Pharmaceutical treatment of spinal cord injuries in the acute phase

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ABSTRACT

The initial treatment of spinal cord injuries during the acute phase is very important as it largely determines the prognosis of patients. The purpose of this study is to review the medical interventions in the acute phase after spinal cord injury. In the PUBMED database, a search was performed with the following keywords: ("methylprednisolone" OR "riluzole" OR "rho inhibitor" OR "cethrin" OR "G-CSF" OR "minocycline" OR "TRH" OR "GM-1") AND "spinal cord injury". Only prospective, randomized, placebo-controlled studies written in English were included in the study. Studies published in non-English language, incident reports, retrospective studies, observational studies, systematic reviews, experimental animal studies were excluded from the review. Finally, 17 studies were included in the present review, including the following drugs: methylprednisolone (8 studies), rizulole (1 study), G-CSF (1 study), rho inhibitors (2 studies), minocycline (1 study), TRH (1 study), ganglioside GM-1 (2 studies), combination of progesterone and vitamin D (1 study). There is currently no drug with a high level of evidence that can be administered against acute spinal cord injuries. There is not enough convincing evidence that high doses of methylprednisolone for acute spinal cord injury are beneficial, given the high rate of complications. The role of steroids in acute spinal cord injury remains unclear, and some studies have shown that the risks of steroids outweigh the benefits. With many promising therapeutic agents and strategies being studied in ongoing trials for spinal cord injury, there is great hope of finding an effective treatment that would make significant progress while also benefiting patients with other neurological conditions.

Key Words: Spinal Cord Injury, Drug Therapy, Acute Phase

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Introduction

Acute spinal cord injury (ASCI) is, to this day, known to be an incurable condition. ASCIs result in a high morbidity rate and can also present an increased risk of death. The initial treatment of spinal cord injuries during the acute phase is very important as it largely determines the prognosis of patients. While clinical management of patients with ASCI is likely to have made considerable progress with medical advancement, the development of neural regeneration therapy has yet to be effectively implemented. Clinical research on efficacy of pharmacological treatment for ASCI reveals minimal and controversial clinical evidence [1, 2]. The purpose of this study is to review the medical interventions in the acute phase after spinal cord injury.

Materials & Methods

Based on the literature, we focused on the following drugs: methylprednisolone, riluzole, granulocyte colony stimulating agent, rho inhibitors, TRH, ganglioside GM-1, minocycline and others. In the PUBMED database, a search was performed with the following keywords: ("methylprednisolone" OR "riluzole" OR "rho inhibitor" OR "cethrin" OR "G-CSF" OR "minocycline" OR "TRH" OR "GM-1") AND" spinal cord injury". Only prospective, randomized, placebo-controlled studies written in English were included in the study. Studies published in non-English language, case reports, retrospective studies, observational studies, systematic reviews and animal studies were excluded from the review.

Results

As shown in the flowchart below (Figure 1), search results included 988 papers. After checking titles and abstracts and applying a filter that included only prospective, randomized, double-blind studies, 932 articles were rejected. From the individual analysis of the studies references another 1 study emerged, while 40 studies were excluded for specific reasons. Finally, 17 studies were included in the present review, including the following drugs: methylprednisolone (8 studies), rizulole (1 study), G-CSF (1 study), rho inhibitors (2 studies), minocycline (1 study), TRH (1 study), ganglioside GM-1 (2 studies), combination of progesterone and vitamin D (1 study).

Discussion

Steroids

Methylprednisolone is the only medication recommended to improve patients' neurological outcomes with acute, nonpenetrating ASCI in randomized clinical trials. The objective evidence for the effectiveness of glucocorticoids in acute ASCI, however, is limited and, to many, unconvincing. In animal studies, glucocorticoids administration after spinal cord injury reduces edema, avoids intracellular potassium loss, and promotes neurological regeneration. Administration within the first eight hours after damage showed the best outcomes [3]. Some scholars suggest that the vital effect of methylprednisolone on the regeneration of the spinal cord was the suppression of lipid peroxidation and that late administration of steroids could have no impact on lipid peroxidation and could interfere with regenerative processes [4].

NASCIS [5] was a multi-center (included nine hospitals) double-blind, randomized trial that was conducted to examine the efficacy of a high dose of methylprednisolone (1000 mg bolus and daily after that for ten days—250 mg every 6 hours in 165 patients, a total of 11,000 mg) compared with the standard dose of methylprednisolone (100 mg bolus and daily after that for ten days —25 mg every 6 hours in 165 patients, a total of 1100 mg). A total of 330 patients with acute spinal column injury were evaluated and assessed after six weeks and six months of injury. Inclusion criteria were any loss of sensation or motor function below the lesion. Exclusion criteria were nerve root injury, equine cauda injury alone, admittance to the center >48 hours after injury, use of steroids before admission, severe comorbidity, other life-threatening conditions, patients younger than 13 years old, failure of consent, pregnancy, diabetes, severe vascular disease, gastrointestinal bleeding, or vascular disease. At six weeks, 47 patients were not evaluated:

- Twenty-six patients had died.
- Eighteen were unavailable for follow-up.
- Three patients had incomplete neurological examinations.

