Review of clinical trials of neuroprotection in acute spinal cord injury

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In this paper the authors review the clinical trials of neuroprotection that have been performed for the treatment of acute spinal cord injury (SCI). The biological rationale for the selection of each treatment modality is discussed with reference to current knowledge of the principles in the management of acute SCI as well as the primary and secondary injury mechanisms identified by experimental and clinical studies of the pathophysiology of acute SCI. The trials are evaluated with regard to the availability and use of accurate clinical outcome measures, and the methodologies of the trials are critically evaluated with an emphasis on prospective randomized controlled studies. A detailed description and critical analysis are provided of the results of the 10 clinical trials conducted to date in which a randomized prospective controlled design has been used. The issue of the therapeutic time window in acute SCI is discussed. To date, methylprednisolone is the only effective neuroprotective agent that has been established for use in human SCI, and the only therapeutic time window established in human SCI is a maximum trauma-to-treatment time of 8 hours.

Key Words * clinical trial * neuroprotection * acute spinal cord injury

BIOLOGICAL RATIONALE FOR NEUROPROTECTION IN ACUTE SPINAL CORD INJURY

The results of studies on human spinal cord injury (SCI) have shown that the spinal cord can be injured through a variety of primary injury mechanisms that include one or more of the following processes and forces (Table 1): acute compression, impact, distraction, laceration, sheer, and missile injury.[29] The most frequent mechanism in most countries is the combination of acute impact with persisting compression, which occurs with burst fractures or fracture dislocation with persisting compression of the cord by bone, disc, hematoma, or combinations thereof. In most countries, these injury mechanisms are usually caused by motor vehicle accidents, other traffic accidents, injuries at work or during sports and recreation, falls, and gunshot wounds.[31] Gunshot wounds and other missile injuries create additional forces on the spinal cord that usually result in major loss of spinal cord tissue and are seldom associated with persisting compression. To date, in almost all clinical trials gunshot injuries have been considered to be untreatable by currently available neuroprotective strategies and patients with gunshot injuries have been excluded from the trials.
The authors of experimental studies of acute SCI have identified a large number of secondary injury mechanisms that can be categorized as systemic, extracellular, and intracellular mechanisms (Table 1), although there is considerable overlap.[29,34] Systemic mechanisms of secondary injury include hemodynamic and hypoxic events, whereas extracellular events are mainly edema and vascular injuries that lead to vasospasm, ischemia, and hemorrhage. Intracellular events in the neurons and glia consist of many secondary injury processes such as excitotoxicity, free radical production, and many others (Table 1). These categories are not isolated and can interact. For example, extracellular events invariably lead to cellular damage. The counteraction of these injury processes provide the basis for the neuroprotective strategies examined in the clinical trials. Indeed, it is likely that methylprednisolone (MP) was effective because it has the potential to counteract several of the secondary injury mechanisms.

The importance of these secondary injury mechanisms is that, although they are initiated at the time of injury, they have the propensity to worsen during the first few hours after injury, and thus treatment during this "window" of time has the potential to prevent or reduce these damaging processes. The more severe the injury, the earlier and more damaging are the secondary injury processes. Unfortunately, there is incomplete knowledge of the exact time course of many secondary mechanisms, and therefore the exact therapeutic window in which to treat many of these processes is unknown.

**OVERALL PRINCIPLES OF MANAGEMENT OF ACUTE SPINAL CORD INJURY**

The initial management of patients with SCI has improved considerably in most countries for a number of reasons. There has been better training and deployment of first aid personnel, and many private citizens have received special training or are otherwise aware of the necessity for swift, judicious management. There is greater awareness of the importance of preventing hypoxia and hypotension. The importance of early attention to establishing
adequate airway, breathing, and circulation, the "ABCs" of trauma management, is well known. Additionally, there is greater awareness among emergency personnel and the general public of the need for early immobilization of the spine, as well as the necessity of avoiding injudicious movement of the spine. In most countries, there is also awareness of the advantages of regionalization of the acute management of these patients in organized units that possess specialized equipment and trained personnel; there is also awareness that early referral to these units within the first 2 to 3 hours posttrauma is advantageous.[33] If followed, all of these measures have the potential for neuroprotection by preventing or treating the systemic secondary mechanisms of injury, especially hypotension associated with spinal or systemic shock, and hypoxia associated with compromised respiration secondary to airway obstruction or paralysis of diaphragmatic or intercostal muscles.

