REVIEW

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The role of therapeutic hypothermia in acute spinal cord injury

Antoniou G[1]., Vlamis J[2]., Pneumatikos S.[2]

[1]*Department of Physiotherapy, KAT Hospital, Athens, Greece*

[2]*3rd Department of Orthopaedic Surgery, University of Athens, KAT Hospital, Athens, Greece*

ABSTRACT

Ancient Egyptians were the first to use therapeutic hypothermia; thus, it is not a new concept. The term "hypothermia" is defined as a core temperature < 35° C (95° F). A spinal cord injury (SCI) is considered as one of the most significant injuries someone can endure since damage to just a small area of the body could implicate multiple body systems. A wide range of different mechanisms leading to tissue damage in the cord could cause injury.

Various early clinical SCI studies have investigated therapeutic hypothermia as a treatment strategy and have shown that if applied according to certain optimized parameters, the clinical use of hypothermia is most successful. Such parameters are temperature, time from injury to initiation of cooling, and rewarming time. Both local hypothermia and systemic hypothermia could be beneficial for acute SCI according to experimental evidence and some clinical evidence. The underlying mechanisms by which small reductions in central nervous system temperature can improve outcomes in brain and spinal cord injury models are still under investigation.

KEY WORDS: therapeutic hypothermia, spinal cord injury

Introduction

Ancient Egyptians were the first to use therapeutic hypothermia; thus, it is not a new concept. Hippocrates had the idea that cooling a person can slow biological processes that lead to death and thus he advised packing wounded soldiers in the snow (circa 450 B.C). During the French invasion of Russia (decade of 1800), a battlefield surgeon noticed that wounded soldiers placed closer to fire died sooner than those placed in colder bunks. At that time, surgeons used cryoanalgesia for amputations and noticed that hypothermia acted as an analgesic and at the same time slowed bleeding. The clinical interest of therapeutic hypothermia began in the 1930s with case reports on drowning victims who were resuscitated successfully despite prolonged asphyxia.[1]. One of the first scientific papers referring to therapeutic hypothermia was

CORRESPONDING AUTHOR, GUARANTOR

Georgia Antoniou
14, Pavlou mela St., Agia Paraskevi 15343,
Athens, Greece
+0306972260142, georgoula.antoniou@gmail.com

