



Role of Methylprednisolone in Spinal cord injury

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SPINAL CORD TRAUMA

- ◆ Mostly young and otherwise healthy, become paraplegic or quadriplegic because of spinal cord injuries.
- ◆ Most spinal cord injuries in civilian life result from damage to the surrounding vertebral column from fracture, dislocation, or both.
- ◆ Vertical compression with flexion is the main mechanism of injury in the thoracic cord, and hyperextension or flexion is the main cause of injury in the cervical cord.

PATHOPHYSIOLOGY AND PATHOLOGY OF SPINAL CORD INJURY

- ◆ The causes of permanent loss of neuronal function following spinal cord injury are not completely understood.
- ◆ Damage to the neurons occurs in 2 phases.
- ◆ **Primary injury** results from the shearing of axons and blood vessels at the time of trauma and causes pericapillary hemorrhages that coalesce and enlarge, particularly in the gray matter. Infarction of gray matter and early white matter edema are evident within 4h of experimental blunt injury. Eight hours after injury, there is global infarction at the injured level, and only at this point does necrosis of white matter and paralysis below the level of the lesion become irreversible. The necrosis and central hemorrhages enlarge to occupy one or two levels above and below the point of primary impact. Gliosis in these regions results in necrotic areas over several months and may cavitate causing a progressive syringomyelic syndrome.
- ◆ **Secondary injury**- Microvascular and neuronal injury due to a 'response to injury cascade'
 - Immune system reactions
 - Oxidative damage
 - Calcium release and excitotoxicity
 - Necrosis and apoptosis
 - Axon damage
 - Secondary injury that results this natural response to injury must be distinguished from additional injury, sometimes referred to as secondary injury that may result from movement of the patients with spinal cord injury without adequate spinal immobilization.
 - Ischemia results from reduced blood flow; free radical release, calcium overload, and increased excitotoxicity contribute to secondary injury and have been targets of therapeutic intervention.
 - Lipid peroxidation secondary to free radical formation is thought to occur rapidly in response to trauma and to be

major detrimental results of response of injury. Peroxidation disrupts the structure and function of the plasma membrane.

- ◆ Conflicting action of some of the elements of the natural response to injury contribute to the difficulty in treating Acute Spinal Cord Injury (ASCI). The same molecules may be both neuroprotective and neurotoxic. Thus the challenge of therapeutic intervention is to limit neurotoxicity without interfering with reparative process.
- ◆ The critical factor for recoverable function is the time from injury to institution of any therapy. Complete axonal disruption from the immediate trauma or from secondary phenomena precludes recovery.

TYPES OF SPINAL CORD INJURY AND THEIR MANAGEMENT

- ◆ Any patient with severe head injury potentially has an associated instability of the spinal column. The care of such patients begins at the scene of the accident.
- ◆ The neck should be immobilized to prevent spinal cord damage, and care should be taken during transport and during the physical and radiologic examinations to avoid extension or rotation of the neck and to prevent torsion-rotation of the thoracic spine.
- ◆ High thoracic or cervical cord trauma regularly causes mild hypotension and bradycardia because of functional sympathectomy, which responds to infusion of crystalloid or colloid (often corroborated by bilateral ptosis and miosis, Horner's syndrome).
- ◆ The neurologic examination in the conscious patient focuses on neck or back pain, diminished limb power, a sensory level on the trunk, and deep tendon reflexes, usually absent below the level of an acute spinal cord injury.
- ◆ Injuries above C5 cause quadriplegia and respiratory failure. At C5 and C6 the biceps are also weak, and at C4 and C5 the deltoid and the supra- and infraspinatus are weak. C7 injuries cause weakness of the triceps, wrist extensors, and forearm pronators. Injuries at T1 and below cause paraplegia; the precise level can be determined from the level of sensory loss.
- ◆ Compression in the low thoracic and lumbar region causes a conus medullaris or cauda equina syndrome. Cauda equina injuries are usually incomplete, involving peripheral nerves rather than spinal cord, and therefore are surgically remediable for longer periods after injury than spinal cord compression.



