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Modest Systemic Hypothermia: A Promising Therapeutic Tool in the Management of Acute Spinal Cord Injuries

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Aims: Primary and secondary injury mechanisms contribute to neuronal dysfunction, neuronal cell death, and subsequent loss of function following acute spinal cord injury (SCI). This endogenous response to neuronal injury typically proceeds unabated resulting in progressive loss of anatomical and functional integrity. Modest systemic hypothermia (MSH) is defined as systemic cooling of the core body temperature to a range between 32-34℃; i t may have a potential neuroprotective role in patients with acute SCI.
Study Design: Review Article.
Place and Duration of Study: Department of Medicine SABA University School of Medicine.
Methodology: Electronic search of PubMed and Google Scholar databases were conducted from 2014 to 2015. Studies published prior to year 2000 were excluded with preference being given to studies completed in the last five years. Electronic search of PubMed revealed four human studies (published between years 2009-2013) which evaluated functional outcomes and complications of modest systemic hypothermia following SCI. The types of studies included one case report,

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feasibility study, retrospective comparative case series, and retrospective and prospective case series. Eight randomized controlled studies (published between years 2000-2015) were selected that reported histological and/or function outcomes following treatment with modest systemic hypothermia in animal models of SCI.

Results: Functionally, significantly higher mean Basso, Beattie, and Bresnahan scale locomotor scale scores were reported in hypothermia-treated groups at the endpoint behavioral assessments compared to normothermia groups. Histologically, hypothermia significantly increased total white and gray matter volume compared to normothermic control groups. Significantly reduced immunohistochemical expression of apoptotic and inflammatory factors were reported in hypothermia groups following SCI. Biochemically, hypothermia inhibited free radical induced lipid peroxidation significantly more than methylprednisolone alone. Electrophysiologically, hypothermia enhanced the preservation of ascending sensory electrophysiological signals following SCI. Clinically, the application of modest systemic hypothermia after SCI has been shown to be relatively safe and appears to improve functional outcomes in patients with acute SCI when compared to the natural history of complications and recovery.

Conclusion: The results of several basic science studies have shown that modest systemic hypothermia improves functional, histological, biochemical, and electrophysiological outcomes in animal models of acute SCI when compared to normothermic control groups. Although randomized clinical trials must be completed before a clear conclusion can be made, modest systemic hypothermia seems to have a promising role as a therapeutic tool in the management of acute SCI.

Keywords: Neuroprotection; modest systemic hypothermia; spinal cord injury.

1. INTRODUCTION

Spinal cord injury (SCI) is a devastating event currently lacking a proven neuroprotective therapy [1]. Approximately 12,000 new cases of spinal cord injuries occur in the United States each year, most of which occur in young to middle aged males [2,3]. The most common cause is motor vehicle accidents (48%), followed by accidental falls (16%), firearm injuries (12%), sports related injuries (10%), and other injuries (14%) [3]. Cervical SCI is most clinically encountered, C4 and C5 (fourth and fifth vertebrae of the spinal column) being the most common site of injury [4]. Current management following acute spinal cord injuries involves ABCD (airway, breathing, circulation, disability/mental status) prioritization scheme, spinal stabilization, and decompression [4]. Early induction of high dose steroid therapy remains controversial because of variable clinical outcomes and complications [5]. Physical Medicine and Rehabilitation is often employed to optimize quality of life and function of these patients. Unfortunately, the natural history of spontaneous recovery in patients complete cervical SCI is poor with less than 1% achieving full recovery [3,6]. Most affected individuals will ultimately suffer permanent disability due to the resultant motor, sensory, and functional deficits as well as face economic, social, and emotional distress [3].

The pathophysiology of SCI is complex and not completely understood. Primary and secondary injury mechanisms contribute to neuronal dysfunction, neuronal loss and subsequent loss of function following acute SCI [7]. Primary (acute) injury refers to the immediate mechanical injury and is associated with relatively localized cell death by necrosis [8]. Within minutes of the initial insult multiple secondary (sub-acute) injury cascades ensue, resulting in further expansion of the initial area of tissue destruction. Secondary injury is mediated by multiple exacerbating processes including structural barrier and vascular alterations, derangements of transmembrane ion and neurotransmitter gradients, glutamate excitotoxicity, free-radical formation, inflammatory cell infiltration and release of cytokines, and multiple cell death mechanisms. These secondary injury alterations contribute significantly to the post-traumatic pathological changes that produce long term functional deficit [7]. The multifactorial nature and dynamic interplay between the processes involved in secondary injury complicates the pursuit of finding a beneficial therapy for patients with SCI.

Therapeutic hypothermia has been shown to have a broad-spectrum of neuroprotective properties contributing to the attenuation of multiple secondary injury processes that follow neurological insult [9]. Hypothermia may exhibit

its protective effects through the reduction of metabolic and energy demand, free radical formation, glutamate excitotoxicity, metalloproteinase-mediated extracellular matrix disruption, inflammatory cell infiltration and cytokine release, hemorrhage and edema, mitochondrial dysfunction, apoptosis and calpain-mediated proteolysis [9,10].

Induced hypothermia has shown neuroprotective promise in many different patient populations [11]. Modest systemic hypothermia (systemic cooling of the core body temperature to 32-34℃) has been proven to significantly improve neurologic outcome and reduce mortality in patients who had been resuscitated following cardiac arrest due to ventricular fibrillation [12]. It has continued to show neuroprotective promise, being increasingly applied to protect organs and limit CNS injury, especially in cases of traumatic brain injury with intracranial hypertension, acute ischemic stroke, ischemic neonatal encephalopathy, hepatic encephalopathy, and cardiovascular surgical interventions (e.g., spinal cord protection during thoracic aortic aneurysm repair) [13].

Therapeutic hypothermia can be divided into three cooling phases: (1) Induction phase, in which the subject is cooled at a specific rate (℃/time) in order to achieve a target temperature. (2) Maintenance phase, in which the target temperature is maintained for a specific amount of time. (3) Rewarming phase, in which normal temperature (37℃) is re-established at a specific rate. Therefore, there are several therapeutic parameters (local vs. systemic cooling, timing, degree, and duration) that must be considered regarding this therapy. In general, there are two main methods of inducing hypothermia – local or systemic. Although both methods of cooling present advantages and disadvantages, a modest degree (32-34℃) of systemic cooling has shown to provide more neuroprotection following SCI without significant adverse effects [1,14].

The purpose of this paper is to provide experimental evidence that modest (32-34℃) systemic hypothermia (MSH) improves functional and histological outcomes in animal models of acute SCI. Biochemical and electrophysiological outcomes are mentioned briefly. The basis of functional recovery and histopathological improvement is then discussed, with an emphasis on attenuation of inflammatory and apoptotic factors involved in secondary injury mechanisms. In addition, clinical studies evaluating the use of modest systemic hypothermia in human SCI versus the natural history of recovery after SCI are also discussed.