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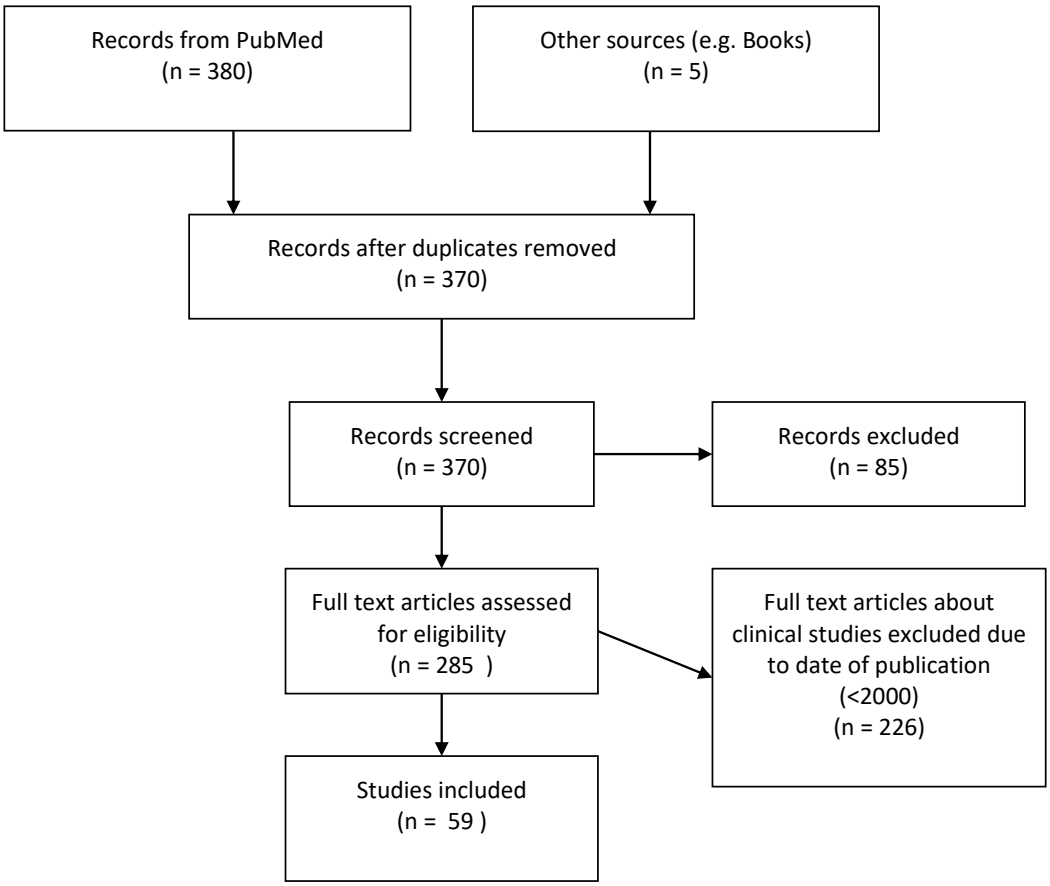
Flowchart
THE ROLE OF THERAPEUTIC HYPOTHERMIA IN ACUTE SPINAL CORD INJURY
TABLE 1



published in 1943 and described improvement after traumatic brain injury when temperatures were lowered to 32.7° C. In the decades of 1950 and 1960, clinical trials using deep hypothermia were started but abandoned soon because of adverse effects. During the decade of 1990, mild hypothermia was applicated in three cases of cardiac arrest after successful resuscitation, and all three made a complete recovery without residual neurological damage [2].

Definition of hypothermia is as a core temperature below 35° C. A more detailed classification of hypothermia is the following

- mild 35° C to 32° C
- moderate 32° C to 28° C
- severe 28° C to 20° C
- profound < 20° C [3].

Spinal cord injury refers to the damage of spinal cord due to trauma or disease. Immediately after the injury, different mechanisms lead to tissue damage in the cord. These include destruction of spinal cord neurons from direct trauma, compression by bone fragments or hematoma, ischemia from damage or compression of the spinal arteries and swelling of the cord tissue.

Patients with SCI experienced deficits in motor, sensory or autonomic functions. These clinical outcomes are closely related to the level of the injury.

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The International Standards for Neurological and Functional Classification of Spinal Cord Injury published by American Spinal Injury Association (ASIA) are based on clinical examination and evaluation of motor function and sensory. Depending of the level of SCI, patients experience tetraplegia or paraplegia. Tetraplegia is the injury to the spinal cord in the cervical level that result to partial or complete loss of motor or sensory in all four limbs. On the other hand, paraplegia is defined as loss of motor or sensory in lower extremities. Another significant classification is the complete or incomplete SCI. Patients are classified as having a complete SCI when no voluntary motor or sensory is described below the level of SCI. According to ASIA, a SCI is complete when the patient has any spinal level below, which there is no neurological function. [4,5].

In this paper we review the literature considering therapeutic hypothermia and acute spinal coed injury. The database that we mostly used was PUBMED and the keywords for our search were therapeutic hypothermia, systemic and local and spinal cord injury. We investigate all studies published from 1980 until 2020 containing the above terms, with both clinical and experimental evidence. Our study included also papers with animal trials. We excluded the studies about therapeutic hypothermia that were performed before 2000.

