Clinical Neurology and Neurosurgery 154 (2017) 79–88

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

The role of therapeutic hypothermia in the management of acute spinal cord injury

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ARTICLE INFO

Article history:
Received 11 November 2016
Received in revised form
30 December 2016
Accepted 2 January 2017
Available online 17 January 2017

Keywords:
Acute spinal cord injury
Circulatory arrest
Endovascular cooling
Hypothermia, local
Hypothermia
Systemic
Ischemia

ABSTRACT

This review paper investigates the history, efficacy, and administration of systemic and local hypothermia for spinal cord injury (SCI). It summarizes the published experimental and clinical evidence on hypothermia for SCI and analyzes the potential for further research. Early experimental animal research showed that local hypothermia improved recovery and gain of function after acute SCI. However, in the early 1970s, clinical research findings did not coincide with results of these animal trials, which led to a loss of interest in local hypothermia. Since the 1980s, systemic hypothermia has been successfully used to treat SCI in both animals and humans. An abundance of positive evidence suggests that clinical trials are needed to determine the effectiveness of hypothermia for SCI. As a first step, we investigated the published clinical and experimental evidence on the use of hypothermia for SCI patients, who have few available treatment options. We searched PubMed for English-language reports published from 1940 to 2016 containing terms related to SCI treatment using hypothermia. We reviewed all articles on local hypothermia and acute SCI or on systemic hypothermia and acute SCI. Bibliographies of retrieved publications were also screened for additional citations. Ninety-six papers were selected. The clinical use of hypothermia is most successful if applied according to certain optimized parameters (e.g., duration, temperature, time from injury to initiation of cooling, and rewarming time). Preliminary data suggest that modest systemic hypothermia applied for 48 h provides the best therapeutic value, but the parameters for use of local hypothermia vary greatly. Experimental evidence and some clinical evidence suggest that both local hypothermia and systemic hypothermia are beneficial for acute SCI. Future research should focus on defining the optimal levels of parameters. Large, multicenter, controlled clinical trials are needed to investigate its therapeutic potential.

Contents

Abbreviations: AAA, abdominal aortic aneurysm; ASIA, American Spinal Injury Association; BBB, Basso, Beattie, and Bresnahan; ISNCSCI, International Standards for Neurologic Classification of Spinal Cord Injury; NFL, National Football League; SCI, spinal cord injury; TNF-α, tumor necrosis factor α.

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http://dx.doi.org/10.1016/j.clineuro.2017.01.002
0303-8467/

1. Introduction

Acute spinal cord injury (SCI) is a severe and sudden event that carries serious health, financial, social, and quality-of-life burdens. For the 11,000 new cases of SCI every year in the United States, fewer than 5% of the patients with American Spinal Injury Association (ASIA) Grade A injuries ever improve to Grade B, C, or D [1,2]. Although a few potential treatments for this devastating injury exist, such as corticosteroids or decompressive surgery, no therapeutic agent clearly protects against the damage precipitated by acute SCI [3,4]. The damage and pathology related to SCI are categorized in 2 phases: primary and secondary. The primary phase of damage is characterized by the mechanical insult to the spine, which results in damage to white matter tracts, gray matter neurons, major vasculature, and microvasculature [5]. The second phase of damage begins moments after the injury, lasts for years, and is facilitated by hypoxia, hemorrhage, glial scarring, and altered immune pathways [6]. Most treatments for SCI focus on mitigating the secondary phase of damage, with the goal of preventing further damage and altering the neurological course of the patient. Researchers believe that reducing the metabolic demand and the inflammatory processes of the spinal cord leads to a better chance that the patient will recover neurological function [6]. However, many therapies, such as methylprednisolone, are supported only by inconclusive evidence or are effective only under specific circumstances [7]. One potential treatment that has shown promise over the past few decades is therapeutic hypothermia.