2. METHODOLOGY

In order to identify and review the required literature for this paper, PubMed and Google Scholar database searches were conducted from January 2014 to March 2015. The goal of the initial research was to provide a solid foundation of understanding. General review papers involving hypothermia and spinal cord injury were collected and studied. This was followed by a collection of primary literature studies.

Mesh terms used were “hypothermia” and “spinal cord injury” OR “contusion injury”. Studies published prior to year 2000 were excluded with preference being given to studies completed in the last five years in order to keep the discussion current. The search was further limited to studies in humans and studies in animals. Only studies that induced hypothermia systemically to a core temperature range between 32-34℃ following SCI where selected.

A total of eight animal studies were selected all of which induced modest (32-34℃) systemic hypothermia after SCI. In the selected studies, rats were subjected to either cervical or thoracic spinal cord contusion, or persistent thoracic spinal cord compression. In addition, two of these reviewed studies compared measurable outcomes between multiple therapy groups including moderate epidural hypothermia (MEH) and methylprednisolone (MP). Functional (behavioral) and histopathological outcome parameters following the use of MSH in animal models of acute SCI are of particular emphasis. Most of the reviewed studies followed the course of functional recovery by using the 21 point Basso, Beattie, and Bresnahan (BBB) scale which ranges from 0 (complete hind limb paralysis) to 21 (normal locomotor function). Histological assessments of total healthy tissue area and volume (as assessed on H&E stained sections) and white and gray matter volume (as evaluated with Luxol fast blue stained sections) were reported. A detailed chart presented in Table 1 of the appendix provides an overview of the study population (species, sex, and weight), injury device mechanism, injury site, therapy parameters (timing and duration), treatment and control groups, and key results from each of the selected animal studies.

Electronic search of PubMed revealed four human studies (published between years 2009-2013) evaluating the effects of modest systemic hypothermia following acute SCI. The types of studies included one case report, feasibility study, retrospective comparative case series, and retrospective and prospective case series. These studies were obtained to discuss important findings regarding safety, complications, and functional outcomes. An overview of the study population, injury mechanism, reported complications, and the salient features from the studies is presented in Table 2 of the appendix.

3. RESULTS

3.1 Animal Studies Evaluating Modest Systemic Hypothermia following Spinal Cord Injury

3.1.1 Functional (behavioral) assessments

In a study by [15] on post-injury day 1-4, BBB locomotor scale scores were significantly higher (P< 0.002) in the hypothermic group compared to the normothermic control group. On post-injury day 5-18, no statistically significant difference between groups was seen. However, on post-injury day 19-28, BBB locomotor scale scores were significantly higher (P<0.00004) in the hypothermic group compared to the normothermic group. At completion of the study (post-injury day 28) investigators found that the hypothermic group achieved remarkably more total functional recovery, compared to the normothermic group (15.2±2.1 vs. 11.1±1.9: P<0.00004).

Similarly, the study by [16] reported significantly improved BBB scores with progressive improvement in locomotor function up to the concluding assessment at 6 weeks in hypothermia group compared to normothermia group (13.3±0.47 vs. 10.8 ±0.4; P=.0024).

In a comparative study by [14] on moderate systemic hypothermia (MSH) versus moderate epidural hypothermia (MEH) significantly higher BBB scores were found in the MSH (10.2±3.6) and MEH (8.0±2.5) groups compared to the normothermic control group at 6 weeks post-injury (P< 0.05).

In a recent study by [17] significantly higher (P< 0.05) BBB locomotor scale scores at 2 and 3 weeks post-SCI were demonstrated in all treatment groups (EH, LH, LH+MP, and MP) compared to the normothermic trauma control group. Overall, no statistically significant difference (P=0.1) in BBB score was found between the treatment groups 6 weeks post-SCI. However, within the treatment groups, the animals that received immediate IV high dose methylprednisolone followed by delayed hypothermia (LH+MP) demonstrated marginally (P=0.054) better improvement in locomotor function.

A study by [18] reported no statistically significant difference in BBB locomotor score in the hypothermic group (11.3±1.0) compared to the normothermic group (10.8±0.8) at 8 week (end point) assessment. However, the hypothermic group demonstrated significantly faster recovery rate with significantly greater BBB locomotor scores compared to normothermic group during weeks 1-3 after cervical SCI (P<0.01). In addition, there was a significant increase in upper forelimb strength (43% increase weight-supported forelimb hanging time and 25% increase in forelimb grip strength) at 8 weeks post-SCI injury in the hypothermic group compared to the normothermic group.

A study by [19] evaluated whether modest (33ºC) hypothermia was able to limit neurological decline during 45% compressive injury to the mid-thoracic spinal cord; decompression was performed at 0, 2, and 8 hours, respectively. Although functional decline increased with the duration of compression, MSH significantly reduced the magnitude and rate of this neurological decline (Fig. 1). Functionally, the hypothermic group had significantly a higher mean BBB score (9.5±0.9) compared to the normothermic group (5.3±0.6) after 8 hours (primary outcome measure) of compressive injury; P<0.0005. In addition, a highly significant difference was seen with the step ladder test in the hypothermia group compared to the normothermic group (51.8±6.2% vs. 15.1 ±6.8%, correct foot placements, respectively; P<0.0005). Regression analysis confirmed a close relationship between BBB scores and the step ladder test (R=0.85, R^2=0.72).

A single study [20] assessed animal behavior by observing the frequency of hind-limb motor function (vertical standing frequency). There was no significant difference in vertical standing frequency between hypothermic and normothermic rats at 24 hours after compression injury. However, the normothermic group

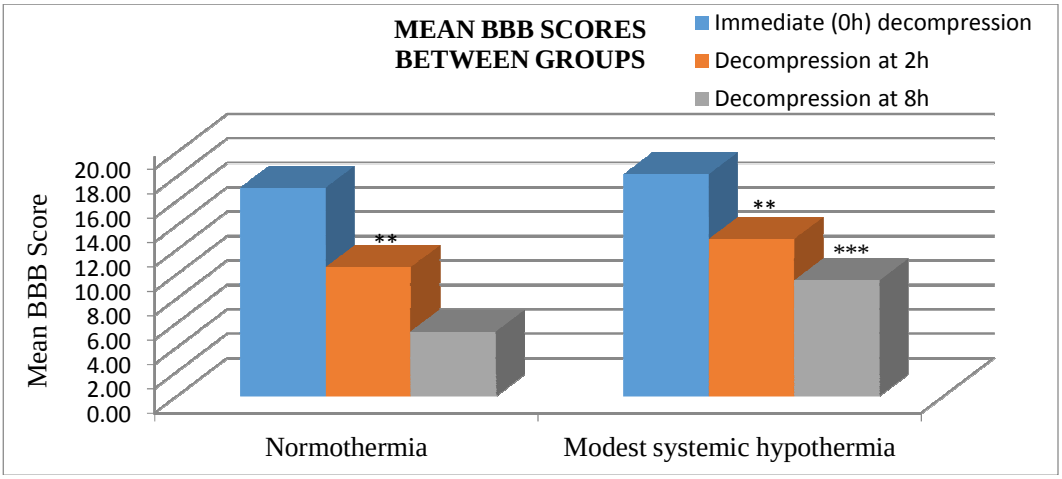

Fig. 1. Attenuation of neurological decline prior to decompressive surgery. Modest systemic hypothermia (33ºC) significantly reduced the magnitude and rate of functional decline compared to normothermia at 8 weeks (completion of the study) following SCI (18.2±0.9, 12.9±1.1, and 9.5±0.9 vs. 17.1±1.0, 10.6±1.1, and 5.3±0.6, after decompression at 0, 2, 8 hours, respectively)