(Table 1)

Discussion

Therapeutic hypothermia

Therapeutic hypothermia has been investigated in many clinical studies [6]. During the decade of 1960, local hypothermia was induced in patients by administering cold saline to the exposed spinal cord after laminectomy and during decompression surgeries [7, 8]. These studies combined with experimental observations described that local hypothermia resulted in neurological improvement [8-10].

The bias of the previews studies was the fact that hypothermia was combined with surgical techniques, such as decompression. Furthermore, the administration of corticosteroids such as methylprednisolone in SCI as anti-inflammatory therapy is probably also a bias error [8, 12,13]. Another difficult issue in analysis and interpretation of the results of therapeutic hypothermia was the kinds of methods that the researchers choose to apply to the patients with SCI. Different approaches were used to improve reduction of the temperature such as cold fluids, ice baths and cooling blankets. These techniques were very inefficient, and therefore difficult to maintain therapeutic levels and adequate time of hypothermia. [14, 15].

Hypothermia is believed to have neuroprotective role against periods of ischemia that occur during time of spinal cord compression or aortic reconstruction surgery [16-18]. In other studies, therapeutic hypothermia has been shown to improve neurological outcome and recovery of motor and sensory function, when applied in models of compression injury [19]. Both local and systemic hypothermia has as a result the reduction of neurological deficits caused by spinal cord ischemia in studies which the aorta is clamped for specific period of time [20, 21].

Methods of local cooling lead to low levels of hypothermia without adverse effects, such as hypotension, bradycardia, and respiratory infection that can be seen in cases where systemic hypothermia is used [22-24]. The disadvantage of local cooling is that the procedure cannot be initiated until rather invasive surgical approaches are completed to allow the application of cold fluid onto the surface of the injured spinal cord. The realization that only relatively moderate levels of hypothermia are required to produce improved outcome has allowed for systemic hypothermia to be evaluated in clinically relevant animal models, as well as targeted patient populations [24, 25]. During the decades of 1960 and 1970, the interest in therapeutic hypothermia for the treatment of acute neurological disorders had decreased because new pharmacological agents were developed with similar and in some case better neuroprotective results.

Studies with animal models showed that local hypothermia improved recovery and improvement of motor and sensory function after

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SCI. Latest clinical research findings did not match with the results of these animal trials, and thus the role of local hypothermia in therapy of SCI had gradually underestimated. Since the 1980s, systemic hypothermia has been successfully used to treat SCI in both animals and humans. [26].

Therapeutic hypothermia decreases free radical production, inflammation and intracranial pressure, and improves cerebral metabolism after traumatic brain injury and cerebral ischemia, thus protecting against central nervous system damage [27].

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). Experimental evidence and some clinical evidence suggest that both local hypothermia and systemic hypothermia are beneficial for acute SCI [27].

Many researchers have approved that the use of hypothermia provides neuroprotection after SCI. The clinical studies that were mostly focused on local cooling techniques had mixed and complicated results. More recent data for the therapeutic role of systemic hypothermia proved its safety and its benefits. Methods used to induce systemic hypothermia such as endovascular cooling seemed to be safe and reliable [27].

Local cooling was utilized to cool areas of the damaged spinal cord. In those investigations, relatively profound levels of hypothermia were shown to produce marked neurological and functional recovery after spinal cord trauma [28]. Modest hypothermia (32°C–34°C) can deliver the potential benefits of hypothermia without incurring the complications associated with deep hypothermia. Mild hypothermia introduced after a traumatic or compressive spinal cord injury improved function and reduced histopathological damage [27,29-32]. Moderate hypothermia introduced after cervical spinal cord injury improved histopathological and behavioral outcomes. Likewise, improved forelimb function, preservation of motor neurons, and decreased contusion volumes occur in rats cooled after cervical traumatic insult [33]. This evidence shows that mild to moderate hypothermia improves outcome in models of both cervical and thoracic spinal cord injury [32].

