Hypothermia for spinal cord injury

TO THE EDITOR: We read with great interest the recent paper by Hansebout and Hansebout⁹ on local cooling for spinal cord injury (SCI) (Hansebout RR, Hansebout CR: Local cooling for traumatic spinal cord injury: outcomes in 20 patients and review of the literature. Clinical article. *J Neurosurg Spine* 20:550–561, May 2014). The authors describe the long-term clinical outcome in 20 patients who had American Spinal Injury Association Impairment Scale (AIS) Grade A SCI in either the cervical spine (n = 14) or thoracic spine (n = 6). This report includes the 10 patients described by the author in a previous report in 1984.¹² The patients were accrued for 10 years starting from 1977 with a mean follow-up of around 5 years. Dexamethasone was given to patients for 18 days. A local cooling apparatus placed in the epidural space cooled the dura to 6°C for up to 4 hours while the instrumentation was being done after decompression. Overall, 65% of the patients improved from AIS Grade A to B, C, or D, with 2 patients regaining ambulatory function. The outcomes reported in this study are better than what would usually be expected for an AIS Grade A injury.⁷

Local spinal cord cooling was more popular in 1970s and early 1980s when several groups had used local cooling in humans and animals with variable but generally good results.^{3,4,8,10,11,16,18,20,21} The potential benefits of providing hypothermia directly to the injured region obviated many of the risks of deep systemic hypothermia and resulted in many studies in large animals, leading to application in humans. Local cooling trials for SCI in humans in that era were facilitated by the common performance of laminectomy as part of the treatment regimen. Wide laminectomy particularly after cervical injuries is now much less common, particularly with the advent of anterior cervical plating for cervical fracture-dislocations.¹⁹ While the outcomes of some of these studies were encouraging, several factors, like the lack of control group, variable treatment window, confounding variables such as the administration of steroids, and small sample size led to failure in drawing any strong conclusions and gradual abandonment of local hypothermia for SCI.

In contrast, there is very encouraging data from our center that modest systemic hypothermia (32°–34°C) can lead to both histological and functional recovery after SCI in animal models.^{2,14,15,17,22} We have reported our technique and clinical data on the outcome and safety profile of modest systemic hypothermia for 48 hours after cervical AIS Grade A SCI.^{1,5,6,13,15} In our initial study, 6 of

the 14 patients (42.8%) improved one AIS grade or better. The majority of the patients who improved in this original study did so within the first 3 months, but none did so within the first 2 weeks. This suggested that patients with spinal shock were not inadvertently included in the study. In our subsequent follow-up study, which included the original group as well as subsequent patients accrued over a 6-year period (n = 35), 15 of the 35 patients (42.8%) improved at least one AIS grade or greater.⁵ This compared favorably to published natural history outcome data.⁷ The current guidelines from the AANS/CNS joint section on spine provide a Grade C (Level 4 evidence) for the use of modest systemic hypothermia for SCI.¹

The authors acknowledge some of the drawbacks of the current local hypothermia study. The most obvious is the need for laminectomy before cooling can be started. At that time, cooling was continued for 4 hours while fusion was being performed. In the current era of spinal instrumentation, constructs are shorter, stronger, and faster to apply, with many patients avoiding decompression via laminectomy with restoration of alignment. Also, this study was done prior to the modern imaging era, which means that we do not know the extent of injury to the spine and spinal cord, and the injury could range from a bad form of central cord damage (with better prognosis) to complete cord transection (with no chance of improvement). With systemic hypothermia, cooling can potentially be initiated at the time of injury by administering intravenous ice-cold saline, such as in the Advanced Cardiac Life Support (ACLS) guidelines for the reduction of neurological brain injury after cardiac arrest. With modest hypothermia, many of the complications of deep systemic hypothermia can be avoided while preserving many of its benefits. Endovascular cooling is fast and reliable, and, unlike local hypothermia, can be started in the emergency department without delaying the surgery if the patient is going to the operating room. It also can be administered to patients who do not need surgery. Considering that there is no proven therapy for SCI and there is now a growing body of literature supporting the use of hypothermia for this devastating injury, larger multicenter trials should be conducted to further assess safety and efficacy in a prospective, randomized study.

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RESPONSE: We wish to thank Drs. Ahmad and Levi for their excellent research on hypothermia for traumatic SCI and their comments on our cord-cooling series.