Hypothermia can be delivered via 2 main approaches: local and systemic. Systemic hypothermia focuses on cooling the core temperature of the body, whereas local hypothermia focuses on cooling only the region of the injury or the spinal cord. Both approaches are hypothesized to mitigate the damages related to SCI by retarding the subsequent inflammatory and metabolic changes [8–12]. Therapeutic hypothermia is a unique approach that was developed in the 1940s and has been shown to be effective in treating acute SCI and various other conditions. Over the years, evidence has confirmed the neuroprotective effects of therapeutic hypothermia during ischemic injury after circulatory arrest and during surgical repair of an aortic aneurysm [4,13,14]. However, not all implementations of therapeutic hypothermia have shown promise. For instance, in 2005, a large multicenter trial investigated the use of intraoperative systemic hypothermia (33 °C) during craniotomy for patients with acute subarachnoid hemorrhages. This study of 1001 patients found that systemic hypothermia failed to improve outcomes [15].

In recent years, systemic hypothermia has taken the spotlight for its use after SCI more often than local hypothermia [5,12,16,17]. Animal trials have repeatedly shown its benefit in protecting the spinal cord after spinal cord lesions, ischemia, and contusions, and many reviews have encouraged researchers to move forward with clinical trials of this treatment method [10,12,16,18,19]. In contrast, the use of local hypothermia for SCI has produced variable results in animal and clinical studies [6,10,18,20]. Investigation into the delivery of, and the approach to, local hypothermia is still in its early stages. In this article, we will thoroughly describe the history of the use of local hypothermia for spinal cord injuries and will examine whether future experiments are indicated. We will also describe the clinical development of systemic hypothermia.

2. Mechanism of action of hypothermia

Although the entire scope of the effect of hypothermia on the spine is not fully understood, a few observations are notable. In addition to reducing the overall metabolic demand of neuronal tissue, hypothermia has been shown to reduce neutrophil invasion during, and even after, hypothermic states [8,9]. Hypothermia also exerts other immunosuppressive effects, such as the inhibition of microglia and the expression of tumor necrosis factor α (TNF-α) [10,11]. Apoptotic and autophagic systems have also been shown to be suppressed during therapeutic hypothermia through reduced expression of various caspases and decreased staining of biomarkers associated with autophagy, LC3 (microtubule-associated protein 1 light chain 3), and Beclin-1 [12]. These important changes in the inflammatory and apoptotic pathways may play a part in the neuroprotective effects of hypothermia. Furthermore, cooling has been found to help preserve white and gray matter and overall axonal connections [14,21,22]. These findings suggest that the primary protective mechanism of hypothermia is stagnation of the immune-mediated and metabolic damage that occurs after SCI.

3. Administration of hypothermia

The human body possesses important mechanisms to combat accidental hypothermia. These mechanisms must be avoided when hypothermia is administered for therapeutic purposes because they can hinder the process or even be life-threatening [8]. The mechanisms are circumvented in patients who are anesthetized and intubated. The approaches to local and systemic therapeutic hypothermia can be achieved through various methods, including surface cooling, endovascular cooling, or the use of a localized epidural heat exchanger [18,23].

3.1. Surface cooling

Surface cooling is the most common method of inducing hypothermia. Older and simpler methods include ice packs, alcohol baths, cooling blankets, and fans. Depending on the distribution and extent of the cooling method, the patient will experience local or systemic cooling. Surface cooling is an inherently crude method of inducing hypothermia; consequentially, one of the main difficulties with its use is appropriate temperature regulation. The use of surface cooling to induce hypothermia is slow and difficult to control, and its effectiveness is reduced in obese patients [13]. However, a unique benefit of surface cooling is its versatility. The use of ice packs and cooling blankets allows the process of hypothermia to be initiated immediately and on site. In the hospital setting, newer and more efficient machines are available, such as the Alsius CoolGard 3000 (Zoll Circulation, Inc., Sunnyvale, CA) and the Arctic Sun Temperature Management System heat-exchange device (Medivance, Louisville, CO). These machines are equipped with gel- or water-based cooling pads that can cool faster than ice packs to