At six months, 179 patients were evaluated (91 high-dose and 88 low-dose). They reported no statistical difference in their neurological recovery of motor func-

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tion, pinprick, and light touch sensation between the two groups at six weeks or six months. The lack of a treatment effect was not correlated to the severity of the initial trauma or the time from injury to starting treatment. Although not statistically significant, early case fatality was more remarkable in the high-dose protocol, with a higher relative risk for wound infections.

The same lack of statistical significance between the two regimen groups was shown in the 1-year follow-up results that were published by the same authors [4]. Adjusting for potential confounding factors, there was no significant difference considering the neurological recovery of motor function, pinprick response, or touch sensation between the groups (the same findings of the first study). Case fatality rate was 10.7% and did not associate with steroid doses. None of the deaths could be linked to steroid treatment, according to the authors.

Bracken et al completed a second multi-center randomized, double-blind clinical trial in North America (NASCIS II) investigating the effectiveness and safety of methylprednisolone and naloxone in patients with acute spinal injury (95 percent were treated within 14 hours of injury). Methylprednisolone was administered to 162 patients in bolus (30 mg/kg followed by an infusion of 5.4 mg/kg/h for 23 h); naloxone was administered to 154 patients (5.4 mg/kg bolus followed by an infusion of 4 mg/kg/23 h), and 171 patients received placebo. Patients were assigned to groups within 12 hours of the diagnosis of SCI [6]. Neurological assessment was conducted at six weeks and six months after injury. Authors recorded that, at six months, patients treated with methylprednisolone had a substantial improvement in motor control relative to placebo within 8 hours of their injury, as well as an improvement in the perception of pinprick and touch. There was also some neurological recovery in the steroid cohort relative to naloxone or placebo. The naloxone or methylprednisolone cohort's findings after 8 hours of injury did not significantly differ in their neurological outcomes from those for placebo. This research introduced the first guideline regimen for the use of methylprednisolone.

The research group published data of one year of follow-up to the NASCIS II group [4]. The same improvement in recovery following administration of methylprednisolone was observed one year after the initial injury. Patients receiving methylprednisolone (P = 0.08) or naloxone (P = 0.1) after 8 hours of injury had less motor function than those receiving placebo. In all cohorts, adverse effects were similar. The authors suggested that methylprednisolone should be indicated for acute TSCI when started within 8 hours of injury.

The third NASCI-III trial [7] also recorded enhanced motor recovery in patients receiving methylprednisolone therapy within 3–8 h of ASCI and explicitly observed that this correlation was present at six weeks and six months (long-term follow-up) in patients receiving extended methylprednisone therapy (48 h) compared to those receiving a shorter treatment period (24h). Adverse effects were similar between the three groups, with some exceptions: severe sepsis reported in 2.6 percent of patients in the 48-hour MP treatment group compared to 0 percent in the 48-hour tirilazad group and0.6 percent in the 24-hour MP group (P = 0.07) and severe pneumonia reported in 5.8 percent in the 48-hour MP, 0.6 percent in the tirilazad group and 2 percent in the 48-hour MP group. Survival was similar in the three groups. They concluded that a substantial change in motor control was observed at six weeks and six months in the MP-receiving community for 48 hours compared to 24 hours when care began 3–8 hours after injury. In the first 3 hours of therapy, patients had precisely the same recovery pattern in the three groups. Although statistically meaningful, the differences in motor function were slight and usually limited to upper body function.

Bracken et al [8] announced the findings of a 1-year follow-up of a multi-center randomized, double-blind clinical trial in North America (NASCIS III). According to the authors, the results endorsed the 48-hour methylprednisolone regimen in patients treated between 3 and 8 hours after injury, but this could require caution due to a higher risk of pneumonia and respiratory complications. More deaths from pneumonia and respiratory distress syndromes were found in the 48-hour MP regimen and the tirilazad group.

A randomized controlled trial by Wang et al concluded that intermittent methylprednisolone infusion was effective in treating ASCIs, complicated by incomplete paraplegia, with a low incidence of adverse re-

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actions [9]. On the contrary, Pointillard et al found no clinical benefit of the use of methylprednisolone in acute management of SCI [10]. Elderly patients with cervical SCI may be more likely to have side effects after high-dose methylprednisolone and therefore deserve special care [11].