When this series was first conceived, it was decided to include only patients with neurologically complete SCI as they do not often recover significant neurological function, allowing improvement to be more easily attributed to the intervention. Corticosteroid therapy was standard treatment at the time and it was not considered ethical to withhold it. We wanted to begin cooling early, since the secondary autodestructive processes in severe SCI can progressively aggravate spinal cord damage, particularly within the first 8 hours of trauma.¹ It was extremely difficult to get severely injured patients into the operating room for cooling in this time period; we consequentially used only plain radiographs and systemic emergency management to save time. During this study, some of the more modern imaging modalities, such as CT scanning, were available, but MRI was in its inception. We did not obtain CT scans as, during the period in which the study was completed, doing so would have substantially increased the time to application of cooling. We did visualize the dura and, occasionally, the cord through torn dura at the site of injury during decompression. In one case a complete cord transection was noted, and cooling was therefore not undertaken.

There has been discussion about the comparative beneficial effects of deep local versus modest systemic hypothermia. We hypothesized that selectively and deeply cooling injured tissue would be most likely to arrest the progressive secondary autodestructive processes within the spinal cord while avoiding potential cardiac, respiratory, or other complications of systemic hypothermia. Lower temperatures are more safely and easily obtained in target tissues through the use of local cooling. A question is whether this profound yet local decrease in temperature is beneficial; some data indicate it might be so. A 2010 study⁶ showed preservation of ischemic human dorsal root ganglia to be facilitated by the use of deep hypothermia. Cooling the cultured ganglia to 20°C resulted in a 4.5-fold increase in neuronal viability; cooling in combination with heightened culture medium alkalinity increased viability 26-fold. Decreasing temperature also decreases neural metabolic rate³ and has, in some cases, been shown to provide superior cerebral protection as compared to milder cooling.⁵ It is possible that the ideal temperature to protect acutely injured neural tissue is lower than that feasibly approached by systemic hypothermia. As another note, the time to achieve spinal cord target temperature is very rapid using local cooling, likely being reached within 5 minutes, according to studies in large animals.¹²

In comparing different durations of hypothermia in dogs,¹³ we showed that 4 hours of cooling was better than either 1 hour or 18 hours. A 1994 study⁸ explored whether deep cooling increased the risk of neuronal apoptosis after dendrite transection. This study demonstrated in vitro that cooling at 17°C for 2 hours protected damaged neurons. However, this protection was lost after cooling for 6 hours, suggesting that the beneficial effect of hypothermia was lost with prolonged cooling. Conversely, Dididze and colleagues² systemically and modestly (33°C) cooled patients for 48 hours. This duration was informed⁷ by findings from a meta-analysis¹⁰ of controlled trials studying systemic hypothermia for traumatic brain injury. Perhaps the optimal duration of cooling is different for modest hypothermia than for deep hypothermia, with the more profound hypothermia possible in local cooling requiring a shorter duration for maximal effect.

Drs. Ahmad and Levi suggest that laminectomy is now much less common, particularly with the advent of anterior cervical plating for cervical fracture-dislocations. We agree. However, local cooling is possible during anterior cervical fixation. In our series, the injured cords of 5 patients were cooled, using a different saddle, through an anterior approach with satisfactory results. Furthermore, there will likely remain a subset of patients in whom cord decompression is indicated. These patients will undergo surgical intervention regardless of whether cooling is performed. Some experimental techniques^{9,11} have also been shown to decrease spinal temperature while leaving systemic temperature normal, leading to the possibility of less invasive regional cooling.

Results from series examining the effect of modest systemic hypothermia on recovery from SCI have been encouraging and we welcome continued study on this treatment modality in the hopes it will be of benefit to injured patients. Given that patients in our series likewise enjoyed better outcomes than would be expected,⁴ we believe there is value in also continuing research into local cooling. The effects of systemic and local cooling might well have a role in the treatment of patients with SCI. For example, systemic hypothermia could be started in severe cord injuries during transport and diagnostic studies, with deep local cooling adjunctively performed if permissive surgery is needed. As such, we believe that controlled trials examining the effect of profound regional hypothermia after both complete and incomplete SCI are indicated, particularly when surgical intervention is deemed necessary and such cooling can be instituted in a timely manner.