*Data was taken from the study by [19]. ** P ≤0.05; *** P≤0.0005*

demonstrated a progressive decline in vertical standing frequency after SCI (39.1±13.4%; mean±s.e.m), 36.2±16.8%, 28.7±15.6% at 24, 48, 72h, after compression, respectively. Conversely, the hypothermic group demonstrated a significant increase in vertical standing frequency (86.6±23.8%) at 48h after compression injury (*P*=0.0495). Furthermore, full recovery of hind-limb function (104.0±19.3%) was observed at 72 h after compression injury in the hypothermic group (*P*=0.0495).

3.1.2 Histopathological and immuno-histochemical assessments

In the study by [16] sixteen longitudinal sections taken from the center of the injury revealed that hypothermia significantly reduced the total extent of rostrocaudal tissue damage and cavitation size compared to the normothermic control group (37% decreased area of tissue damage on day 7 and 15% decreased area of tissue damage on day 44; *P*<0.01).

In the primary outcome 8-hour decompression cohort, preserved total tissue volume (assessed on H&E stained sections) was 53% greater in the hypothermic group compared to the normothermic group (7.17±0.8 mm^3 and 4.68±0.55 mm^3, respectively; *P*≤0.01) [19]. Similarly, 53% more preserved tissue area was found at the injury epicenter in the hypothermic group compared to the normothermic group (0.081±0.022 mm^3 and 0.032±0.009 mm^3, respectively; *P* ≤0.05). In the 8-hour decompression cohort, when compared to the normothermic group, the group that received hypothermia demonstrated significantly greater preservation of white matter (4.10±0.43 mm^3 and 6.01±0.57 mm^3, respectively; *P* ≤0.01) and gray matter (0.76±0.14 mm^3 and 1.37±0.16 mm^3, respectively; *P*≤0.005).

In [18] modest (33°C) systemic hypothermia induced 5 minutes after cervical SCI for a duration of 4 hours, significantly increased healthy-appearing white matter (31% increase) and gray matter (38% increase) tissue volumes compared to normothermic controls (*P*<0.01). In addition, Hypothermia significantly increased sparing of retrogradely traced axonal projections in the reticulospinal tract (127% increase) and the extent of rostrocaudal neuronal preservation (four fold), compared to the normothermic group (Fig. 2).

In a study by [15] significantly more preservation of dorsal (sensory) and ventral (motor) horn gray matter and remarkably less tissue destruction was found in the hypothermic group compared to the normothermic group on post-injury day 3. On post-injury day 28, there was greater preservation of gray matter in the hypothermic group; however, no significant observable difference in morphology was reported between the hypothermic and normothermic group.

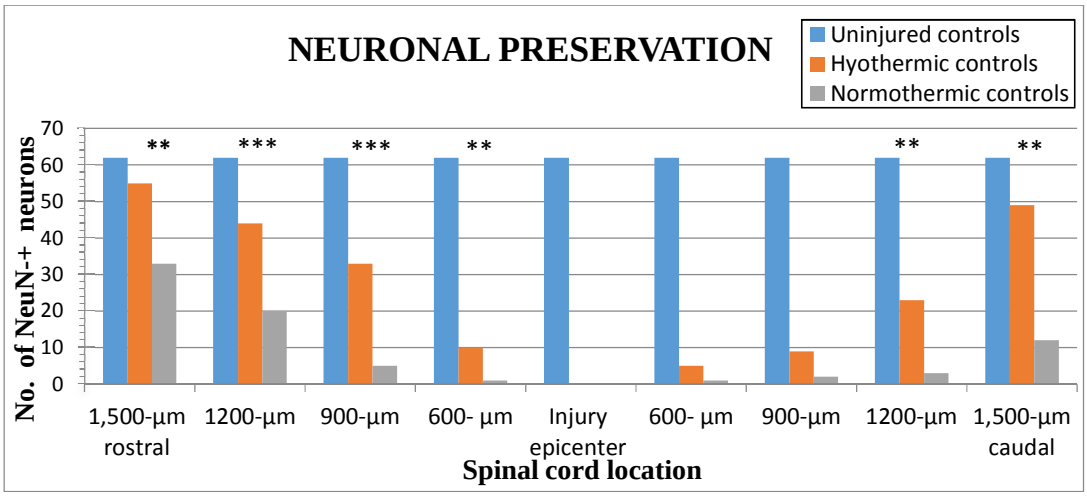

Fig. 2. Neuroprotective effects of modest (33°C) systemic hypothermia after cervical spinal cord trauma in rats

*Transverse sections were taken at 300-µm interval both rostral and caudal directions from the injury epicenter for histological and immunohistochemical analysis. Hypothermia significantly increased the extent of rostrocaudal neuronal preservation ($NeuN^+$ immunoreactivity) at distances of 900-µm and greater from the injury epicenter at 10 weeks after injury when compared with normothermic group. No significant neuronal preservation was seen at distances less than 900-µm from the injury epicenter in either group. Data was taken from the study by [18] and is reported as the average number of $NeuN^+$ neurons compared to normothermic controls. *** (t_{132} =8.54, P<0.001); ** (P <0.01)*

In a study by [20] MSH significantly inhibited the degree of microglia proliferation as assessed by isolectin-B4 staining (10.9±3.2 mm^{-2}: *P*=0.0272 and 8.0±2.3 mm^{-2}: p=0.0339) at 48 and 72 h, after compression, respectively, compared to the normothermic group (41.4±13 mm^{-2} and 41.4±13 mm^{-2}) at 48 and 72h, after compression, respectively. In addition, Tumor necrosis factor alpha (TNF-α) content in the compressed spinal cord was measured by using the ELISA method. At all points in time investigated, TNF-α concentration and TNF-α staining intensity was less in the hypothermia group than the normothermic group. However, no significant difference in TNF-α concentration in the compressed spinal cord between hypothermic and normothermic rats at 24, 48, and 72h after compression injury.

In a study by [21] hypothermia significantly reduced neuronal and supporting cell apoptosis (DNA fragmentation) as measured by using terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining, both rostral and caudal to the focus of injury at 24 hours, 72 hours, and 7 days after SCI compared to the normothermic group (*P* < 0.05).