Riluzole

Riluzole is a benzothiazole that inhibits voltage-gated sodium channels and glutamate release and is currently the only licensed medication for treating amyotrophic lateral sclerosis. Riluzole works by blocking the sodium channels in neurons and may prevent increases in the intracellular concentration of sodium, finally leading theoretically to cellular death inhibition in ASCI. Grossman et al [12] conducted the first prospective, multi-center, phase I trial of riluzole safety and pharmacokinetics for ASCI. Riluzole was administered every 12 hours either orally or by nasogastric tube, within 12 hours after injury. The control group received the standard of care but no riluzole. Mean motor score for cervical injury patients treated with riluzole increased from admission to 90 days, compared to control patients, representing a statistically significant difference.

Rho-inhibitors

Following ASCI, Rho activation contributes to the collapse of axonal growth cones, axonal regeneration failure, and neuronal loss. Cethrin (VX-210) is a recombinant inhibitor of Rho that has been shown to promote axonal outgrowth on inhibitory substrates both *in vitro* and *in vivo*. Fehlings et al conducted a phase I/IIa clinical study to examine the safety and tolerability of Cethrin for acute SCI. No serious adverse events were noted in this study. The most considerable change in motor score was observed among cervical patients treated with Cethrin [13]. A subsequent, randomized, double-blind, placebo-controlled phase 2b/3 study [14] that evaluated the efficacy and safety of local delivery of Rho inhibitor VX-210 9 mg at the site of the injury during spinal decompression/stabilization surgery within 72 hours after injury in patients after acute traumatic cervical SCI, was ended prematurely after the preliminary results met the predefined futility stopping rule.

Granulocyte Colony-Stimulating Factor

Granulocyte Colony-Stimulating Factor (G-CSF) is a significant growth factor in the activation and division of granulocyte colonies in the bone marrow. Several clinical studies have been performed to examine the impact of G-CSF on acute SCI. Inada et al [15] performed a prospective, non-randomized, controlled, multi-center clinical trial to investigate the neuroprotective effects of G-CSF on acute SCI. Patients were split into two cohorts. G-CSF was intravenously initiated for five straight days within 48 hours of injury in the G-CSF group. Patients in the monitoring community were handled equally, except for G-CSF management. A substantial increase in the ASIA score was observed in the G-CSF group 1 week after administration relative to the control group. Some random changes in the motor score were also observed in the control group, but the G-CSF group's substantial improvement was retained until one year of follow-up.

Minocycline

Minocycline is a tetracycline antibiotic that has neuroprotective and anti-inflammatory effects. Casha et al [16] performed a single-center, placebo-controlled, double-blind clinical trial to determine the effectiveness and safety of intravenous minocycline within 12 hours of ASCI. Twenty-seven patients were assigned to received minocycline, and 25 received a placebo. Patients treated with minocycline demonstrated better motor recovery compared to control. Although no distinction in recovery was noted with thoracic SCI, statistical significance was recognized in the subpopulation with cervical injury. The study revealed a tendency to improve motor scores in incomplete cervical SCI in the absence of any significant adverse effects.

TRH

Thyrotropin-releasing hormone (TRH) is a hormone produced by the hypothalamus that stimulates the release of thyroid stimulating hormone (TSH) and prolactin from the pituitary gland. TRH has been used as an anti-aging agent in experimental animals and has a wide range of actions suggesting that TRH plays a fundamental role in regulating metabolic and hormonal functions [17]. In a randomized-controlled trial, in 20 ASCI patients, TRH treatment was associated with sig-