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Local cooling for traumatic spinal cord injury

TO THE EDITOR: We read with great interest the recent article by Hansebout and Hansebout¹⁰ (Hansebout RR, Hansebout CR: Local cooling for traumatic spinal cord injury: outcomes in 20 patients and review of the literature. Clinical article. *J Neurosurg Spine* 20:550–561, May 2014). The authors reported the clinical outcome of 20 patients with traumatic spinal cord injuries (SCIs) after local cooling of the cord to 6°C for up to 4 hours after surgical decompression. They concluded that patients treated with their protocol involving “combination of surgical decompression, glucocorticoid administration, and regional hypothermia...had better recoveries than might have been expected in patients undergoing traditional forms of treatment.”

Given the devastating impact on quality of life and overall poor clinical outcome after complete SCI, the search for treatments that can potentially improve func-

tional outcome in these patients has been a subject of numerous studies in humans and animals. There has been increasing interest in the role of both local and systemic hypothermia in patients who have sustained an SCI, with studies reporting mixed results.^{1,3,6,9,12,13,17} We applaud the authors' effort in conducting this study in pursuit of improving clinical outcome in patients with SCIs. However, there are various points that need to be kept in mind while interpreting the results from this study. First, the biggest limitation of this study is the patient selection. The inclusion criteria required the enrolled patients to be "alert and cooperative; between the ages of 16 and 65 years; and have no motor or sensory function below the level of cord injury, no perianal sensation, and no anal sphincter contraction." However, none of these patients had bulbocavernosus reflex as stated by the authors, despite the absence of conus injuries. This essentially means that the authors only selected patients who were in "spinal shock" by definition.^{7,11,16} While we understand that waiting for spinal shock to resolve may lead to delaying treatment to the point where it would have lost substantial efficacy, the chances of improvement in patients with spinal shock cannot be underscored and it would be unreasonable to attribute recovery in this group of patients completely to any form of surgical or medical intervention. The "spinal shock" we refer to here is defined as by Sherrington in 1897 as "depression or suppression of nervous reaction, which ensues forthwith upon a mechanical injury of some part of the nervous system, and is of temporary nature."⁷ It has been well known that patients in spinal shock have a much better chance for spontaneous clinical recovery since a component of the deficits is, by definition, transient.^{11,16} An example at the extreme end of such a scenario would be spinal cord concussion, which is defined as a "transient deficit which resolves completely within 48 hours, in the absence of instability or structural deficiency"; patients with spinal cord concussion will have complete recoveries despite being completely quadriplegic at initial presentation.^{2,19} Therefore, the outcome of this study may be merely the effect of the natural history of these patients with spinal shock and not due to local cooling. Second, results from the recently conducted Surgical Timing in Acute Spinal Cord Injury Study (STASCIS)⁸ have demonstrated possible improved outcome with early surgical intervention (< 24 hours from the time of injury). The patient cohort in this study underwent surgical decompression 2.25–11 hours after initial injury; this could have significant impact on the clinical outcome of these patients based on the STASCIS results and thus confound the actual effect of local cooling of the spinal cord on the clinical outcome. Third, all of these patients received steroid treatment. While there has been increasing consensus on the lack of benefit of steroids in SCI,^{5,15,18} steroid treatment as mentioned by the authors may provide potential benefit on functional recovery,⁴ introducing yet another confounding variable. Finally, the patients included in the study were generally young. Other than the 2 patients 51 and 64 years of age, the remaining patients were in their 20s and 30s, which might have contributed to a better outcome in the study.¹⁴

We again applaud the authors' effort in conducting

such research with the hope of improving patient outcome after SCI. While hypothermia may have a significant impact on improving the clinical outcome in patients with complete SCI, the generalizability of this study is severely limited by the lack of control group and various aforementioned confounding factors. While the results of this study are intriguing, a well-designed randomized study is needed to truly demonstrate an additive beneficial effect of regional hypothermia in these patients. Clinicians should be aware of these limitations when counseling patients and families.

