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Therapeutic Hypothermia for Spinal Cord Injury

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Introduction

Spinal cord injury is a devastating problem that affects approximately 11,000 individuals each year in the United States. According to NIH's National Institute of Neurological Disorders and Stroke, some 280,000 Americans are living with the debilitating consequences of SCI (Tuszynski et al. 2006). This injury mainly effects young males and leaves them with devastating consequences including loss of motor and sensory function, a range of autonomic problems, and bowel and bladder dysfunction. As with other neurological disorders, recent experimental and clinical work has been directed toward targeting secondary injury mechanisms with new treatments that may limit the progression of neurological symptoms, including paralysis. Although various pharmacological strategies including steroids, gangliosides and excitatory amino acid antagonists have been tested on SCI patients, no clinical trials have resulted in a proven treatment for acute spinal cord injury.

Researchers are increasingly aware of the importance of systemic and nervous tissue temperature after brain and spinal cord injury (Bernard and Buist, 2003). Recent experimental studies have shown that even modest levels of hypothermia (33-34 degrees celsius) can reduce many of the devastating consequences of cerebral ischaemia and trauma and improve structural and functional outcome in clinically relevant animal models. Indeed, recent success in terms of translating findings from the laboratory to the bedside has been reported in cardiac arrest patients (Bernard et al. 2002). Good clinical outcomes have also been recently reported with modest hypothermia after neonatal asphyxia and other indications such as traumatic brain injury (Gluckman et al. 2005; Marion et al. 1997; Polderman et al. 2004).

Spinal Cord Injury

The history of hypothermia for treating SCI is full of studies showing inconclusive findings. Clinical studies were begun in the 1960s following promising experimental reports (Albin et al. 1967; Tator et al. 1973). In those early studies, local profound cooling induced by cold saline irrigation during customary surgical decompression was shown to be feasible for acute SCI. Nevertheless, these early clinical studies were difficult to evaluate because of a limited number of patients, lack of randomised control groups, and concomitant interventions including spinal cord compression and the use of steroids such as methylprednisolone. Also, a major problem with utilising hypothermia in the clinical arena is the need for prolonged anaesthesia to prevent shivering. The need in some cases to monitor neurological function and the potential risk of adverse effects including pneumonia, bleeding and cardiac problems have complicated the use of prolonged cooling in some patient populations.

Recently, the emergence of intravascular heatexchange catheters as well as progress in the development of more efficient surface cooling devices has helped advance the therapeutic hypothermia field. In addition, shivering can now be controlled with a new generation of drugs, which act by lowering shivering threshold.

Experimental studies of spinal cord cooling have consistently shown benefits in reducing lesion volume and improving functional outcome. In the mid 60s, studies by Albin and colleagues (1967) showed that profound levels of hypothermia improved outcome. In the 1970s, Green and colleagues (1973) showed that hypothermia was effective in decreasing the degree of hemorrhage after SCI. Most recently, modest levels of

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hypothermia have been shown to also improve outcome in rodent models of SCI. Yu and colleagues (2000) reported that modest levels of hypothermia (33°C) administered acutely for a four hour period improved open-motor function and decreased the degree of both grey and white matter damage. Thus, it is clear the modest levels of hypothermia can be used to improve outcome in experimental models without introducing the potentially devastating effects of profound hypothermia on a variety of biological processes.

How Hypothermia Works

A rich body of literature exists that describes how modest levels of hypothermia can be neuroprotective. In addition to lowering the metabolic demand of the injured tissue, modest hypothermia affects various injury processes involved in cell death including excitotoxicity, apoptosis, free radical generation, and inflammation. In a study by Chatzipanteli and colleagues (2000), modest hypothermia after SCI reduced the recruitment of inflammatory mediators including polymorphonuclear leukocytes into the contusion site. Other studies have reported that post-injury cooling alters cell signaling cascades involved with programmed cell death and apoptosis. **Thus, the reason why hypothermia is such a strong neuropro- tectant strategy is it affects multiple pathophysiological mechanisms important in cell death mechanisms. This is in contrast to various drug treatments that primarily affect only one injury mechanism.**

Discussions regarding the importance of temperature in CNS injury must also consider the detrimental effects of mild elevations in temperature. Periods of fever are common in critically injured brain and spinal cord patients (Kilpatrick et al. 2000), and experimental studies have shown that artificially induced periods of mild hyperthermia significantly worsen outcome. Yu and colleagues (2001) reported that elevated spinal cord temperature to 39°C for four hours following SCI worsened behavioural outcome and led to an increase in contusion volume. Experimental studies have shown that elevations in temperature aggravate many of the injury mechanisms that are attenuated with hypothermia. Thus, it is critical to establish intensive care unit procedures to effectively inhibit periods of fever, in addition to possibly inducing modest hypothermia.