In the comparative study by [14] immunofluorescence detection of apoptosis (TUNEL positive cells) and activated microglia (labeled with OX-42, an antibody against the type-3 complement receptor) 6 weeks after SCI, was the greatest in the normothermic control group, followed by the high dose MP group, the MEH group, and lowest in the MSH group (*P* < 0.05). In addition, western blot analysis was used to compared to evaluate inflammatory (p38 MAPK) and apoptotic (caspase-3, -8, -9) protein expression. The expressions of p38 MAPK (p38 activated mitogen activated protein kinase) was significantly lower in the treatment groups than the normothermic control group (*P*=0.03); however, there was no statistical significance between treatment groups (*P*=0.21). Similarly, the expressions of caspase-9 was significantly lower in all treatment groups compared to the normothermic control group (*P*=0.03), and there was no statistical significance between treatment groups (*P* <0.05). However, caspase-3 and caspase-8 expressions were significantly lower in the MSH group compared to all other groups. Furthermore, only the group that received MSH demonstrated significantly lower caspase-3 expression than the normothermic control group (*P*< 0.05).

3.1.3 Electrophysiological assessment

In a study by [15] investigators used electrophysiology monitoring of somatosensory evoked potentials (SSEPs) to measure bilateral

ascending somatosensory pathway integrity; this was seen as voltage responses (SSEPs) in the corresponding somatosensory cortex following the electrical stimulation of peripheral nerves. One week prior to SCI rats underwent electrode implantation to determine baseline recordings for SSEP monitoring and were randomly assigned into two arms: the hypothermic group (n=10) and normothermic control group (n=11). From the time of initial insult to day 4, the hypothermic group demonstrated significantly smaller drop in SSEP amplitude from baseline recordings compared to the normothermic controls (P <0.1); this greater retention of ascending somatosensory pathway integrity (greater average SSEP amplitude and longer SSEP latencies) in hypothermia-treated rats compared to the normothermic controls following SCI continued up to day 28 (the completion of the study). Importantly, investigators reported that no adverse effects from hypothermia treatment were detected in any hypothermic-treated rats which would have been indicated by a decrease in SSEP amplitude.

3.1.4 Biochemical assessment

A study by [17] investigated the combination immediate IV high dose methylprednisolone in the setting of delayed hypothermia 3 hours after SCI (LH+MP). Malonyldialdehyde (MDA) level was used as an index of lipid peroxidation. The normothermic trauma control group had significantly higher (P=0.006) MDA level (92.50±22 nmol/gww) than all other treatment groups (EH, LH, LH+MP, and MP). Statistical significance was seen between the treatment groups. MDA level was significantly lower (P=0.004) in the early hypothermia group (54.00±19.83 nmol/gww) compared to the late hypothermia group (59.00±18.33 nmol/gww). The early onset hypothermia group (EH) inhibited MDA (54.00±19.83 nmol/gww) significantly more (P=0.035) than methylprednisolone (MP) alone (74.00±29.16 nmol/gww). However, the group that received immediate IV high dose methylprednisolone followed by delayed hypothermia inhibited MDA (47.00±36.66 nmol/gww) significantly more (P=0.0001) than early hypothermia alone.

3.2 Human Studies Evaluating Modest Systemic Hypothermia following Spinal Cord Injury

Refer to Table 2 in the appendix for an overview on the human studies which applied modest systemic hypothermia following acute severe cervical spinal cord injury.

3.2.1 Neurological outcomes

In the case report [13] Kevin Everett, a professional football player for the Buffalo Bills, suffered a complete (AIS A) cervical SCI during play on September 9th, 2007. Intravenous methylprednisolone and cold saline were administered in the ambulance, approximately 15 minutes after injury. On hospital arrival, his temperature was 36.6℃ (98℉). CT scan confirmed C3-C4 facet fracture dislocation; MRI showed 55% spinal canal compromise. Mr. Everett subsequently underwent prompt surgical decompression and stabilization. A decision was made to induce modest (33℃) systemic hypothermia for 48 hours via insertion of a femoral vein intravascular heat exchange cooling catheter. Functionally, Mr. Everett experienced a rapid and remarkable neurological recovery (conversion from complete AIS-A to AIS-D) over a period of 4 months.

Between April 2006 to June 2008, a relatively small cohort of fourteen acute complete (AIS-A) cervical SCI patients, who met inclusion and exclusion criteria for University of Miami-approved systemic hypothermia SCI protocol (age 16–65 years, nonpenetrating, complete AIS-A SCI, temperature <38.5℃ on admission), were treated with decompression and stabilization followed by modest (33℃) systemic intravascular hypothermia maintained for 48 hours [22,1].

Patients were excluded from the study if there was significant improvement within the first 12 hours after SCI. No patients in the hypothermic group received steroids. In a study by [1] the clinical outcomes of the original fourteen patients at approximately one year follow up (50.2 weeks) were compared to a historical normothermic control group matched for age, injury mechanism, completeness of the lesion, and time lapse between SCI and surgery (SCI + hypothermia: 39.4 year median age, 10/14 MVA/MCC, 14/14 AIS-A, and 12/14 < 24 h time lapse between SCI and surgery; SCI + normothermia: 34.5 year median age, 10/14 MVA/MCC, 14/14 AIS-A, and 7/14 <24 h time lapse between SCI and surgery). Only 3/14 of the patients in the normothermic control group received methylprednisolone protocol. 42.8% (6/14) of patients treated with hypothermia following SCI converted to a higher AIS grade at

one year follow up (Fig. 3). Although, more patients in the hypothermic group converted to AIS grade B and C (5 patients) compared to normothermic matched control group (2 patients), no statistically significant difference was seen in final AIS grade in the hypothermic group compared to normothermic controls.

Finally, in a clinical case-controlled study [23] the effect of modest systemic hypothermia following SCI in a total of thirty-five patients was evaluated (retrospective pooled analysis of the original cohort of fourteen patients between April 2006 and June 2008 and prospective analysis of twenty-one patients between May 2009 and April 2012). 43% (15/35) of patients in the hypothermic group improved one or more AIS grades at one year follow up (Fig. 3). Although all patients were complete AIS-A on admission, 4 patients spontaneously converted to AIS-B within the first 24 hours. Therefore, correcting for this 35.5% (11/31) of patients in the hypothermic group improved one or more AIS grades at one year follow up.

3.2.2 Clinical complications

Precise regulation of systemic temperature with the endovascular cooling catheter technique was shown to be relatively safe and feasible [22,1]. No complications were reported in the case study [13]. In the remaining clinical studies the most common complications were of respiratory nature [1,23]. There was no statistically significant difference in complications or increase in risk factors, except for a greater number of cases of pleural effusions (*P*=.01) and anemia (*P*=.02) in the hypothermia cohort compared to matched normothermic controls [1]. In the clinical case-controlled study [23] despite prophylactic anticoagulation, thrombotic complications were reported in 37% (5/21) of the prospectively analyzed patients. In contrast, no thrombotic complications were reported in the original cohort of fourteen patients [1].