Hypotension frequently occurs after SCI due to systemic or spinal shock.[16] The restoration of any systemic hypotension to normotension, an emerging principle of first aid management in SCI, is based on the recognition that there is vascular compromise of the injured spinal cord by local microcirculatory events including vasospasm and small vessel thrombosis,[2,17] which would be made worse by hypotension. The authors of several recent papers on patients with SCI have advocated "aggressive" medical management that includes invasive monitoring and the administration of vasopressors as required.[18,37] Invasive monitoring consists of insertion of an arterial line to maintain the mean systemic arterial pressure at 85 mm Hg, a central venous line to maintain central venous pressure at 5 to 10 mm Hg, and insertion of a pulmonary catheter to maintain a pulmonary artery capillary wedge pressure of greater than or equal to 18 mm Hg. In most cases, these parameters can be achieved with the liberal use of crystalloid and colloid solutions, but vasopressors such as dopamine (2.5-5.0 µg/kg/minute [or dobutamine]), or even Levophed (0.01-0.2 µg/kg/min [37]) are advocated, if necessary, to restore adequate hemodynamic homeostasis. These measures are designed to ensure optimum conditions for spinal cord recovery. However, without a randomized trial, it is not known if such aggressive medical management improves patients' neurological recovery. Invasive monitoring combined with frequent clinical observation by trained personnel in an intensive care setting will prevent fluid overload and minimize the risk of pulmonary edema. The autonomic hemodynamic manifestations of spinal shock and the reflex loss may last for several days or weeks after injury. In contrast, the somatic motor and sensory deficits of spinal shock usually terminate within an hour of injury. Thus, structural damage to the cord is usually the cause of motor and sensory neurological deficits that persist for more than 1 hour after SCI rather than spinal shock.

The principles of early management also include the concept of "treating the whole patient," which requires attention to prevention of gastric dilation and vomiting with its attendant risk of aspiration, prevention of bladder distension, pressure sores, and deep venous thrombosis. These protective measures against the known complications of SCI are essential for trials of neuroprotection to enhance spinal cord recovery, because the recovery potential of the injured spinal cord will be adversely affected by the hypoxic, hypotensive, inflammatory, or infectious complications associated with SCI.

THE NATURAL HISTORY OF NEUROLOGICAL RECOVERY AFTER ACUTE SPINAL CORD INJURY

To assess the results of current clinical trials in neuroprotection, it is helpful to consider the documented natural history of neurological recovery from SCI in the absence of major attempts to alter the prognosis. There is strong evidence that the majority of patients will make some neurological recovery,[27] although the potential is much greater in those with incomplete injuries. Neurological recovery includes recovery of nerve root function at the level of the injury or caudally and spinal cord recovery at the level of the injury or caudally. The biological basis for such recovery includes the following: resolution of acute injury events such as hypoxia or ischemia; resolution of secondary injury events such as ionic, neurotransmitter, or vascular changes; and recovery by long-term processes such as axonal regeneration or remyelination. The National Spinal Cord Injury Database, reported by Stover, et al.[25] provides a rich source of information about neurological recovery in almost 10,000 SCI patients and was compiled by the Model Spinal Cord Injury System Program in the United States at 19 centers during 1973 to 1985. The Frankel[11] grading system was used to show that even a small number of patients with complete spinal cord injury can recover, a finding confirmed by Hansebout[14] in his extensive review of neurological recovery in
patients with complete spinal cord injury; Hansebout found that approximately 1% of patients with complete injuries recovered the ability to ambulate. Stover, et al., found the best recovery in the Frankel B and C categories of incomplete injuries in which 30 to 50% of patients improved by one grade. Currently, 50 to 60% of patients with SCI have incomplete spinal cord injuries. These high rates of natural recovery, especially among those patients who sustained incomplete spinal cord injuries and who received the standard of care during this era prior to the development of formal clinical trials make it mandatory to enact rigorous study methodology and accurate outcome measures in clinical trials of neuroprotection or other measures.