Histologically, the application of hypothermia after spinal cord injury significantly increased normal-appearing white matter (31% increase) and gray matter (38% increase) volumes, greater preservation (four-fold) of neurons immediately rostral and caudal to the injury epicenter, and enhanced sparing of axonal connections from retrogradely traced reticulospinal neurons (127% increase) compared to normothermic controls[32]. Case reports and clinical studies have provided encouraging results regarding the safety and efficacy of moderate hypothermia following severe spinal cord injury [34]. In compression injury models, hypothermia reduced blood flow to the focal area of the injured spinal cord [29]. Also, when used before decompressive surgeries, hypothermia can prevent neurological decline [35].

Numerous studies have investigated the underlying mechanisms by which small reductions in central nervous system temperature can improve outcomes in brain and spinal cord injury models [36].

Mechanisms of hypothermic protection

The following will summarize the current thinking regarding basic mechanisms of hypothermic protection:

(i) Reduced cerebral metabolism: Cerebral metabolism decreases by 6% to 10% for each 1°C reduction in body temperature during cooling. However, reduced metabolic rates are only one of many mechanisms underlying hypothermia's protective effects [37, 38].

(ii) Apoptosis, calpain-mediated proteolysis, and mitochondrial dysfunction: Hypothermia can interrupt the apoptotic pathway, thereby preventing cellular-injury-induced apoptosis. Effects of hypothermia include inhibition of caspase enzyme activationprevention of mitochondrial dysfunction, modification of intracellular ion concentrations, and reduce overload of excitatory neurotransmitters. The c-Jun NH2-terminal kinase pathway mediates traumatic injury-induced apoptosis in astrocytes. Prolonged hyperthermia as

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a secondary insult worsens apoptosis by increasing c-Jun NH_2-terminal kinase activation. These studies indicate that apoptotic cell death is another important target by which temperature may affect long-term outcome in various models of central nervous system injury [39,40].

(iii) Ion pumps and neuroexcitotoxicity: Reperfusion and ischemia interrupt the delicate balance between calcium influx and sequestration at the cellular level. Even a relatively small decrease in temperature can significantly improve ion homeostasis, whereas the occurrence of fever can trigger and stimulate these destructive processes [41].

(iv) Immune and inflammatory responses: Numerous animal experiments and clinical studies have shown that hypothermia suppresses ischemia-induced inflammatory reactions and the release of proinflammatory cytokines. Hypothermia may block ischemic damage by blocking cytochrome c release or caspase activity after both transient focal and global ischemia. It also prevents or mitigates reperfusion-related DNA damage, lipid peroxidation, and leukotriene production, and decreases the production of nitric oxide, which is a key agent in the development of post-ischemic brain injury. Moreover, the proinflammatory response of stimulated microglial cells is significantly reduced after moderate hypothermia [42-43].

(v) Free radical production: Free radicals can oxidize and damage numerous cellular components. ascorbate is known to be involved in many neurochemical processes. It is one of the most significant antioxidants and free radical scavengers that relieve oxidative stress in the central nervous system. Compared with other tissues, the high concentration of ascorbate in the nerve tissue also strongly suggests that ascorbate plays a very important role in neurophysiological and pathological processes. Preliminary conclusions are drawn that a significant reduction in spinal cord ascorbate concentration in rats with spinal cord injury under mild hypothermia may be related to protective mechanisms associated with secondary spinal cord injury. Thus, under hypothermic conditions, significantly fewer free radicals are generated, even though free radical production is not completely prevented. This allows the endogenous antioxidative (protective) mechanisms to better cope with free radicals that are being released, thereby preventing or significantly mitigating oxidative damage [44].

(vi) Vascular permeability, blood-brain barrier disruption, edema formation, tolerance to ischemia: Mild hypothermia significantly reduces blood-brain barrier disruptions and also decreases vascular permeability following ischemia-reperfusion, further decreasing edema formation [45].