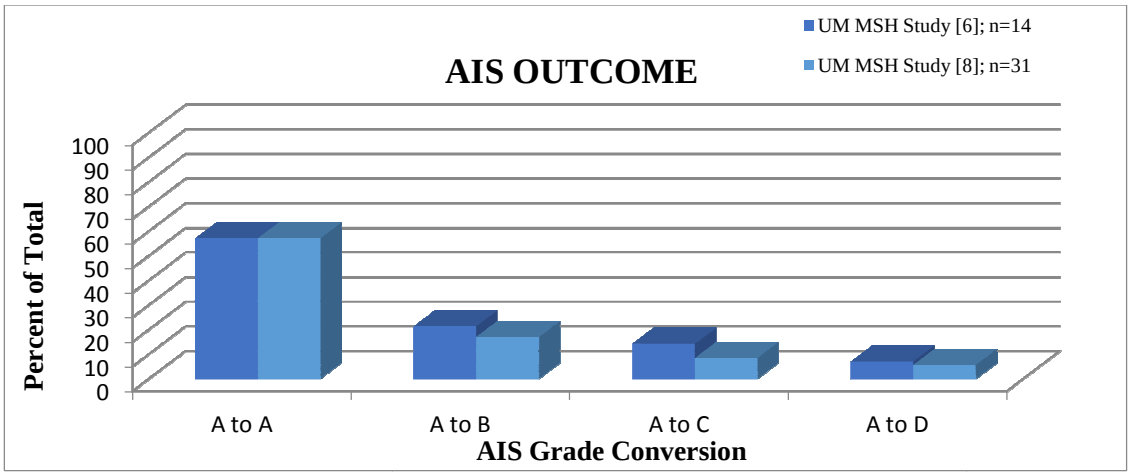

Fig. 3. Percent of complete AIS-A cervical SCI conversion at one year follow up. Of the original cohort of 14 patients, 57.1% of the patients treated with modest systemic hypothermia with complete AIS-A cervical SCI remained AIS-A, 21.4% converted to AIS-B, 14.3% converted to AIS-C, and 7.1% convert to AIS-D [1]. Of the 31 patients who did not convert to an improved AIS grade within the first 24 hours, 57.1% of the patients with complete AIS-A cervical SCI remained AIS-A, 17.1% converted to AIS-B, 8.5% converted to AIS-C, and 5.7% convert to AIS-D [23]

Data combined from the University of Miami (UM) modest systemic hypothermia studies [1,23] were used to generate this chart.

**** The American Spinal injury Association Impairment Scale (AIS) categories were used to measure functional outcomes in patients following SCI. AIS categories are scored from A to E: A (complete sensorimotor loss), B (complete motor loss, incomplete sensory loss), C (incomplete sensorimotor loss; with < half of key muscles below the neurological level graded ≥ 3), D (incomplete sensorimotor loss with ≥ half of key muscles below the neurological level graded ≥ 3), (incomplete sensorimotor loss), and E (reestablishment of normal sensorimotor function) [4]*

4. DISCUSSION

The results of several experimental studies have shown that modest systemic hypothermia improves functional [16,19,14,17,15,18,20], histological [16,19,15,18], biochemical [17], and electrophysiological [15] outcomes in animal models of acute SCI compared to normothermic controls. Significantly higher mean BBB locomotor scale scores were reported in hypothermia-treated groups compared to normothermia control groups at the completion of the study in [16,19,14,17,15]. Significantly increased total healthy tissue area and volume, as well as, white and gray matter volume were observed in hypothermia-treated groups compared to normothermic control groups at the completion of studies [16,19,15,18].

Preservation of histological integrity was accompanied by improved functional recovery following the induction of modest systemic hypothermia after cervical [18] and thoracic [16,15] spinal cord contusion and after 8 hours of persistent thoracic spinal cord compression [19]. This evidence shows that modest systemic hypothermia improves both functional and histopathological outcomes in animal models of cervical and thoracic spinal cord injury.

Surgical decompression of the spinal cord is often performed to reestablish normal spinal canal diameter after acute traumatic spinal cord injury [19]. Functional and histological outcomes have been shown to worsen as compression injury time increases. When compared to normothermic conditions, immediate induction of hypothermia significantly delayed the magnitude and rate of functional decline after 8 hours of compressive injury. With this evidence, investigators suggested that hypothermia may serve a promising role as the “bridging therapy” that could delay neurological decline prior to surgical decompression, possibly through the attenuation of secondary injury processes associated with compression, such as axonal membrane damage and ischemia.

Most studies that follow the course of functional recovery after SCI in rats rely on the open field functional BBB scale test, which is conceivably subjective and has been reported to display variable reproducibility and sensitivity based on the severity of the injury [24]. Moreover, higher locomotor BBB scale scores may not necessarily correspond with true functional recovery and axonal tract integrity [15]. Therefore, although this standardized scale is generally accepted, these factors can still raise questions about the true efficacy of the therapy.

Monitoring of somatosensory evoked potentials (SSEPs) is an impressive tool that can be used to assess the impact of the injury and justify benefits of a prospective SCI therapy. In the study by [15] remarkable functional recovery and clear preservation of morphological integrity were accompanied by greater preservation of ascending somatosensory electrophysiological signals after SCI. Investigators concluded that the early application of modest systemic hypothermia initiated within 2 hours after SCI, for a duration of 2 hours, may provide long term recovery benefits as indicated by overall greater and persistent preservation of ascending sensory electrophysiological signals (SSEPs) in acute and post-acute periods after SCI.

The rationale behind the early application of hypothermia in the setting acute SCI is understandable. Lack of an observable benefit has been reported with delayed administration of methylprednisolone (>8 h) in patients with acute SCI [23]. Similar to methylprednisolone, the neuroprotective efficacy of hypothermia is most beneficial when administered as early as possible although further research is required in order to establish the therapeutic window of hypothermia. There are several factors that can limit early induction of hypothermia in the setting acute SCI [1]. Some of these factors include stabilization, transportation, clinical evaluation, imaging studies, and endovascular catheter insertion [23]. However, cooling patients in the field and/or en-route to the trauma facility by the application of cooling blankets or administration of iced saline is a potential solution to treatment delay which could be applied to cases of cardiac arrest and acute spinal cord injury.

One possible area of future study is to combine therapeutic hypothermia with different neuroprotective agents. A recent study by [17] investigated the combination immediate IV high dose methylprednisolone in the setting of delayed hypothermia (3 hours) after SCI. Although early hypothermia had significantly better biochemical neuroprotective effects (as assessed by inhibition of free radical induced lipid peroxidation) than delayed hypothermia and hypothermia had significantly better biochemical neuroprotective effects than methylprednisolone alone the extent of functional recovery between these groups was insignificant. However, the

animals that received immediate IV high dose methylprednisolone followed by delayed hypothermia demonstrated marginally better improvement in locomotor function and inhibited lipid peroxidation significantly more than early hypothermia alone. Interestingly, this study suggests that methylprednisolone may extend the neuroprotective therapeutic window and efficacy of delayed hypothermia.