- ◆ In a comatose patient, absent reflexes, especially with small pupils or paradoxical breathing, signify a high cervical cord injury.
- ◆ The next priority is to exclude a surgically remediable and potentially reversible cord compression due to dislocation of a vertebral body.
- ◆ Many traumatic myelopathies have no clearly associated fracture or dislocation.
- ◆ If x-rays suggest any aberration in the position of vertebrae, then reduction should be undertaken quickly.
- ◆ Examination by MRI, when available, can be more useful.
- ◆ Decompression within 2 h of severe injury may lead to some recovery of spinal cord function. With incomplete myelopathies, especially if the limbs are becoming progressively weaker, early decompression is strongly recommended, even many hours after injury.
- ◆ The surgical approaches to decompressing the spinal column depend on the specific nature of the injury. In complete transverse myelopathies beyond 6 to 12 h after injury, decompressive laminectomies are usually unsuccessful in restoring function.

ROLE OF METHYLPREDNISOLONE

Mechanism of action of Methylprednisolone :

- ◆ Experimental studies provide direct evidence that the primary mechanism of action Methylprednisolone (MP) in Acute Spinal Cord Injury (ASCI) is inhibition of lipid peroxidation.
- ◆ MP treatment results in preservation of spinal cord blood flow, preservation of aerobic metabolism, reduced damage from high levels of extracellular calcium and excitotoxicity; reduced protease mediated damage to neurofilament proteins and preserved Na/K homeostasis.
- ◆ The inhibition of lipid peroxidation by MP is thought to occur through stabilization of the membrane structure by intercalation of MP. If the concentration of MP at the site of injury is too low, the membrane will not be adequately stabilized. If the concentration is too high, MP incorporation may serve to destabilize the structure leading to enhanced lipid peroxidation. So, the dose of MP is critical.
- ◆ The neuroprotective action of the MP results from inhibition of lipid peroxidation and improved spinal cord blood flow. Lipid peroxidation and diminished blood flow, which lead to ischaemia and dependence on anaerobic metabolism, occurs within minutes of spinal cord injury. And continue for 24 to 48 hours of injury. Moreover damage from lipid peroxidation is irreversible. The earlier MP is administered and inhibit this process, the less damage is thought to occur.
- ◆ Initiating treatment after 8 hour of injury is detrimental rather than simply ineffective. The reason for this is not entirely understood. Inhibition of phospholipase A2 by MP may reduce clearance of peroxidized lipids. In addition, recent experimental evidence suggests that MP inhibits release of neurotrophins necessary for neuronal regeneration. The presence of MP at the site of injury after 48 hours may inhibit neuronal sprouting or some other process necessary for regeneration.

Administration of MP in non penetrating ASCI is a three step process.

- ◆ STEP I: Initial bolus of 30 mg/kg body weight given over 15 minutes.
- ◆ STEP II: 45 minutes pause
- ◆ STEP III:
 - Treatment initiated within 3 hours of Injury: 23 hour infusion of 5.4 mg/kg/hour.
 - Treatment initiated within 3 and 8 hours after Injury: 48 hour infusion of 5.4 mg/kg/hour.
- ◆ Infusion is necessary following the initial bolus dose.
- ◆ Two lines of experimental evidence suggested that prolonging the duration of treatment would improve efficacy.
 - First, compared with the single dose, increased anaerobic metabolism, energy charge, and inhibition of the calcium protease activities were increased with repeated doses of MP.
 - Second in a cat model, 48 hour antioxidant regimen resulted in improved motor recovery at 4 weeks.
- ◆ Further more, the neuroprotective action of the MP followed tissue pharmacokinetics. In untreated animals, lactate levels increased after injury. After MP treatment, lactate levels are reduced to preinjury levels coincident with maximal MP tissue concentrations.
- ◆ However, as the steroids are eliminated from the tissue, the lactate returns to high levels. This result indicated that additional dosing could prolong MP support of aerobic metabolism.
- ◆ The recommended dosage and administration of MP are designed to parallel the pharmacokinetics of MP in spinal cord tissue. After an injection, 1 hour is required for peak tissue concentration to be reached. Tissue concentration declined rapidly following the peak.
- ◆ The recommended bolus dose of 30mg/ kg over 15 minutes followed by 45 minutes pause allows optimal tissue concentrations to be reached. The infusion rate of 5.4 mg/kg/hour has been calculated to sustain effective concentration of MP in spinal cord tissue.

PRECAUTIONS

- ◆ As Dexamethasone does not have antioxidant activity (neuroprotective) it should not be substituted for MP in the treatment of ASCI.
- ◆ Initiation of MP treatment more than 8 hour of injury is not recommended.
- ◆ Treatment with MP is not recommended for acute penetrating spinal cord injury.

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