**METHODOLOGY OF OUTCOME STUDIES AND OUTCOME MEASURES**

A variety of outcome study methodologies and outcome measures have been used in clinical trials in acute SCI (Table 2). In earlier years, retrospective analyses of case series predominated. Although much has been learned from many of these retrospective analyses, such as the natural history of recovery noted previously, many therapeutic studies have failed to prove the effectiveness of the treatments being offered because of faulty study design. Metaanalysis performed on groups of retrospective studies might improve the quality of the analysis and the validity of the results in some instances. However, individual case series in which retrospectively collected data are used provide minimal opportunity to establish new treatment modalities. The optimum method for studying new treatment is the prospective randomized controlled trial in which a statistically sound design is used during a reasonably practical period of time, such as 3 to 5 years. To date, there have been only 10 such studies mainly because of the costs involved and the reluctance of some investigators to participate.

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Method</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>clinical neurological exam</td>
<td>compare nos. of pts who change 1 or 2 grades, or changes between baseline &amp; FU in mean motor or sensory scores (use either raw data or %)</td>
<td>ASIA/MSCP is more useful than the others, but there is a ceiling effect for Grade D, &amp; uncommon improvement from Grade A to B</td>
</tr>
<tr>
<td>Frankel grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASIA/MSCP grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunnybrook grade</td>
<td></td>
<td></td>
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<tr>
<td>Benzel grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASIA/MSCP motor score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASIA/MSCP sensory score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>functional assessment</td>
<td>compare the mean raw scores of clinical ability</td>
<td>FIM has only been applied to 2 randomized prospective control trials in acute SCI</td>
</tr>
<tr>
<td>FIM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>functional MR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>neurophysiological studies</td>
<td>measures of sensory or motor conduction in the cord: compare mean latencies or amplitudes or presence &amp; absence</td>
<td>SSEP has been used to predict prognosis &amp; not been been used in a controlled trial</td>
</tr>
<tr>
<td>SSEP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>motor evoked potential</td>
<td></td>
<td></td>
</tr>
<tr>
<td>imaging features</td>
<td>MR best for spinal cord and nerve roots; CT best for spine</td>
<td>MR has not yet been used as an outcome measure for cord recovery</td>
</tr>
<tr>
<td>relief of compression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>restoration of alignment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mortality/morbidity</td>
<td>compare complication rates for sepsis, etc. between treatment groups &amp; centers</td>
<td>frequently used &amp; provides important data about side-effects of drugs &amp; performance of centers</td>
</tr>
</tbody>
</table>

*CT = computerized tomography scanning; FU = follow up; MR = magnetic resonance imaging; SSEP = somatosensory evoked potential.

The most important outcome variables in clinical trials of acute SCI are neurological recovery and functional improvement. Other useful outcome variables include mortality rate, morbidity rates in terms of specific complications, length of acute and rehabilitation hospital stay, incidence of intractable pain, return to work, and patient satisfaction. Radiological outcome variables such as adequacy of decompressive surgery and confirmation of restoration of spinal alignment and stability are also useful. It is unfortunate that neurophysiological tests have not been included as outcome measures in any of the published trials, although tests such as the recording of somatosensory evoked potentials have been shown to be of prognostic value[24] and are often used to monitor SCI patients undergoing surgical treatment.[19]
It is indeed fortunate that the American Spinal Injury Association (ASIA) in collaboration with the International Medical Society of Paraplegia (IMSOP) have developed very useful scales for the neurological grading and assessment of neurological recovery of patients with acute SCI.[1] In most countries, the ASIA/IMSOP system has superseded other systems such as the Frankel[11] and Sunnybrook[35] systems for the grading of neurological function and assessment of neurological recovery in SCI patients because it is more precise and more comprehensive. For these reasons, the ASIA/IMSOP method has been used in most of the recent clinical trials. Comparisons between treatment groups can be made on the basis of the numbers of patients who show a change in neurological grade or on the basis of change in motor or sensory scores that are obtained by adding the individual values given for muscle strength and dermatome sensitivity, respectively. It is not essential for all clinical trials to use the same outcome measures, as long as the measures used have been verified on the basis of interrater reliability and other measures of consistency.

