

Hypothermia and Human Spinal Cord Injury: Updated Position Statement and Evidence Based Recommendations from the AANS/CNS Joint Sections on Disorders of the Spine & Peripheral Nerves and Neurotrauma & Critical Care

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Recommendation:

Grade I - There is insufficient evidence to recommend for or against the practice of either local or systemic therapeutic hypothermia as a treatment for acute spinal cord injury.

Grade C - There is level IV evidence based on one retrospective comparative cohort study and one prospective cohort study to suggest that systemic modest hypothermia might be applied safely to this population.

Future Directions for Research:

Further research is essential to determine if the preclinical promise of systemic hypothermia for acute spinal cord injury can be realized in humans. If prospective randomized controlled trials prove too challenging to conduct in this patient population, prospective comparative cohort studies (ideally at multiple centers) should be conducted to define the effectiveness and safety of this intervention.

Background:

Both local and systemic hypothermia have been of interest for decades as potential therapies for acute spinal cord injury (SCI).^{1,2} In 2007 the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Joint Section on Disorders of the Spine & Peripheral Nerves and Joint Section on Neurotrauma & Critical Care released a position statement and evidence-based review on hypothermia after SCI.⁷ In that review, Resnick et al found a lack of evidence to either support or refute the use of local or systemic hypothermia for acute SCI in humans. The reviewers advocated for controlled clinical trials investigating the safety and efficacy of this intervention prior to its adoption in clinical practice. In an effort to keep the position statement current, an *ad hoc* committee was formed to generate an updated evidence-based recommendation founded upon a review of the literature from the intervening time period since the 2007 statement.

Methodology:

Literature Search:

A computerized search of the National Library of Medicine database was performed using PubMed with the search terms "hypothermia AND spinal cord injury." The search was limited to the years 2005 to present since the prior review covered 1965-2005. One hundred and thirty-one references were obtained. The titles and abstracts of

these references were then reviewed, and all publications not pertaining to the clinical use of hypothermia after acute SCI in humans were eliminated including laboratory, preclinical, and vascular surgical reports. Only papers published in English were included. Case series and case reports as well as systematic reviews/meta-analyses were included, but general review papers were excluded. The bibliographies of selected papers were also reviewed for additional references. This yielded four publications of relevance.

Grading of the Evidence and Elaboration of Recommendations:

Publications were graded according to the attached Levels of Evidence for Therapeutic Studies (Table 1) similar to that used by the North American Spine Society and other professional societies. Each member of the committee individually graded the publications and these grades were then compared. Differences were adjudicated by discussion and consensus voting. These grades were then synthesized with the evidence from the 2007 position statement to elaborate a recommendation using the attached guide (Table 2).

Scientific Foundation of Recommendation:

The four new publications included one case report, one retrospective feasibility case series, one retrospective comparative case series and one pooled retrospective and prospective case series.³⁻⁶ The details and critique of the evidence can be found in the attached evidentiary table (Table 3).

Briefly, the case report from Cappuccino et al³ described the treatment of a professional football player who sustained a blunt cervical SCI (ASIA A) during play that was treated with systemic hypothermia one day after undergoing anterior-posterior decompression and fusion for C3-4 dislocation. He eventually recovered to ASIA D by four months postoperatively, and the authors felt the degree of recovery was more than would be expected in the absence of hypothermia. Unfortunately, this single case example (level IV evidence) provides inadequate evidence to judge the safety or efficacy of hypothermia in this clinical situation.

The remaining three studies were all published from the same institution and all included the same retrospectively reviewed cohort of 14 patients with complete (ASIA A) acute cervical SCI treated with operative decompression and stabilization followed by 48 hours of modest (32-34°C) systemic hypothermia via an intravascular cooling catheter.⁴⁻⁶ The first report from Levi et al in 2009⁶ was a technical feasibility and early safety study that provides level IV evidence that the authors' method of hypothermia was reproducible and that systemic hypothermia can be used safely in acute SCI patients.

