Gray Area: Methylprednisolone in Spine Trauma

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BUENOS AIRES — Glucocorticoid steroids are widely used to treat acute spinal cord injuries, but there is no clear consensus on their use, reported Dr. Keith D.K. Luk at the annual conference of the International Society of Orthopaedic Surgery and Traumatology.

The initial spinal cord injury triggers a complex cascade of molecular and cellular events. Lipid peroxidation of cellular membranes occurs as a secondary effect of spinal cord injuries and results in irreversible damage, said Dr. Luk, chair professor and head of the department of orthopedics and traumatology at the University of Hong Kong.

The National Acute Spinal Cord Injury Study (NASCIS) group conducted the first randomized, multicenter clinical study to examine the efficacy of methylprednisolone for acute spinal cord injury. The prevailing assumption of the benefits of methylprednisolone precluded the inclusion of a placebo group in the study design, as it was considered unethical to deny patients a treatment considered to be the standard of care. Thus, all patients in NASCIS I received methylprednisolone.

NASCIS I, initiated in 1979, compared functional outcome in 330 patients randomized to receive a 10-day regimen of methylprednisolone by intravenous bolus of either a low dosage of 100 mg per day or a high dosage of 1,000 mg per day (JAMA 1984;251:45-52). Outcome was assessed at 6 months and 12 months. Unexpectedly, the results showed no significant differences in neurologic benefit. The higher dose of methylprednisolone was associated with increased risk of infection, with no apparent increase in neurologic benefit.

A second clinical study (NASCIS II) was undertaken in which 162 patients were given a higher dose of methylprednisolone over a shorter period of time, and 171 patients received a placebo (N. Engl. J. Med. 1990;322:1405-11). The methylprednisolone regimen consisted of an intravenous bolus of 30 mg/kg, followed by a 23-hour infusion of methylprednisolone at 5.4 mg/kg per hour. A third treatment group of 154 patients received 24-hour dosing with naloxone, an opiate receptor antagonist.

High-dose methylprednisolone treatment initiated within 8 hours showed significant neurologic benefit, and the functional benefits were sustained at 6 weeks, 6 months, and 1 year. Treatment had to be given within an 8-hour window after the initial injury, before the onset of lipid peroxidation.

Conclusions of NASCIS II were controversial. The study analyses were criticized, particularly regarding the issue of post hoc stratification based on time of treatment (J. Neurosurg. 2000;93[Suppl 1]:1-7).

A third randomized, controlled clinical trial, known as NASCIS III, compared three treatments in 499 patients with acute spinal cord injury (JAMA 1997;277:1597-604). The methylprednisolone regimen in NASCIS II served as the active control. All patients were treated within 8 hours of the initial injury. Before randomization, all patients received an initial intravenous bolus of high-dose methylprednisolone (30 mg/kg). Patients in the methylprednisolone treatment groups then were given methylprednisolone infusion at 5.4 mg/kg per hour for 24 hours (active control group) or for 48 hours. The third treatment group received infusions of tirilazad mesylate over a 48-hour period.

The results showed that all treatment regimens were comparable in patients treated within 3 hours of injury. Those treated within 3 hours who received methylprednisolone for 48 hours had significantly better neurologic recovery, although the 48-hour treatment group experienced more side effects associated with steroid use. Controversy over data analysis in NASCIS II and NASCIS III remains.

A summary statement from the Spine Focus Panel suggested indications for methylprednisolone use in acute nonpenetrating spinal cord injury (Spine 2001;26[Suppl 24]:55). Treatment initiated within 3 hours should follow the methylprednisolone regimen used in NASCIS II (24 hours), and treatment initiated after 3 hours but before 8 hours should follow the high-dose regimen used in NASCIS III (48 hours). Methylprednisolone treatment should not be started after 8 hours, nor is it recommended in acute penetrating spinal cord injury, according to the Spine Focus Panel statement.

The Canadian Association of Emergency Physicians issued a position statement in 2003 declaring that "methylprednisolone for acute spinal cord injury is not a standard of care; it is only a treatment option." ■