It should be noted that both the Frankel and ASIA methods of grading neurological function have significant shortcomings, such as the "ceiling" effect noted for Grade D patients who may have near-normal neurological function such as sufficient strength to allow ambulation. For these patients to improve to Grade E, they would have to recover fully and achieve normal neurological status. Other classifications such as the Benzel method[3] and the Sunnybrook scale provide a larger number of categories, especially for patients with incomplete injuries (Benzel, Grade 7; Sunnybrook, Grade 10); however, these scales have been used much less often, and there is no definite proof that they are superior to the ASIA system for avoiding the ceiling effect.

Ideally, the methods used to compute the results of clinical trials should be clearly stated, and the statistical tests performed to assess significance of the results should be reliable and appropriate. Unfortunately, some investigators have used difficult mathematical formulae to compute neurological recovery and have conducted statistical tests not easily understood by the practitioners. These difficulties have led to some controversy over the results of some of the trials. For example, instead of clearly stating the exact percentage increase in motor score, some studies have computed other outcome parameters such as the percentage increase in the recovery potentially possible in an attempt to deal with the differing baseline neurological status of patients enrolled in the trial. Such manipulations serve to equalize the opportunities for recovery from injuries at different levels and of varying severity. For example, a patient with cervical incomplete injury has the potential to recover more muscle groups than a patient with lumbar incomplete injury. Ideally, the reports of clinical trials should contain all the raw data and the derived data for each outcome measure to assess recovery.

Clinical trials should augment the neurological recovery data with outcome measures designed to assess the functional significance of the neurological recovery. Only recently has this feature been recognized and included in the design of clinical trials. The functional measure now used most often in clinical trials of SCI is the test of Functional Independent Measure (FIM) test.[15] However, with respect to trials of neuroprotection for SCI, FIM's value has not been established because it has only recently been applied to this issue.

**ELIGIBILITY AND STRATIFICATION**

All 10 clinical trials to date that have used a randomized prospective controlled methodology include both men and woman (men comprise 80-85% of all patients with acute SCIs). The criteria in most trials restrict the age range to between approximately 16 and 75 years of age. The younger age groups have been typically excluded because of the difficulties of obtaining informed consent, and the older age groups have been excluded because of the high mortality rate associated with SCI in those patients over age 75 years,[31] especially those with complete spinal cord injuries. Other common exclusion criteria include patients with preexisting neurological diseases, previous SCI, and major medical conditions such as heart failure or multiple trauma that may be lifethreatening or that may cause hemodynamic instability. These exclusion criteria underline the importance discussed previously of the need to prevent secondary injury caused by such factors. In one clinical trial patients who experienced hypotension for a defined period of time were specifically excluded.[22] All trials have excluded patients who had been drinking or who sustained head injuries sufficiently severe to prevent reliable scoring of neurological function.

Because of the important relationship between severity of neurological injury and potential for recovery,[30] the
authors of most studies have stratified patients into those with complete and incomplete spinal cord injuries to ensure equal numbers of similarly injured patients in each treatment group. In some studies the authors have also stratified for level of injury—with cervical spinal injuries being separated from thoracic only or combined thoracic and lumbar spinal injuries. Indeed, there is some evidence that neurological recovery is related to level of injury.[30] Due to the slowness of the neurological recovery processes after SCI, most of the trials have required a 1 year follow-up examination and have based the primary outcome measure on a comparison of the initial and 12-month neurological examinations. Accordingly, in most trials patients with uncertain follow-up evaluations, such as travellers and convicts, have been excluded.