The second report from Levi et al in 2010⁵ examined this same cohort of patients but compared them to a similar group of SCI patients who did not undergo systemic hypothermia in an attempt to establish baseline safety for this intervention. The authors found no statistically significant difference in complications between the groups except for an increased incidence of pleural effusions and anemia in the hypothermia group. The authors concluded that systemic hypothermia for acute SCI is safe and that phase 2 and 3 trials are feasible. This study suffers from limitations, outlined in the evidentiary table

that downgraded its level of evidence to IV. It therefore provides low-level evidence that hypothermia may be applied safely to acute spinal cord injury patients.

The final report from this group, Dididze et al in 2013⁴, presented a pooled analysis of the previously reported retrospective cohort of 14 patients with an additional prospectively treated cohort of 21 patients all undergoing systemic hypothermia in which they investigated clinical outcomes and complications. Comparison of pre- and post-treatment ASIA scores at 12 months revealed that 43% of patients improved at least 1 ASIA grade at follow-up (35% when excluding 4 patients that spontaneously improved in first 24 hours). Most common complications were pulmonary, as seen previously. Overall, 14% had venous thromboembolic events (VTE) (24% in prospective group, none in the smaller retrospective cohort). The authors conclude that systemic endovascular hypothermia for cervical acute SCI is safe and results in higher rates of neurological improvement than seen in previously reported population studies on SCI. As with the prior publications, the absence of a true control group precludes the formulation of definitive inferences on the actual safety or efficacy of systemic hypothermia for acute cervical SCI. This study provides low-level (level IV) evidence for the safety of modest systemic hypothermia in this patient population.

Conclusions:

Scientific studies have documented a potential benefit of systemic hypothermia in animal models of acute spinal cord injury; however there remains a paucity of clinical evidence to recommend for or against the practice of either local or systemic hypothermia for acute SCI in humans. The level IV evidence suggesting the safety of modest systemic hypothermia is promising, but controlled, comparative clinical studies investigating safety and efficacy must be performed prior to the introduction of hypothermia in the routine clinical care of patients with acute SCI.

Table 1. Levels of Evidence

Therapeutic Studies	
Level I	<ul style="list-style-type: none"> • High quality randomized trial with statistically significant difference or no statistically significant difference but narrow confidence intervals • Systematic Review of Level I RCTs (and study results were homogenous)
Level II	<ul style="list-style-type: none"> • Lesser quality RCT (e.g. <80% follow-up, no blinding, or improper randomization) • Prospective comparative study • Systematic review of Level II studies or Level 1 studies with inconsistent results
Level III	<ul style="list-style-type: none"> • Case control study • Retrospective comparative study • Systematic review of Level III studies
Level IV	<ul style="list-style-type: none"> • Case Series • Case Reports
Level V	<ul style="list-style-type: none"> • Expert Opinion

Table 2. Grades of Recommendation

Grade of Recommendation	Alternate Language	Levels of Evidence	
A	Recommended	Two or more consistent Level I studies	
B	Suggested	One Level I study with additional supporting Level II or III studies	Two or more consistent Level II or III studies
C	May be considered; is an option	One Level I, II or III study with supporting Level IV studies	Two or more consistent Level IV studies
I (Insufficient or Conflicting Evidence)	Insufficient evidence to make recommendation for or against	A single Level I, II, III or IV study without other supporting evidence	More than one study with inconsistent findings*