Cooling Approaches

A recent advance in inducing hypothermia in patient populations is the development of new approaches to produce systemic cooling. External cooling devices such as ice packs or forced air or water circulation blankets may not critically control temperature during the cooling and rewarming phases and may limit the ability to transport and access patients. Endovascular catheters have now been developed and tested where venous blood is cooled as it passes around a cold saline filled balloon. This approach allows for a satisfactory rate of cooling and the critical maintenance of the desired temperature for several days. New energy transfer pads have also been developed that are more conductive and adhesive to the skin surface. In addition to utilising these new devices for producing modest hypothermia, these approaches can also be used to reduce fever burden, an important clinical problem in the intensive care unit.

In addition to systemic hypothermia, local cooling approaches are also being developed especially in the area of brain injury. However, local cooling approaches after SCI have been developed and tested in limited experimental and clinical conditions. A major question regarding the use of local cooling in SCI is the level of hypothermia that is most protective. Although early studies used cold saline irrigation to induce profound cooling, it is not known whether these low temperatures were nec essary or possibly produced harm by affecting the local hemodynamic state of the injured tissue. More research is therefore required to clarify these questions before these approaches should be translated to the clinic.

Clinical Protocols

Use of hypothermic circulatory arrest for descending thoracic aortic resection has been shown to afford excellent preservation of spinal cord function in a number of clinical studies. However, a recent high profile case has brought the use of hypothermia in acutely spinal cord injured patients to the forefront in terms of new therapeutic treatments. In that situation, a variety of medical modalities including early cord stabilisation, neuroprotective treatments, imaging and surgical interventions, and intensive care management all likely contributed to the good outcome recently reported in the popular press. It is clear that more experimental and clinical data are required before one can conclude whether or not therapeutic hypothermia is safe and effective in treating acute spinalcord injury. Modest hypothermia is an experimental procedure and certainly has potential risk factors and unwanted side effects associated with its use. Based on clinical data from studies in other types of neurological disorders, periods of hypothermia may need to be extended for days, thereby increasing the potential for adverse consequences. As sufficient randomised clinical trial data on the use of modest hypothermia in acute spinal cord injured patients is lacking, it is clear that controlled studies need to organised and conducted and the potential benefits carefully weighed relative to potential risks.

Recently the AANS/NSS joint sections of disorders of the spine and the AANS/NCNS joint section of trauma published a position statement regarding the use of systemic therapeutic hypothermia for the treatment of acute SCI. In that document, Resnick and colleagues (2007) recommended that clinicians should be aware that systemic hypothermia has been associated with medical complications in the head injured population prior to considering this treatment modality. Also, after reviewing the published literature on hypothermia and SCI this group found insufficient evidence available at this time for either local or systemic therapeutic hypothermia to be recommended as a treatment for acute SCI. Thus, it is clear that continued investigation is required if this potentially exciting therapy is to advance to more acutely injured spinal cord injured patients.

Summary

Although a large amount of experimental and clinical evidence supports the continued study of modest hypothermia as a neuroprotective strategy after SCI, this treatment is experimental and certainly not the "standard of care".

This is an important point for the public as well as treating physicians to keep in mind. Ongoing studies are determining various unknown factors associated with the cooling procedure including the therapeutic window for hypothermia treatment, length of cooling, and how to best rewarm the

patient. In addition, important questions regarding pharmaceutical agents that may be combined with modest hypothermia to extend the therapeutic window and/or provide more complete protection are being tested. To advance this treatment, well-designed prospective controlled trials to accumulate sound evidence for this experimental therapy are required. Based on ongoing clinical studies, available data indicates that treatment with modest hypothermia in a controlled protocol/environment can be safely applied in a number of clinical conditions, but its effectiveness in terms of clinical outcome after SCI remains to be determined.

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