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Non-pharmacological experimental treatments for spinal cord injury: a review

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Abstract
Introduction Spinal cord injury is a complex result of primary mechanical damage and the secondary vascular compromise and inflammatory reactions. Depending on timing, different treatment modalities may have various effects.
Conclusions We review the latest advances in terms of non-pharmacological experimental treatments.

Keywords Spinal cord injury · Treatment · Non-pharmacological · Therapies

Introduction

Hypothermia

In stroke patients, fever of 37.9 °C or above has been shown to be an independent risk factor predicting worse outcomes and patients with high fevers were far more likely to die within the first 10 days than those with lower temperatures [1]. A prospective study classified 390 consecutive cases of acute stroke into three admission temperature groups: hypothermic (36.5 °C or less), normothermic (36.6 to 37.5 °C), and hyperthermic (above 37.5 °C). These authors showed that admission body temperature was highly correlated with initial stroke severity, size of the infarct, mortality rate, and poor outcome. For a 1 °C difference in body temperature, the relative risk of poor outcome was more than doubled [2]. Randomized controlled trials of therapeutic hypothermia have demonstrated improved outcomes following cardiac arrest where the initial cardiac rhythm was ventricular fibrillation. However, hypothermia's effect on spinal cord injury (SCI) is uncertain and less documented [3]. One study with moderate epidural cooling immediately after SCI was not beneficial in terms of neuroprotection, tissue sparing, or motor outcome [4]. However, in pigs and after aortic cross clamping, mild hypothermia down to 32 °C dramatically increased the immediate tolerance of the spinal cord compared to normothermic pigs although there was a delayed ischemia with resultant paraplegia [5].

In another study, selective spinal cord cooling with cold saline infusion into the isolated aortic segment and transvertebral cooling by application of cooling pads showed reduced neurological damage [6]. Such hypothermia can be achieved systemically or regionally (Table 1). Systemic hypothermia with currently used medications, such as acetaminophen, NSAID, and steroids, has been shown to have minimal effects on fever. For instance, a controlled trial showed that acetaminophen only lowered the systemic temperature of 0.4 °C compared to controls [7].

Other experimental approaches for lowering the systemic temperature have used a local central venous cooling system. In this approach, an intravenous temperature exchange system is placed in the inferior vena cava via the femoral, subclavian, or jugular veins. The tip of the catheter is wrapped with a cooling balloon. Only the balloon is internally cooled with cool saline with no exchange between the cooled saline and venous blood. This cooled venous blood returns to the heart for redistribution to the body. In a relatively large controlled study in humans, when this system was compared to the use of acetaminophen in patients with SAH, traumatic cerebral injury or stroke, and the endpoint was only the fever burden during the first 72 h, it showed 2.87 h of fever burden compared to 7.92 h in the control groups. The neurologic outcome was not an endpoint and it should be noted that the overall numeric mortality rate was higher in the experimental group,

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Table 1 Classification of different types of spinal cord hypothermia

Hypothermia		
Systemic	Drug-induced	Acetaminophen
		NSAID
		Steroids
	Cutaneous	Cooling blankets
	Venous	Intravenous cooling balloon
Regional	LSCC	Arterial: antegrade cooling through segmental arteries
		Venous: retrograde cooling through azygos system
	Local	Percutaneous
		Paraspinal

LSCC local spinal cord cooling

but the mortality rate in the different groups of patients did not differ [8].

In terms of regional hypothermia, the following approaches have been used. One animal study with 24- to 48-h duration of low spinal cord perfusion pressure in 32 °C hypothermia suggested that hemodynamic manipulation together with hypothermia may allow routine complete preservation of normal cord function despite sacrifice of all segmental arteries [9]. One study has shown that short intensive hypothermia may decrease the spinal cord temperature more than percutaneous hypothermia but the neurologic outcome was more positively affected by a longer hypothermia that was provided by percutaneous cooling [10].