**THE 10 RANDOMIZED PROSPECTIVE CONTROLLED TRIALS IN ACUTE SPINAL CORD INJURY**

To date, there have been 10 randomized prospective trials in acute SCI (Table 3). In four of these trials the role of MP has been examined, in two GM-1 ganglioside (GM-1) has been studied, and in one each thyrotropin releasing hormone (TRH), gacyclidine (GK-11, an n-methyl-D-aspartate receptor antagonist), or nimodipine (a calcium channel blocker) has been examined. In the remaining trial early and late decompressive surgery were compared and assessed.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year Results Reported</th>
<th>Agent(s)</th>
<th>Placebo</th>
<th>No. of Patients</th>
<th>Outcome Measures</th>
<th>FU Duration (yrs)</th>
<th>Result</th>
<th>Other Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASCIS-1</td>
<td>1984</td>
<td>low &amp; high dose MP</td>
<td>no</td>
<td>306</td>
<td>9 &quot;dysfunction&quot; scores for motor and sensory complication rates</td>
<td>1</td>
<td>no difference</td>
<td>increased wound infectious in high dose group</td>
</tr>
<tr>
<td>NASCIS-2</td>
<td>1990</td>
<td>MP, naloxone, or placebo</td>
<td>yes</td>
<td>487</td>
<td>10 &quot;expanded&quot; motor &amp; sensory scores, complication rates</td>
<td>1</td>
<td>MP improved neurological recovery</td>
<td></td>
</tr>
<tr>
<td>NASCIS-3</td>
<td>1997</td>
<td>MP + Tirilazad</td>
<td>no</td>
<td>499</td>
<td>16 ASIA grade, ASIA motor scores, FIM</td>
<td>1</td>
<td>MP improved neurological recovery</td>
<td>duration of MP varies w/duration of delay; MP better than tirilazad, more sepsis &amp; pneumonia in 48-hr group</td>
</tr>
<tr>
<td>Japanese MP</td>
<td>1994</td>
<td>MP or placebo</td>
<td>yes</td>
<td>177</td>
<td>42 &quot;expanded&quot; motor score, sensory score, complication rates</td>
<td>0.5</td>
<td>MP improved neurological recovery</td>
<td></td>
</tr>
<tr>
<td>GM-1 #1</td>
<td>1991</td>
<td>GM-1 ganglioside</td>
<td>yes†</td>
<td>34</td>
<td>1 Frankel grade, ASIA motor score</td>
<td>1</td>
<td>GM-1 improved neurological recovery</td>
<td></td>
</tr>
<tr>
<td>GM-1 #2</td>
<td>1998</td>
<td>GM-1 ganglioside</td>
<td>yes‡</td>
<td>800 (ap)</td>
<td>28 ASIA grade, Benzel grade, ASIA scores, FIM</td>
<td>1</td>
<td>final result pending</td>
<td>comparison of Benzel w/ASIA systems</td>
</tr>
<tr>
<td>TRH</td>
<td>1995</td>
<td>TRH or placebo</td>
<td>yes</td>
<td>20</td>
<td>1 Sunnybrook scale</td>
<td>1</td>
<td>no difference</td>
<td></td>
</tr>
<tr>
<td>GK-11 in progress</td>
<td>1998</td>
<td>GK-11 or placebo</td>
<td>yes§</td>
<td>280 (p)</td>
<td>26 ASIA grade, ASIA motor &amp; sensory scores</td>
<td>1</td>
<td>no difference</td>
<td></td>
</tr>
<tr>
<td>Nimodipine</td>
<td>1998</td>
<td>nimodipine, MP, both or placebo</td>
<td>yes</td>
<td>100</td>
<td>1 ASIA grade, ASIA motor &amp; sensory scores</td>
<td>1</td>
<td>no difference</td>
<td>more infections in MP groups early surgery not better no change in stay in ICU or rehabilitation</td>
</tr>
<tr>
<td>Decompression (Vaccaro et al)</td>
<td>1997</td>
<td>decompression at &lt;72 hours vs. &gt;5 days</td>
<td>no‡</td>
<td>62</td>
<td>1 ASIA grade, Frankel grade, ASIA motor</td>
<td>1 (av)</td>
<td>no difference; 20 pts in trial lost to FU</td>
<td></td>
</tr>
</tbody>
</table>