Remyelination or regeneration interventions such as stem cell and autologous schwann-cell transplantation therapies are areas research that offer unprecedented hope in patients suffering with neurological injuries [15]. The ability of hypothermia to mitigate neurological decline prior to surgical decompression and provide greater preservation of at-risk axonal projections surrounding the initial site of injury is remarkable. Therefore, therapeutic combination of post-traumatic hypothermia with potential regeneration therapies may help enhance the total extent of neuronal repair and neurologic function.

Therapeutic hypothermia has been shown to have a broad-spectrum of neuroprotective properties contributing to the attenuation of multiple secondary injury processes that follow neurological injury [9]. In early studies the application hypothermia was reported to decrease cerebral metabolic rate (6% to 7% decrease for every 1℃ drop in body temperature) and glucose utilization [6]. This decrease in metabolic and energy demand would prove to be beneficial in cases of global ischemia due to cardiac arrest [6]. Although several possible mechanisms are thought to contribute to the neuroprotective benefits of hypothermia, one of the major mechanisms may be the mitigation of post-traumatic inflammatory cascades and neuronal cell death mechanisms [2].

Spinal cord injury elicits an inflammatory response which involves the pathological activation of microglia and other immune cells which then exacerbate neuronal loss through the release of superoxide free radial species, nitric oxide, and various pro-inflammatory cytokines [20]. Interestingly, the microglia inflammatory response has been reported to correlate well with motor dysfunction. Induction of modest systemic hypothermia after SCI significantly inhibited microglia activation and blunted the subsequent release of pro-inflammatory cytokine TNF-α. Investigators in this study concluded that hypothermia was effective at abating delayed motor dysfunction via the inhibition of the microglia inflammatory response. Similarly, other studies have reported that modest hypothermia significantly reduced post-traumatic inflammatory recruitment of polymorphonuclear leukocytes (neutrophils) and concomitant enzymatic activity myeloperoxidase, which is implicated in oxidative damage [25].

Spinal cord injury induces cell death by necrosis and apoptosis (programmed cell death). The factors that commence and mediate cell death pathways are complex and multifactorial in nature [6]. Post-traumatic modest systemic hypothermia has been reported to significantly reduce apoptosis (endonuclease-mediated DNA fragmentation) as measured by using terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining rostral and caudal to the spinal cord injury epicenter [14,21]. This finding has also been reported in cases of traumatic brain injury and global ischemia [26]. In the comparative study by [14] moderate systemic hypothermia showed significantly more anti-inflammatory and anti-apoptotic effects than locally applied moderate epidural hypothermia (MEH). Post-traumatic modest systemic hypothermia significantly reduced the expression of caspase-3, which is important in the execution phase of apoptosis. Furthermore, mitigation of caspase-3 and caspase-8 expression more effectively than other therapeutic interventions after spinal cord injury suggests that modest systemic hypothermia maybe a more effective inhibitor of the extrinsic pathway of apoptosis.

In recent clinical studies, modest systemic hypothermia has been shown to be safe and it appears to improve outcomes in patients with acute severe SCI [1,23]. According to a updated position statement by the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Joint Section on Disorders of the Spine and Peripheral Nerves and Joint Section on Trauma there is a grade C recommendation (level IV evidence) based on the retrospective comparative cohort study [1] and the retrospective and prospective case series study [23] that modest systemic hypothermia may be safely applied following SCI [27]. In addition, there is currently a grade I recommendation (insufficient evidence) to advocate for or against the application of either local or systemic hypothermia as a treatment for acute spinal cord injury [27].

The growing interest in the application of therapeutic hypothermia is, in at least part, due to the realization that only a modest (32-34℃) amount of systemic cooling could provide neuroprotective benefits, without the significant complications seen with more profound (≤30℃) levels of cooling [28]. The application of modest systemic hypothermia through an endovascular cooling has been shown to offer fast induction speed with reliable and precise temperature control in human SCI studies [1]. Importantly, no complications have been reported as a direct result of the endovascular cooling catheter technique. Although cooling has been reported to alter the coagulation factors increasing the possibility of thrombosis, patients with SCI are already at increased risk for coagulopathy due to stasis and immobility [23]. Similarly, respiratory and urinary tract complications are also common in the setting of spinal cord injury due to neurological dysfunction, intubation, and bladder catheterization [28]. Nevertheless, hypothermia-induced physiological changes and complications need to be carefully discerned.

In order to evaluate the efficacy of hypothermia as a prospective therapy for acute SCI, a constellation of factors must be considered. For example, whether or not neurological improvement is attributable to hypothermia or just the natural history of spontaneous recovery is perhaps one of the most difficult outcome parameters to assess [1]. The natural history of recovery varies extensively based on initial AIS grade. While the history of recovery for complete (AIS-A) SCI is relatively restricted and predictable, the extent of recovery in patients initially assessed as incomplete (AIS-B, C, and D) is greater and more variable [29]. Based on this general principle, patients with the severe complete injuries must be selected, as well as, a larger group in order to increase the statistical power. The application of modest systemic hypothermia after SCI appears to improve outcomes in patients with acute SCI, when compared to the natural history of recovery [1,23] (Fig. 4).

Despite the wide range of potential neuroprotective benefits presented throughout the literature, there is still a lack of consensus for the use of modest systemic hypothermia in the setting of spinal cord injury. There are a very limited number of clinical studies evaluating the effects of modest systemic hypothermia in human spinal cord injury. Whether or not preclinical evidence translates from animals to human spinal cord injury is not yet established.