Table 3. Evidentiary Table on Hypothermia and Spinal Cord Injury, 2005-2013

Authors and Year	Description of Study	Comments	Class
Levi et al, J Neurotrauma 2009	Retrospective case series on a subset of patients in a single-institution phase 1 feasibility study for modest (32-34°C) hypothermia in patients with complete (ASIA A) blunt traumatic spinal cord injury (SCI). A total of 14 patients with cervical SCI were included. All patients underwent operative decompression/stabilization. No patient received steroids. An intravascular cooling catheter in the femoral vein was used for 48 hours of cooling. Outcomes included temperature control and complications. Temperature was well controlled using the catheter. Complications included: 12/14 atelectasis, 8/14 pneumonia, 2/14 ARDS, 3/14 arrhythmia, 1/14 thrombocytopenia, 1/14 sepsis and 0/14 VTE.	This phase 1 feasibility study was intended to demonstrate the reproducibility of applying hypothermia to acute spinal cord injury patients. The authors provided limited information regarding methodology, including the ascertainment and definition of complications. Heterogeneity of the cohort exists regarding timing of surgery and demographics. No statistical information is provided. Despite these limitations, the study demonstrates the reproducibility of the technique.	IV
Cappuccino et. al., Spine 2010	A case report of a professional football player who sustained a blunt cervical SCI (ASIA A) during play that was treated with systemic hypothermia one day after undergoing anterior-posterior decompression and fusion for C3-4 dislocation. He also received methylprednisolone and iced saline on the field. A femoral vein intravascular cooling catheter was used to induce the modest hypothermia for 48 hours and normothermia for several days after. He demonstrated improvement in motor function to at least anti-gravity strength in the legs. He eventually recovered to ASIA D by four months postop. No complications were noted. The authors felt the degree of recovery was more than would be expected in the absence of hypothermia.	No validated outcome measures. This solitary case example does not allow any conclusions to be drawn regarding the safety or efficacy of systemic hypothermia for traumatic SCI.	IV
Levi et al, Neurosurgery 2010	(Same cohort reported in Levi 2009). Retrospective comparative case series on a subset of patients in a	Small sample size of cases (possibly nonconsecutive) and controls likely	Potential III,

	<p>single-institution phase 1 feasibility study for modest (32-34°C) hypothermia in patients with complete (ASIA A) blunt traumatic spinal cord injury (SCI). A total of 14 patients with cervical SCI were included. All patients underwent operative decompression/stabilization. No patient received steroids. An intravascular cooling catheter in the femoral vein was used for 48 hours of cooling. Outcomes included pre- and post-treatment ASIA scores for 12 months and complications. A cohort of 14 patients with similar age and SCI treated prior to hypothermia protocol initiation were selected as historical controls for comparison of complications. 6/14 patients in hypothermia group and 3/14 in control group improved their ASIA score at follow-up (no statistically significant difference). No statistically significant difference in complications except for more pleural effusions and anemia in hypothermia group. The authors conclude that systemic hypothermia for acute SCI is safe and phase 2 and 3 trials are feasible.</p>	<p>makes study underpowered to detect significant differences in complication rates. Confounding the differences in the clinical results are the fact that 3 patients in control group received methylprednisolone and only 50% (vs 85% in hypothermia group) underwent early surgery (<24hr). Unclear methodology for collection and definition of complications. Heterogeneous group in regards to timing of surgery, demographics. This study provides low-level evidence that endovascular systemic hypothermia may be applied safely to acute cervical SCI patients.</p>	<p>downgraded to IV</p>
<p>Dididze et al, Spinal Cord 2013</p>	<p>Pooling of same retrospective cohort of 14 patients from Levi 2009 and Levi 2010 with prospective cohort of 21 patients at same single-institution for modest (32-34°C) hypothermia after complete (ASIA A) blunt traumatic spinal cord injury (SCI). All patients operative decompression/stabilization. No patient received steroids. An intravascular cooling catheter in the femoral vein was used for 48 hours of cooling. Outcomes included pre- and post-treatment ASIA scores for 12 months and complications 43% of patients improved at least 1 ASIA grade (35% when excluding 4 patients that spontaneously improved in first 24 hours). Most common complications were respiratory as seen previously. Overall, 14% had VTE (24% in prospective group, none in smaller retrospective cohort). The authors</p>	<p>The absence of a control group precludes the drawing of inferences on the true safety or efficacy of systemic hypothermia for acute cervical SCI. The heterogeneity of the cohort (with respect to surgical timing and demographics), potential non-consecutive allocation to treatment, and failure to define method of complication ascertainment makes valid comparisons to previously published studies difficult. This study provides low-level evidence for the safety of systemic hypothermia in this patient population.</p>	<p>IV</p>

conclude that systemic endovascular hypothermia for cervical acute SCI is safe and results in higher rates of neurological improvement than seen in previously reported population studies on SCI.

References:

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