* ap = approximately; av = average; FU = follow up; ICU = intensive care unit; p = planned.
† All patients received MP at lower than NASCIS-2 dose.
‡ All patients received MP at NASCIS-2 dose.
§ MP not given.
Three of the four trials in which MP was studied were conducted by the National Acute Spinal Cord Injury Study (NASCIS) group, led by Dr. Michael Bracken, which comprised a large number of centers primarily from the United States and two from Toronto, Canada. Not all centers participated in all three NASCIS trials. The NASCIS trials were well organized, involved large numbers of patients and sophisticated methodology, and were supported by the National Institutes of Health in the United States and by the Upjohn Company, which supplied the agents and other funds. Indeed, the NASCIS group is credited with performing the first multicenter randomized prospective controlled trial of any treatment modality in the field of SCI; it has performed a major public service. In the NASCIS-1 trial the value of two doses of MP was assessed: the low dose was a daily intravenous dose of 100 mg for 10 days; the high dose was a daily intravenous dose of 1000 mg for 10 days. This trial involved 330 patients in nine centers, and no difference in the neurological recovery based on a novel system of classification of motor and sensory "dysfunction" was found.[4,7] There was no placebo group because many investigators had been using MP in their practices based on favorable reports of experimental studies and had ethical concerns over withholding the drug. The study did identify a significantly increased rate of wound infections in patients from the high-dose group. Thus, when NASCIS-2 was planned, there was less concern about including a placebo group, and certainly this was a key component of the NASCIS-2 trial which then proceeded to provide the compelling result that MP produced improved neurological recovery compared with both the placebo group and with a second treatment group that received the drug naloxone, which had also been selected for study based on favorable experimental results.[6] The MP was administered in very high doses but only for 24 hours. The initial intravenous dose of 30 mg/kg was followed by a dose of 5.4 mg/kg/hr for the next 23 hours. There were 487 patients randomized in 16 centers. The improvement was evident in both complete- and incomplete-injured cases, but only in patients in whom the drug was administered within the first 8 hours of injury. Furthermore, subsequent detailed analysis of the type of neurological recovery yielded strong evidence that there was significant recovery at both the level of spinal cord injury and at lower spinal cord levels, indicating long tract recovery.[5]

Unfortunately, for a number of reasons, some investigators and practitioners have questioned the results. It was surprising, for example, to note that one of the placebo groups (the incomplete-injured group treated after 8 hours of injury).[5] attained the highest neurological recovery at 1 year. Furthermore, it has been questioned whether the division of patients into groups receiving treatment before 8 hours postinjury and after 8 hours postinjury was statistically valid because this stratification was not contained in the primary question. However, the subsequent multicenter trial of MP in Japan[20], which involved several centers and 117 patients, confirmed that MP administered within 8 hours of injury produced increased neurological recovery when compared with a placebo; thus, the findings of this trial provide added weight to the validity of the result of the NASCIS-2 trial. Since these trials were completed, the majority of patients with SCI in North America has received MP according to the NASCIS-2 recommendations. Furthermore, the MP studies have produced two other significant effects. First, investigators in subsequent randomized prospectively controlled trials of SCI in North America have been compelled to include MP in all treatment groups. Second, the 8-hour therapeutic window has been established as a benchmark for other trials, even those not involving drugs, and this time window may or may not be appropriate for other treatment strategies.

The NASCIS-3 group examined a number of issues including the duration of administration of MP (24 hours compared with 48 hours) and the effectiveness of a new agent, tirilazad mesylate, an antioxidant designed to prevent free radical-induced lipid peroxidation.[8] In this multicenter trial, MP produced more recovery than tirilazad in 400 patients. With use of MP, if administration was begun within 3 hours of injury, there was no additional benefit to prolonging the treatment to 48 hours from 24 hours. Furthermore, patients who received MP for 48 hours experienced a higher incidence of severe sepsis and pneumonia than those who received treatment for 24 hours. However, if treatment with MP therapy was delayed to the 3 to 8 hour postinjury interval, then neurological recovery was improved by continuing MP therapy for 48 hours rather than 24 hours. The NASCIS-3 trial is also noteworthy because it was the first randomized trial of patients with acute SCI to include a FIM. This additional outcome measure was useful for confirming the results.