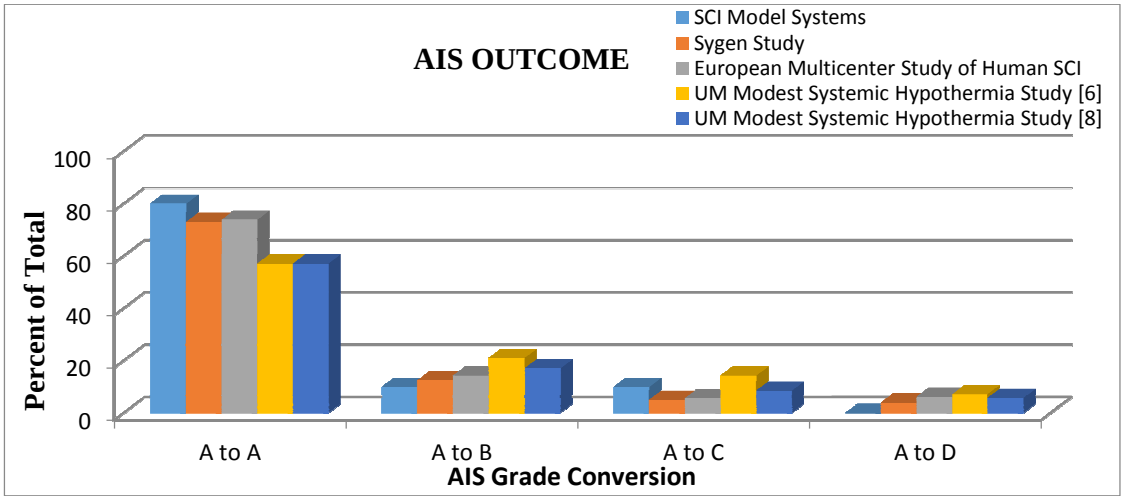

Fig. 4. Percent of complete AIS-A cervical SCI conversion at one year follow up. The natural history of spontaneous recovery after complete (AIS A) cervical SCI is poor with less than 1% of patients achieving full (AIS-E) recovery [3,6]. According to [29] a review of data from the SCI Model Systems, Sygen study, and European Multicenter Study of Human SCI (EM-SCI) databases: approximately 80% of patients with complete AIS-A cervical SCI will remain AIS-A, 10% will convert to AIS-B, and 10% will convert to AIS-C [29]

This chart was generated from combining data from the studies [29,1,23]

The Department of Neurological Surgery and the Miami Project to Cure Paralysis, at the University of Miami, Miller School of Medicine, in collaboration with the Neurological Emergency Treatment Trials Group is currently recruiting participants in a much needed larger randomized multicenter clinical trial in order to determine if modest intravascular hypothermia results in beneficial outcome in acute SCI [6].

In several published preclinical studies, hypothermia has been shown to display greater neuroprotective profiles than other currently administered agents in the setting of experimental SCI treatment, including high dose methylprednisolone [17,14]. However, this greater degree of neuroprotection clearly has not always translated into significantly greater functional recovery as assessed with locomotor tests. The basis for the lack of significant difference in the functional recovery between hypothermia and other agents, such as methylprednisolone, most likely has many reasons.

In the case of acute traumatic spinal cord injury, we have to acknowledge that rather extensive variation exists. The nature of human spinal cord injury is heterogeneous in etiology and outcome. The variation in spinal cord contusion method, injury level, degree of injury, timing of decompression, and spontaneous recovery can make the interpretation and comparison of the results very difficult in cases of both human and animal studies. A reproducible contusion model that is clinically relevant and reflective of a large number of traumatic spinal cord injury cases can help improve interpretation of histopathology and functional outcomes [15].

In addition, many different therapeutic parameters (local vs. systemic cooling, timing, degree, and duration) must be considered regarding this therapy. Ongoing research using animal models of spinal cord injury is essential in order to optimize treatment parameters [17]. In addition, the therapeutic window of hypothermia must be determined which may vary significantly in cases of traumatic contusion versus traumatic contusion with compression and subsequent ischemia.

The bottom line is that even when spinal cord injury or hypothermia is discussed independently much still remains unknown. The multifactorial nature and dynamic interplay between the processes involved in secondary injury suggests that a multidisciplinary approach may be best suited to attack this very complicated problem. It is unlikely that the application of a single intervention will have sufficient neuroprotective profile to provide remarkable recovery in the case of SCI; rather, synergic treatment through the combination of modest systemic hypothermia with other neuroprotective agents may prove most effective in the management of acute spinal cord injury.

5. CONCLUSION

Therapeutic hypothermia has been shown to have a broad-spectrum of neuroprotective properties contributing to the attenuation of multiple secondary injury processes that follow neurological insult. The results of several basic science studies have shown that modest systemic hypothermia improves functional, histological, biochemical, and electrophysiological outcomes in animal models of acute spinal cord injury when compared to normothermic control groups. In human studies, the application of modest systemic hypothermia after SCI has been shown to be relatively safe and appears to improve outcomes in patients with acute SCI, when compared to the natural history of complications and recovery. Although randomized clinical trials must be completed before a clear conclusion can be made, modest systemic hypothermia seems to have a promising role as a therapeutic tool in the management of acute SCI.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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APPENDIX

Table 1. Modest systemic hypothermia following sci in animal models

Author date	Study design evidence level	Study population	Injury method	Therapy groups	Intervention parameters	Functional (behavioral) outcomes	Histological outcomes
Yu et al. (2000)	Prospective RCT; Level 1	female Sprague-Dawley rats (225-275 g)	10 g-x12.5 mm w/ NYU impactor at T10.	Hypothermia (n=7+12) Normothermia (n=9+8)	32ºC induced 30 m after injury for 4 h.	Significant improvement in BBB scores 9d post-SCI with progressive improvement up to the concluding assessment at 6 weeks in hypothermic group compared to normothermic group (13.3±0.47 vs. 10.8±0.4; *P*=.0024)	significant reduction (15.5%, *P*<.01) in lesion size compared to normothermic controls; Significantly diminished area of tissue damage compared to normothermic controls on post-injury day 7 and day 44.
Shibuya et al. (2004)	Prospective RCT; Level 1	male Sprague-Dawley rats	25 g-cm compression lesion at T1.	Hypothermia (n=15) Normothermia (n=15)	32ºC induced immediately after injury for 4h followed by rewarming to body temperature for 48 m;	No reported functional outcomes.	MSH has a neuroprotective effect after SCI by reducing post-traumatic TUNEL-positive cells; rostral & caudal to the focus of injury at 24 and 72 hrs compared to the normothermia group (*P*<0.05).
Morino et al. (2008)	Prospective RCT; Level 1	47 female Wister rats (250-350 g)	20 g-x 3 mm compression lesion for 20 min. at T11.	Hypothermia (n=20) Normothermia (n=19) Sham group (n=8)	33ºC immediately at injury onset;	Hypothermic group demonstrated significantly more improvement in the frequency of hind-limb function (vertical standing) at 48 hr and 72 hrs post-SCI when compared to the normothermic group (*P* =0.0495).	Microglia proliferation and activation was significantly (*P*<0.05) reduced at 48 hr and 72 hrs post-SCI. TNF-α concentration at the compression site was lower in hypothermic group during all points in time;
T.P. LO et al. (2009)	Prospective RCT; Level 1	45 female Fischer rats (180-200 g)	electromagnetic SCI device was used to induce cervical contusion at C5	Hypothermia (n=15) Normothermia (n=15) Uninjured control (n=15)	33ºC induced 5 minutes after cervical contusion for duration of 4 h followed by slow 1ºC/hr rewarming to body temperature.	hypothermic group demonstrated significantly faster recovery rate in BBB locomotor scale scores (weeks 1-3) and significant improvement in forelimb strength compared to normothermic group	MSH increased healthy-appearing white matter (31% increase) and gray matter (38% increase) tissue volumes compared to normothermic controls (*P*<0.01). MSH significantly increased sparing of retrogradely traced axonal projections in the reticulospinal tract (127% increase) and the extent of rostrocaudal neuronal preservation (four fold) at the site of injury compared to the normothermic group.
Batchelor PE et al. (2010)	Prospective RCT; Level 1	female Fischer rats	Compression injury at mid thoracic level. followed by decompression at: 0 (immediately), 2, and 8hr	33ºC followed by decompression at: - 0 h (n=10) - 2 h (n=10) - 8 h (n=16) 37ºC followed by decompression at: - 0 h (n=10) - 2 h (n=9) - 8 h (n=16)	33ºC induced 30 m after injury for duration of 7.5 h,	hypothermic group demonstrated significant improvement in BBB locomotor scale scores (9.5±0.9 vs. 5.3±0.6; *P*<or=.0005) vs. normothermic group	Hypothermic group demonstrated a significantly increase in the amount of healthy tissue & volume of grey and white matter around the initial site of injury.