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RESPONSE: We thank Dr. Tan and colleagues for their remarks on our paper. Our patients underwent 3-pronged therapy, which included corticosteroids, decompression, and local extradural cooling to 6°C, with a probable central spinal cord temperature of 17°C. We compared our patient outcomes with those of large historical and modern series. Having dealt with spinal cord-injured patients for over 35 years, the senior author was impressed with the neurological recovery of many of this series' patients, whose clinical examination findings at presentation were consistent with a neurologically complete SCI (American Spinal Injury Association [ASIA] Grade A). We felt that outcomes in our patients were better than those found in series examining outcomes in other patients with ASIA Grade A injuries. Before application to humans, this study was preceded by 7 years of intense laboratory experimentation.⁵ There were also numerous other studies in the past indicating the value of cord cooling in patients after injury,⁵ both locally and more recently systemically.² In their comments, Dr. Tan and colleagues continued on several points we raised in our paper.

Their main concern was that patients were treated within a short period of injury when still, by definition, in spinal shock. As they indicate, spinal shock can cause a potentially mild injury—in the case of spinal concussion,^{1,9} one that is entirely reversible—to appear to be much more severe than it is. Dr. Tan and colleagues wonder whether our patients truly had a neurologically complete SCI. We believe they did, for 2 reasons: injury severity and course of recovery.

With respect to injury severity, our patients suffered spinal fractures with extensive gross cord pathology. The patients survived, so we could not prepare histological specimens, and we were unable to include modern scans, as our series began before the advent of MRI. We did, however, examine the dura and sometimes the cord through torn dura at surgery. As an example, refer to Fig. 4 in the original article, a photograph of a distended dura through which submeningeal hemorrhage is observable. All the patients had a tight dura over a swollen, sometimes hemorrhagic spinal cord. The second reason relates to the nature of spinal shock. Sir Frank Holdsworth,⁷ referred to by the authors in their letter, wrote “if the paraplegia below a cord lesion remained complete for twenty-four

hours then the cord was irreparably damaged and recovery could never occur,” as well as “return of reflex activity below the level of the cord lesion in the absence of motor power or sensation is a bad prognostic sign.” Stauffer⁸ remarked that in those patients who remained quadriplegic for 24 hours, only 1% ever recovered neurological function. Given this information, we carefully reviewed all neurological examination data collected during the few days following patient injury. In all but 2 cases (Cases 2 and 19), the patients had recovery of only reflex activity or no functional neurological recovery whatsoever before at least 48 hours had elapsed. The patient in Case 2 regained deep tendon reflexes at about the same time as motor power and at just about the 24-hour period. The patient in Case 19 developed complications, which made assessment of his neurological status in the few days after his injury difficult. This would indicate that the acute phase of spinal shock³ had resolved before any sensory or voluntary motor recovery in at least 18 of our 20 patients. Of these injuries in the 18 remaining patients, 7 remained ASIA Grade A, 6 improved to Grade B, 3 to Grade C, and 2 to Grade D.

The authors have commented on other limitations of our study. While it is the largest of its kind, the number of patients in this series is small. It is very difficult to bring patients from the accident scene to the hospital, examine them, prepare them for surgery, and have them in an operating room in less than 8 hours. Accordingly, we were able to select only a small number of patients who met our study's stringent inclusion criteria, although the study took place over a 10-year period. Dr. Tan and his colleagues suggested that concurrent use of multiple treatment modalities makes assignment of any benefit to therapeutic hypothermia difficult. As our study was not a controlled trial, it was considered unethical to provide patients with less than what was then standard-of-care treatment: glucocorticoids and decompressive surgery, in addition to the experimental local hypothermia. We agree that both steroids^{5,6} and decompression⁴ may have had a role in the facilitation of neurological recovery. We described these limitations in our paper. We indicated that definitive conclusions regarding the effectiveness of treatment cannot be unequivocally drawn from this case series. However, in view of the seriousness of our patients' injuries and our comparatively positive results we believe that our management regimen was likely beneficial.

We agree that high-quality trials of spinal cord cooling after trauma should be undertaken, especially for patients with a neurologically complete SCI, although our work indicated that even profound local cooling does not appear to cause damage, as indicated by an incompletely injured patient experiencing remarkable recovery after cooling. Our chief interest in completing this series was to offer hope, grounded in sound basic research, to patients who experienced devastating injury and had otherwise little chance of recovery. In writing the course and results of the series, we desired to spark new interest in a little used treatment modality. We wholly support the development of well-designed randomized controlled trials of local hypothermia.

We thank the authors for their comments.

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