(vii) Intracellular and extracellular acidosis and cellular metabolism: The diminished integrity of cell membranes, the failure of various ion pumps, development of mitochondrial dysfunction, inappropriate activation of numerous enzyme systems with cellular hyperactivity, and the disruption of various other intracellular processes all contribute to the development of intracellular acidosis, a factor that powerfully stimulates the abovementioned destructive processes. All of these factors can be significantly attenuated by hypothermia. Hypothermia during or after reperfusion increases the speed of metabolic recovery, with a better preservation of high-energy phosphates and reduced accumulation of toxic metabolites [46,47].

(viii) Coagulation activation and formation of microthrombi: Hypothermia has some anticoagulatory effects. Mild platelet dysfunction occurs at temperature ≤ 35°C, and inhibition of the coagulation cascade develops at temperature ≤ 33°C; platelet count can also decrease during cooling. In theory, this anticoagulation effect may constitute yet another neuroprotective mechanism. This remains speculative given that no studies directly addressing this issue have been performed [48].

(ix) Vasoactive mediators: Hypothermia affects local secretion of vasoactive substances such as endothelin, thromboxane A2, and prostaglandin I2 in the brain and other organs. The predominance of local vasoconstrictors can be corrected or modified by hypothermia [49].

(x) Influence on genetic expression: Hypothermia

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increases the expression of immediate early genes, which are a part of the protective cellular stress response to injury, and stimulates the induction of cold-shock proteins, which can protect the cell from ischemic and traumatic injury [50].

Combination with other therapies

Because of the benefit of therapeutic hypothermia in SCI, many researchers proceed to a next level and carried out clinical studies with combination of hypothermia with other therapeutic methods [51]. These therapies can be divided into three general categories: cell therapy, pharmaceutical therapy and other alternative therapies [52].

For cell therapy, stem cells are differentiated into a variety of cells within the nervous system in order to be used for the treatment of nerve diseases. Wang and coworkers found that combination treatment with therapeutic hypothermia produced synergistic effects in transplantation to promote the recovery of spinal cord injury [53].

Additionally, many drugs enhanced therapeutic hypothermia neuroprotection in nerve injury. They included chemical drugs, hormones, neuroprotectants and others. For example, valproic acid is a histone deacetylase inhibitor. Valproic acid also enhanced neuroprotective effect of hypothermia against ethanol-mediated neuronal injury, and improved survival in a rat cardiac arrest model [54]. Early post-hypoxia-ischemia administration of phenobarbital may augment the neuroprotective efficacy of therapeutic hypothermia [55]. In a study a series of neuroprotectants including albumin, atorvastatin, baclofen, brain-derived neurotrophic factor, bumetanide, citicoline sodium salt hydrate and cyclosporine A were applied to an oxygen-glucose deprivation and re-oxygenation-mediated neuronal injury. This research showed that combination of therapeutic hypothermia with brain derived neurotrophic factor, glibenclamide, dizocilpine, HUK or neuroglobin provided a better protection compared with a single treatment method [56]. Xenon, MgSO4 and Chinese traditional bloodletting treatment also offered better neuroprotection when combined with hypothermia [57-59].

Overall, an accumulating body of clinical evidence along with several decades of animal research and mathematical simulations has documented that the efficacy of hypothermia is dependent on achieving a reduced temperature in the target tissue before or soon after the injury-precipitating event. Mild hypothermia with temperature reduction of several degrees Celsius is as effective as modest or deep hypothermia in providing therapeutic benefit without introducing collateral/systemic complications. In the past several decades, many different cooling methods and devices have been designed, tested, and used in medical treatments with mixed results. Accurately designing treatment protocols to achieve specific cooling outcomes requires collaboration among engineers, researchers, and clinicians. Although this problem is quite challenging, it presents a major opportunity for bioengineers to create methods and devices that quickly and safely produce hypothermia in targeted tissue regions without interfering with routine medical treatment.

Conflict of Interest Statement

The authors declared no conflicts of interest

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