Author (year)	Study design evidence level	Study population	Injury method	Therapy groups	Intervention parameters	Functional (behavioral) outcomes	Histological outcomes
Kim, Ha, Ok et al. (2012)	Comparative study; Level 1	32 male Sprague-Dawley rats (292-322 g)	25 g-cm compression lesion using MASCIS impactor at T9	MEH (n=8) MSH (n=8) MP (n=8) control (n=8)	MEH group (spinal contusion followed by MEH at 28℃ for 48 Hr); MSH group (spinal contusion followed by MSH at 32℃ for 48 Hr).	Significantly higher BBB scores were found in the MSH (10.2±3.6) and MEH (8.0±2.5) groups compared to the normothermic control group at 6 weeks post-injury (P< 0.05).	Only the MSH group demonstrated significantly lower caspase-3 expression compared to all other experimental groups (P<0.05).
Maybhate et al. (2012)	Prospective RCT; Level 1	21 female Lewis rats	10 g-x12.5 mm w/ NYU impactor at T8.	Hypothermia (n=10) Normothermia (n=11)	32.0±0.5℃ induced 2h after injury for a duration of 2 h,	Hypothermic group demonstrated significantly higher somatosensory evoked potentials (SSEPs) and BBB locomotor scale scores post-SCI and at week 4 compared to controls.	Post-injury histological assessment (day 3) showed greater tissue preservation in the hypothermia group.
Karamouzian et al. (2015)	Retrospective RCT; Level 1	120 male Wistar rats (250 -300 g)	10 g, with 3-mm diameter stainless steel rod impactor at T8-9	EH (n=20) LH (n=20) LH + MP (n=20) MP (n=20) Trauma (n=20) control (n=20)	33.5±0.5℃ induced .5h after injury (EH) or 3h after injury (LH).	No significant difference in BBB locomotor scale scores was seen between the treatment groups.	Early onset hypothermia group inhibited MDA level (lipid peroxidation) significantly more (54.00±19.83 nmol/gww) than methylprednisolone alone (74.00±29.16 nmol/gww) (P=0.035).

n= number of animals assessed in the group.
Level 1= Experimental study, randomized controlled trial (RCT).
Basso, Beattie, and Bresnahan (BBB) locomotor scale score
MSH = modest systemic hypothermia (cooling core temperature to a range between 32-34ºC).
MEH = moderate epidural hypothermia
EH = Early hypothermia -33.5±0.5°C induced .5 h after injury.
LH = Late hypothermia - 33.5±0.5°C induced 3h after injury.
LH + MP = Late hypothermia with methylprednisolone

Table 2. Overview of modest systemic hypothermia following sci in humans

Author (year)	Study type evidence level	Study population	Injury mechanism	Hypothermic therapy*** & other interventions	Reported complications	AIS score outcomes/ other salient features
Levi et al. (2009)	Feasibility case series study 4	Cohort of 14 patients (mean age 39.43) with complete (AIS A) cervical SCI;	- MVA (n=6) - MCC (n=2) - Fall (n=5) - Diving (n=1)	Surgical decompression and modest systemic hypothermia.	- Atelectasis (n=12); - Pleural effusions (n=8); - Pneumothorax (n=4); - Pulmonary edema (n=4); - ARDS (n=2); - Anemia (n=11); - UTIs (n=8); - Thrombocytopenia (n=1) - Thrombotic complications (n=0);	(1) Reproducibility and practicality of endovascular cooling technique was demonstrated. (2) Provided baseline data for future studies; results demonstrated a positive correlation coefficient (>0.4) between temperature and heart rate.
Levi et al. (2010)	Retrospective case series study ** 4	**	**	Surgical decompression and modest systemic hypothermia.	No statistically significant difference in complications in the hypothermic group compared to matched normothermic controls except for a greater number of cases of pleural effusions (P=.01) and anemia (P=.02) in the hypothermia group;	(1) More patients in the hypothermic group converted to AIS grade B and C (5 patients) compared to the normothermic control group (2 patients); however, there was no statistically significant difference seen in final AIS grade in the hypothermic group compared to normothermic controls.
Cappuccino et al.	Case report; 4	NFL football player (age 25); suffered from a complete	- Traumatic sports related SCI (n=1)	Intravenous steroids (methylprednisolone) and cold	No complications were reported;	(1) This patient experienced a more rapid and better neurologic recovery than expected (conversion to AIS-D

Author (year)	Study type evidence level	Study population	Injury mechanism	Hypothermic therapy*** & other interventions	Reported complications	AIS score outcomes/ other salient features
(2010)		(AIS A) C3-4 SCI;		saline were administered~15 min. after injury; followed by surgical decompression and modest systemic hypothermia.		over a period of 4 months).
Dididze et al. (2013)	Retrospective & prospective case series; ** 4	35 patients (mean age 36.1) with complete (AIS A) cervical SCI; retrospective (n=14) and prospective (n=21):	- MVA (n=13) - MCC (n=2) - Fall (n=9) - Diving (n=9) -Hit by car(n=2)	Surgical decompression and modest systemic hypothermia.	- Atelectasis (n=29); - Pleural effusions (n=19); - Pneumothorax (n=8); - Pulmonary edema (n=15); - ARDS (n=4); - UTIs (n=13); - Thrombotic complication (n=5)	(1) 43% of patients (15 out of 35) in the hypothermic group improved in AIS grade. (2) Thrombotic complications were reported in 37% (5/21) of the patients despite prophylactic anticoagulation.

n= number of patients in the group.
Motor vehicle accident (MVA); Motorcycle crash (MCC)
*** Extension of Levi's initial cohort of 14 patients';*
****All patients underwent surgical decompression and stabilization followed by cooling at a rate of 0.5°C/h (max rate 2.5°C/h) to modest (33°C) systemic hypothermia for 48 hours via insertion of a femoral vein intravascular heat exchange cooling catheter (Alsius) with subsequent rewarming to normothermia (37°C) at a rate of 0.1°C/h . No patients in the hypothermic group received methylprednisolone.*

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