maintenance dose will be extended for 48 h.² This translates into 159.6 mg/kg for the first 24 h and 289.2 mg/kg in 48 h. For a 75-kg SCI patient, 11.97 g of MP would be given within 24 h and 21.69 g of MP would be given within 48 h. This is the highest dose of steroids ever be recommended during a 24 or 48 h period for any clinical condition.¹⁰ A measure of 3 g of hydrocortisone daily for 5 days can induce ACM for an asthma patient,¹⁸ 80 mg/kg/day MP for 5 days can induce severe limb and respiratory muscle wasting in rats²² and cortisone acetate 10 mg/kg/day can cause histologic changes within 4 h in the muscles of rabbits.²³ It follows then that 11.97 g of MP in 24 h or 21.69 g of MP in 48 h may cause some degree of damage to the muscle of a 75 kg acute SCI patient.¹⁰ In animal studies, the earliest and most marked changes were noted in the diaphragm.^{22,23} Clinically, high-dose MP increases the risks of severe sepsis and pneumonia.^{26–28} These risks are dose dependent.²⁸ Sepsis and pneumonia lead to intubation, which involves manipulation of the neck, and ACM may contribute to difficulty in weaning the

SCI patients from the ventilators.^{26–28} This prolongs hospitalization of the SCI patients and increases costs of the SCI patient care.²⁶

In the cases we presented, the muscle biopsies from cases 1 and 2 were performed 5 and 7 days after MP treatment and showed clear evidence of muscle necrosis and severe type II muscle atrophy. Muscle samples from cases 3 and 4 were obtained 3 days after MP and showed only mild myofiber necrosis and muscle atrophy. Muscle sample in case 5 was obtained immediately prior to the patient completing the 24-h infusion of MP, and muscle in this case failed to show muscle damage. However, if MP does cause myopathy in human subjects, it can be speculated that at least 5 to 7 days are needed for the muscle biopsy to show significant histological changes.

EMG showed abnormal spontaneous activities at 2 and 4 weeks in those patients treated with MP and underwent EMG studies (except the patient in case 3 who refused EMG). In cases 2, 4 and 5, EMGs demonstrated abnormal spontaneous activities at above and below the SCI levels. For the patient in case 1, his SCI level was so high (at C4) that EMG could only be performed below his SCI level and showed abnormal spontaneous activities. It is difficult to evaluate recruitment and motor unit potentials in the muscles below the SCI level because of the lack of voluntary muscle contraction. In cases 2, 4 and 5, recruitment patterns could only be tested in the muscles above the SCI levels and showed increased recruitment and decreased amplitudes of the motor unit potentials. Recruitment could not be tested in the patient in case 1 because all the testing muscles were below the SCI level and were not voluntarily moveable. In the three patients who did not receive i.v. MP (cases 6, 7 and 8), EMGs were normal. Nerve conduction studies were performed in all the patients participated in this study and did not show peripheral nerve injury. These data, from an electrodiagnostic point of view, suggest that the muscles in the patients who received MP were undergoing myopathic changes.

ACM has a natural healing process and the improvement of ACM is usually between 6 and 8 months.¹⁸ In NASCIS studies, acute SCI patients were followed for 6 weeks and 6 months.^{1,2} Coincidentally, this is just within the same window for the spontaneous motor recovery of the ACM. If the high-dose MP does cause ACM, and ACM recovers naturally within 6 months, the improvement of neurological recovery (especially the motor scales) showed in NASCIS may in part be due to the natural motor recovery associated with ACM, rather than any additional neuroprotection that MP offers to the injured spinal cord.¹⁰

Conclusion

Our limited data suggest that the i.v. MP protocol recommended by the NASCIS trials may cause ACM. Further research is needed to confirm these preliminary findings. If this is proved to be true, it is going to be critical to differentiate the reported therapeutic effects of

MP from the spontaneous recovery of muscle after MP-induced myopathy. Nevertheless, based upon these data and other reports,^{3–9} we support the belief that the treatment of acute SCI with MP may have been adopted very quickly. We feel that additional prospective, randomized clinical trials of neuroprotective strategies are necessary and that it is not unethical to withhold MP from the SCI patients.

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