GM-1 is a complex acidic bovine glycolipid that was shown in experimental studies to enhance neuronal sprouting
and regeneration and to counteract some secondary injury processes. The first GM-1 study of SCI patients was a single center randomized prospective control trial of only 34 patients and included a placebo group.[12] Patients received daily intravenous administration of GM-1 (100 mg) for a mean of 26 days with the first dose given at a mean of 48 hours after injury. All patients also received MP but at much lower doses than in NASCIS-2. There was a remarkable improvement in neurological recovery, including several patients who improved by two Frankel grades. Although the number of patients was small, a statistically significant result was achieved. The outcome measures included both Frankel grade changes and ASIA motor scores. The second GM-1 trial was a multicenter trial that included 28 centers and approximately 800 patients in whom grading was based on ASIA and Benzel scales. As noted previously, the latter system divides those patients with incomplete spinal cord injuries into a larger number of categories in an attempt to overcome the ceiling effect. Although the final report of this study has not been published, the preliminary results indicate that there was no significant difference between the treatment and placebo groups at 26 weeks; however, there was better recovery in the GM-1 treated patients at 8 and 16 weeks after injury. There was also a trend toward better recovery in the patients with ASIA Grade B who received the drug as compared with the ASIA Grade B patients who received only the placebo.[13]

The single-center clinical trial of TRH, an antagonist of endogenous opioids, comprised only 20 patients.[23] The patients received treatment within 12 hours of injury (intravenous TRH at 0.2 mg/kg bolus and 0.2 mg/kg/hr for 6 hours). The study included a placebo group, and the primary neurological outcome measure was the Sunnybrook scale developed by the senior author (C.H.T.) in 1970[35] to expand the number of grades of the Frankel system, which was the only scale in use at the time. There was no significant difference in neurological recovery between the patients in the TRH and the placebo groups.

Gacyclidine is an n-methyl-D-aspartate receptor antagonist currently being investigated in patients with acute SCI in a multicenter randomized prospectively controlled trial in France.[26] The inclusion criteria for this study are very strict and exclude many ASIA Grade D patients with minimal neurological deficits and also those with significant systemic hypotension. This trial is also noteworthy because the first dose of the drug must be administered within 2 hours of injury, and thus the protocol requires the cooperation of all the emergency retrieval and first aid groups in a large region of the country, a remarkable achievement. The ASIA/IMSOP grading system was taught to these groups, and they were often responsible for administering the first dose of the drug or placebo. It is also noteworthy that MP is not required by the protocol. Three different doses of gacyclidine are being examined, and a total of 280 patients are being studied. The trial had not been completed at the time of submission of our paper.

Nimodipine, a calcium channel blocker, was examined in 100 patients with acute SCI in a single-center randomized prospective trial in France that was recently reported.[21,22] Four groups of patients were studied: those receiving nimodipine alone, nimodipine plus MP, MP alone, and placebo. Nimodipine was administered intravenously at 0.015 mg/kg/hr for 2 hours and followed by 0.03 mg/kg/hr for 7 days, and MP was administered at the same dose rate as in NASCIS-2 (30 mg/kg bolus over 1 hour and followed by 5.4 mg/kg/hr for 23 hours). The onset of treatment was within 6 hours of injury in all cases, with the average interval of approximately 3.5 hours. Patients with persistent hypotension were excluded. There was no significant difference among the four treatment groups. With only 100 patients among the four treatment groups, this trial is at high risk of a type 2 error and would have been improved by including of more patients. The authors also examined the results based on the timing of surgical treatment for stabilization of the spine or decompressive surgery and found no relationship between improvement of neurological function and the timing of surgery, although patients were not randomized on the basis of the timing of surgery.