In a small animal study, pigs were randomized to segmental artery sacrifice at 32–37 °C and the spinal cord integrity was assessed with myogenic-evoked potential (MEP) monitoring. Stepwise craniocaudal sacrifice of segmental arteries was continued until MEP diminution occurred and the last segmental artery was then reopened. Fluorescent microspheres were used to measure spinal cord blood flow at baseline, 5 min, 1 h, and 3 h after segmental artery sacrifice. Hind limb function was monitored for 5 days. Almost all segmental arteries could be sacrificed with preservation of spinal cord function. Interestingly, a larger number of the segmental arteries could be sacrificed in the hypothermic group. No major change occurred in the central cord in normothermic animals, but there was significant transient hyperemia in segments adjacent to extra segmental vessels that were reduced by hypothermia, as cord blood flow at 32 °C was 50 % of that at 37 °C [11].

In another small controlled study, 4 °C saline mixed with adenosine was retrogradely injected into the hemiazygos vein showing significant clinical improvement [12]. The previous study was followed by a recent animal study that showed that controlled retrograde normothermic perfusion alone through the azygos system provided some degree of protection from spinal cord ischemia in terms of mild to moderate hind limb movement in pigs compared to none in controls [13]. Most of the human clinical data on the regional hypothermia (local spinal cord cooling) are from thoracoabdominal aorta clamping and has shown some encouraging results [14–18].

CSF drainage

CSF drainage in order to decrease intramedullary pressure in SCI has scarcely been studied. Most of such studies have been performed in association with thoracoabdominal aortic surgery. In one controlled study in dogs, when pre-clamping lumbar drainage was administered prior to thoracic aortic clamping, the perfusion pressure was higher and the risk for paraplegia was lower [19]. In rabbits, CSF drainage showed improved perfusion pressures to the spinal cord, decreased spinal cord damage, and improved functional outcome [20].

Three human trials, with a total of 287 participants, have been performed. In the first trial of 98 patients, neurological deficits in the lower extremities occurred in 14 (30 %) of drained patients and 17 (33 %) of controls. The deficit was observed within 24 h of the operation in 21 (68 %) and from 3 to 22 days in ten (32 %). Drainage did not have a significant benefit in preventing ischemic injury to the spinal cord [21]. The second trial of 33 patients used a combination of drainage and intrathecal papaverine. It showed a statistically significant reduction in the rate of postoperative neurological deficits compared to controls [22]. In the third trial [23], TAAA repair was performed on 145 patients and CSF drainage was initiated during the operation and continued for 48 h after surgery. Paraplegia or paraparesis occurred in 9 of 74 patients (12.2 %) in the control group versus 2 of 82 patients (2.6 %) with CSF drainage. Overall, drainage resulted in an 80 % reduction in the relative risk of postoperative deficits [23, 24]. Percutaneous cooling of the epidural space and CSF drainage have been shown to be effective in reducing postoperative spinal cord injury in patients undergoing thoracoabdominal aneurysm repair [24].

Durotomy and subarachnoid perfusion

Iannotti et al. indicated that dural repair (allograft) can improve CSF flow adjacent to the injury site, which may be due to reduced meningeal scarring at the lesion site. Also, the lesion volume including posttraumatic cyst formation and macrophage/microglia invasion decreased significantly [25].

In a controlled trial, dogs underwent an acute spinal cord compression using an epidural balloon inflated to a pressure of 160 mmHg and maintained for 1 h. Treatment included durotomy only, durotomy with saline perfusion at room

temperature, and durotomy with oxygenated fluosol-DA perfusion at room temperature, with a follow-up of 2 months. Dogs undergoing perfusion of the spinal cord with either saline or oxygenated fluosol-DA had significantly improved motor recovery compared with dogs undergoing durotomy only. Perfusion with oxygenated fluosol-DA resulted in significantly better motor recovery than did perfusion with normal saline. Microscopic examination of the spinal cords failed to reveal a substantial difference between the three groups. However, dogs with better functional results tended to have less destruction of the white matter [26].