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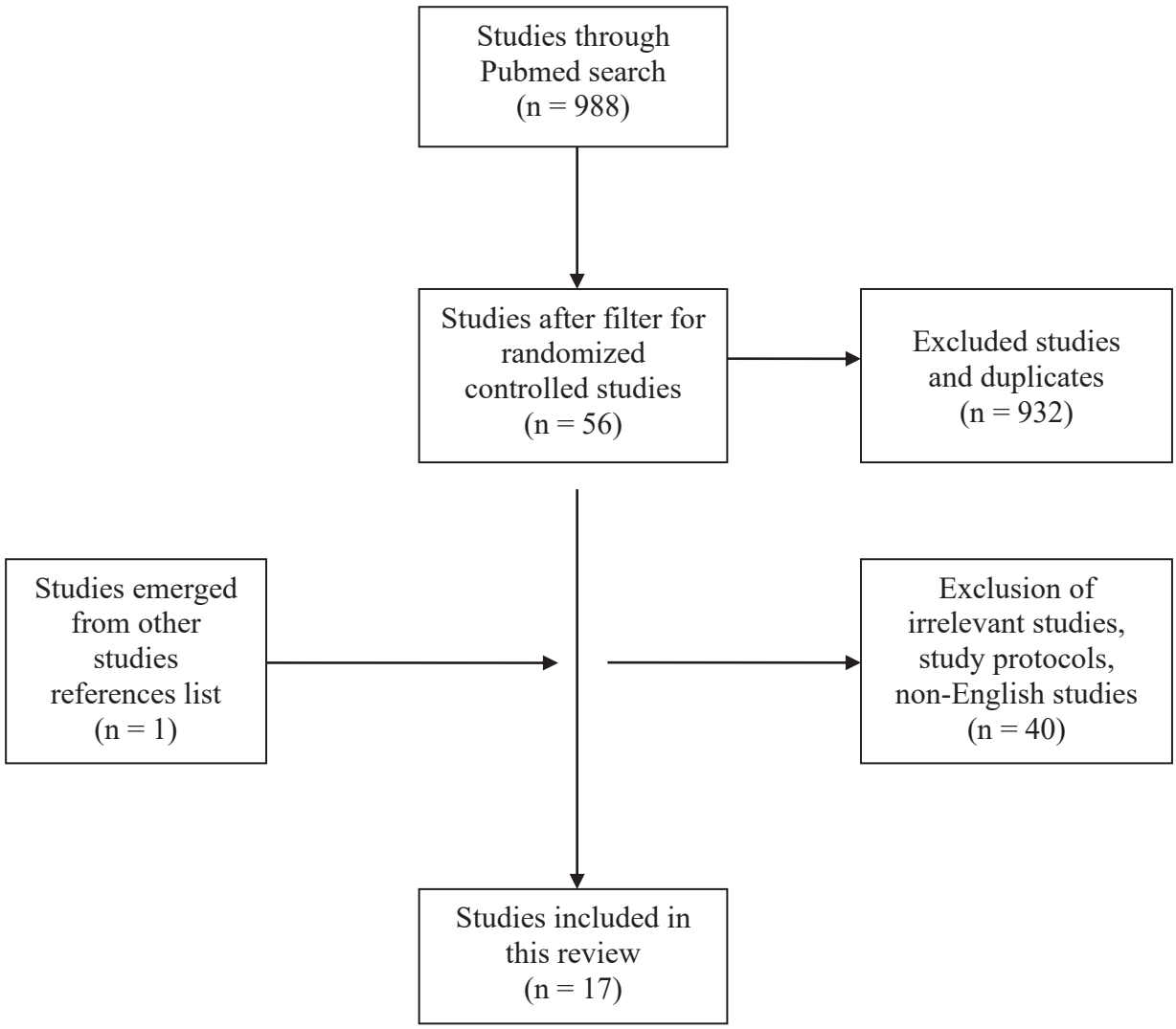
Figure 1. Flowchart



nificantly higher motor and sensory scores compared with placebo treatment [18].

Ganglioside GM-1

GM-1 ganglioside is a glycosphingolipid found in neuronal membranes that binds to secondary proteins that regulate signaling pathways involved in differentiation, regeneration, neuronal apoptosis, and neuroplasticity. A prospective, randomized, double-blind study of GM-1 ganglioside by Geisler et al in 37 patients with SCI showed significant improvement in mobility. Improvement mainly in lower limb function was observed only 48 hours after treatment [19]. These findings led to a large phase III trial in more than 750 patients at 28 institutions published by Geisler et al in 2001. However, the results of this study failed to achieve their ambitious primary outcome. The study showed that patients had improvements in the recovery of bowel and bladder function. Patients in both groups achieved significant improvement in functional independence.

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A major study error was the delay in GM-1 treatment, as most patients received methylprednisolone for the first time as part of their clinical treatment [20].

Progesterone and vitamin D

Aminmansour et al published a prospective, randomized clinical trial involving 64 adult patients with ASCI admitted to hospital within 8 hours of injury. All patients received methylprednisolone upon administration according to the protocol (30 mg / kg as bolus dose and 15 mg / kg every 3 hours to 24 hours). Patients were randomized to receive an intramuscular injection of 0.5 mg / kg progesterone twice daily and 5 μg / kg orally of vitamin D3 twice daily for up to 5 days (n = 32) or placebo (n = 32). Patients who received progesterone and vitamin D had significantly higher motor scores and sensory function after 6 months of treatment. Those treated within 4 hours of injury had significantly improved mobility and sensory function 6 months after treatment in the progesterone and vitamin D groups. The researchers concluded that administration of progesterone and vitamin D in the acute phase of traumatic spinal cord injury was associated with better functional recovery and outcome [21].

Conclusions

There is currently no drug with a high level of evidence that can be administered against acute spinal cord injuries. There is not enough convincing evidence that high doses of methylprednisolone for acute spinal cord injury are beneficial, given the high rate of complications. The role of steroids in acute spinal cord injury remains unclear, and some studies have shown that the risks of steroids outweigh the benefits. With many promising therapeutic agents and strategies being studied in ongoing trials for spinal cord injury, there is great hope of finding an effective treatment that would make significant progress while also benefiting patients with other neurological conditions.

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