The final trial to be evaluated in the present paper is the only randomized prospectively controlled trial reported to date on the timing of decompressive surgery in the traumatized spinal cord in patients with SCI,[36] although there have been several performed in experimental animals. We recently reviewed the entire subject of the timing of surgical decompression in clinical and experimental SCI[10] and it will not be discussed in detail here. The surgical trial by Vaccaro, et al.[36] was a single-center trial in which 62 patients were randomized to an early- or late-surgery group. Early surgery was defined as surgical treatment received in less than 72 hours posttrauma; the mean
time to decompressive surgery was 1.8 days. Late surgery was defined as surgical treatment received more than 5 days posttrauma; the mean time to decompressive surgery was 16.8 days. The investigators found no difference in ASIA motor score or ASIA grade at follow-up approximately 1 year postinjury. Additionally, there was no difference between the groups in terms of length of stay in the intensive care unit or in inpatient rehabilitation time. It should be noted that 20 of the 62 patients enrolled in the trial were lost to follow-up review and that the statistical power of this trial was low.

OTHER TRIAL FORMATS IN ACUTE SPINAL CORD INJURY

Although this review has emphasized the importance of the 10 randomized prospective controlled trials in acute SCI, there is a role for other formats. For example, useful information regarding the treatment of hypotension was obtained from the prospective study performed by Vale, et al.,[37] which was not a randomized controlled trial. They resuscitated 77 patients with acute SCI according to a standard protocol to maintain mean arterial pressure above 85 mm Hg. They also advocated an early surgical decompressive procedure as soon as possible after medical resuscitation. The data were prospectively recorded in a consistent fashion, and standard outcome measures included Frankel and ASIA grades. The authors found improved neurological recovery compared with selected "series of patients" identified by "a search of the literature." In the absence of a randomized prospective controlled trial, it was not possible to prove the value of their approach involving aggressive medical and surgical management. There have been at least two prospective studies, one of which was conducted by the senior author (C.H.T.)[32] of conservative compared with surgical management of patients with acute SCI in which data were collected prospectively, but the patients were not randomized to surgical or control groups. The results of both studies failed to show any significant differences between surgically and non-surgically treated patients.[9,32] The knowledge derived from these nonrandomized trials without proper controls has little impact on influencing therapy, but it does provide some useful information about epidemiology and complication rates. For example, in the prospective study performed by the senior author it was shown that surgery can be performed in SCI patients without causing changes in mortality rate or in the rates of most of the common complications sustained by patients with acute SCI.[32]

CONCLUSIONS

In addition to the major improvements in our understanding of the pathophysiology of acute SCI through experimental studies that have elucidated the primary and secondary injury mechanisms, there have been major advances in our abilities to diagnose and manage patients with acute SCI. These advances include improved first aid care, especially through the rapid deployment of trained personnel skilled in recognition and judicious early management. Improvement has also been derived from the development of regional multidisciplinary units which possess the necessary personnel and equipment for managing acute SCI patients. Improved medical management has evolved from techniques to monitor, prevent, or treat early hypotension and hypoxia, which can worsen any remaining neurological function and reduce the potential for neurological recovery. Diagnostic regimens now include highly accurate and noninvasive techniques to image the injured spinal cord and nerve roots by using magnetic resonance imaging and to visualize of the injured spinal column by performing computized tomography scanning.

Improved surgical techniques now allow decompressive surgery to be performed on the spinal cord through a variety of surgical approaches, and stabilization of the spinal column with a variety of new techniques involving instrumentation can be performed with increased precision and lower rates of morbidity. And finally, the advances include considerably more accurate methods of grading and scoring the clinical neurological examination and the functional outcome of SCI patients, especially by using the ASIA system, which have improved the precision and validity of clinical trials. These advances have prompted clinical investigators, primarily neurosurgeons and orthopedic surgeons, to conduct in SCI patients many outstanding, well designed clinical trials of neuroprotection and other treatment modalities such as surgical decompressive procedures. The methodology used in the trials has also been refined in terms of patient numbers, duration of follow-up periods, and the inclusion of functional outcome measures.
The most reliable and useful information derived from the clinical trials of SCI has been obtained from the randomized prospective controlled trials, although useful information has also been ascertained from other study formats. Methylprednisolone has been proven to improve neurological function if administered within 8 hours of injury. In turn, the results of MP studies show that there is a therapeutic window after trauma that allows time for treatment to be administered to interrupt secondary injury processes. There is a need for further, well-designed clinical trials to study the neuroprotection provided by pharmacotherapy, surgery, and other means in the treatment of acute SCI.

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