Functional electrical stimulation

Functional electrical stimulation (FES) was first evaluated in 1967 by stimulating muscles. Further development of this technique made it possible to stimulate certain divisions of a peripheral nerve. FES is gaining use in clinical rehabilitation. To be helped by FES, the patient must have an upper motor neuron or spinal cord damage, functioning lower motor neuron or peripheral nerve, no osteoporosis, and be in good general health. These methods not only strengthen the atrophied muscles, but also lead to functional mobility of the muscles, directly or indirectly through stimulation of the corresponding nerves.

There has not been much work on stimulating the injured spinal cord in order to achieve regeneration. One study with direct intraspinal placement of electrical microstimulators in the intermediate and ventral gray matter of T10–12 was performed in rats caudal to a thoracic hemisection at T8–9, showing some muscular activity and movement although not enough to cause coordination or weight bearing [27].

Electromagnetic stimulation

Oscillating magnetic stimulation has shown trophic effects on in vitro and positive functional effects in vivo in different animal models with spinal cord injury. Therefore, a human study was performed including patients with complete motor and sensory spinal cord injury but without transection between C5 and T10. Within 18 days after the trauma, an oscillating magnetic field stimulator was implanted and explanted 15 weeks post-trauma. A significant improvement was observed both in sensory and, to some extent, in motor outcomes. The method was considered safe and reliable [28].

Hyperbaric oxygen

In 1963, Breslau and Schwarz reported the protective effects of hyperbaric oxygenation on the spinal cord during the occlusion of the thoracic aorta [29]. In 1975, Balentine reported a relative large series with rats exposed to hyperbaric oxygen in which 25 % had segmental foci of central gray matter necrosis in the cervical and lumbar enlargements, indicating that hyperbaric oxygen may have potential danger to the spinal cord [30].

In 1977, Holbach et al. reported 13 patients with spinal cord injury that underwent ten to fifteen 40-min sessions of 1.5 atm hyperbaric oxygen in which six showed neurological improvement, especially in the motor system. In eight patients, the arterial and CSF oxygen were increased [31]. In the same year, Yeo et al. reported positive results in a controlled contusion model of spinal cord injury in sheep in which hyperbaric oxygen groups showed less cyst formation, degeneration, and better motor outcomes [32]. The same group applied hyperbaric oxygen to ten patients with spinal cord injury and did not observe any harmful effects on the spinal cord [33]. Simultaneously, another group reported positive effects in humans [34]. In 1981, a conduction study in cats showed significant positive effects on spinal cord-evoked potentials if hyperbaric oxygenation was applied within 2 h of trauma and if the compression trauma was less than 400 g/cm [35].

In 1989, a Chinese group reported 12 years of experience with a total number of 1,288 patients, in multiple areas including decompression sickness, osteomyelitis, chronic skin ulcer, burn injury, gas gangrene, retinal artery insufficiency, cerebrovascular stroke, and cerebral and spinal cord injury. In the last combined group, they reported a 45 % improvement. Importantly, they only reported three cases of reversible oxygen toxicity [36]. In 2000, a Japanese group reported a controlled study with 34 patients with spinal cord injury in which hyperbaric oxygenation showed a moderate positive outcome compared to controls [37].

In 2001, Murakami et al. performed a controlled study on the temporal aspect of hyperbaric oxygenation in rats. The injury was though not mechanical but circulatory through infrarenal aortic occlusion. It showed that hyperbaric oxygenation within 30 min of ischemia had significant effects both on the functional as well as histological outcomes [38]. In 2003, Huang et al. showed that the temporal aspect of the intervention can be delayed to 6 h after the trauma if the treatment is repeated [39].

In 2007, Kahraman et al. investigated the oxidative status of the rat spinal cord after a controlled clip compression trial with two different experimental groups: methylprednisolone and hyperbaric oxygen. The hyperbaric and not methylprednisolone group showed significantly lower levels of thiobarbituric acid reactive substances, superoxide dismutases, and glutathione peroxidase in the injured spinal cord [40, 41]. However, the levels in the hyperbaric oxygen group were higher than the sham group [42].

Taken together, multiple non-pharmacological treatment modalities have shown promising results in the treatment of SCI. Our current knowledge of spinal cord regeneration is based on such studies that warrant further investigation via prospective randomized human trials.

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