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Preliminary Safety and Efficacy of Head and Neck Cooling Therapy After Concussion in Adolescent Athletes: A Randomized Pilot Trial

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Abstract

Objective: To determine the safety and efficacy of head and neck cooling when applied up to 8 days after concussion among adolescent athletes. **Design:** A randomized nonblinded pilot trial. **Setting:** Sports Medicine Clinic in a tertiary hospital. **Patients:** Adolescent athletes aged 12 to 17 years diagnosed with a concussion within 1 week of injury. **Interventions and Main Outcome Measures:** The control group (n = 27) received standard treatment (short term brain rest), whereas the treatment group (n = 28) received standard treatment and head and neck cooling. Head and neck cooling treatment was applied to patients at the postinjury assessment visit and at 72 hours post-injury. The SCAT5 (Sport Concussion Assessment Tool) total symptom severity score was collected at postinjury assessment visit, pre- and post-treatment at 72 hours, and at 10 days, and 4 weeks post-treatment. **Results:** Athletes who received head and neck cooling had a faster symptom recovery ($P = 0.003$) and experienced significant reduction in symptom severity scores after treatment ($P < 0.001$). Sport type and gender did not influence the treatment outcome ($P = 0.447$ and 0.940, respectively). **Conclusions:** This pilot study demonstrates feasibility of head and neck cooling for the management of acute concussion in adolescent athletes.

Key Words: concussion, head and neck, cooling, therapy

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INTRODUCTION

Concussions are a significant public health concern and are prevalent among high-school and collegiate athletes, with approximately 1.6 to 3.8 million concussions reported as a result from sport and recreational activity annually in the United States.[1] Acute concussion is diagnosed based on self-reported symptoms such as headache, dizziness, cognitive dysfunction, and mood problems because it does not usually result in any identifiable abnormalities on diagnostic brain scans. About 80% to 90% of concussions resolve in 7 to 10 days; however, the recovery time for young children is longer[1–3] and may result in a long-term neuropsychological impact.[4]

The standard treatment of acute concussion after sports injury is short-term brain rest (24-72 hours)[5–7]; this includes almost all physical and cognitive activity and is intended primarily to reduce the risk for repeat injury and second impact syndrome, as well as length of symptoms.[8,9] Leddy et al[10] showed that short-term brain rest followed by early subsymptomatic exercise result in a quicker recovery in adolescent who sustained a sport-related concussion.

Hypothermia is a therapeutic approach that has shown promising outcomes for brain injury.[11] Induced mild-to-moderate hypothermia has been used since the early 1940s,[12–16] both in experimental brain injuries and in noncontrolled clinical studies of traumatic brain injury. In the 1990s, several investigators reported encouraging results from noncontrolled studies and phase II and III randomized clinical trials for using hypothermia in patients with severe traumatic brain injury.[17] Hypothermia can include the whole body or only the injured region. The physiologic benefit from cooling the injured region is believed to occur at the cellular level[18–20] by 2 mechanisms: (1) by improving neuronal function through reducing apoptosis and decreasing metabolic rate[21] and (2) by minimizing the damage stemming from inflammation caused by the response of the body to injury.[14,22,23] Furthermore, hypothermic therapy has been shown to have clinical efficacy in a variety of other conditions, including cardiovascular injuries, such as cardiac arrest and myocardial infarction.[24] It is also the standard of care for the treatment of neonates with hypoxic–ischemic encephalopathy.[25,26]

The existing literature on the effects of hypothermic therapy for traumatic brain injuries, combined with the continued discussion about benefits of brain rest, provide support for

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evaluating hypothermic therapy as a treatment for concussion. A previous study evaluating the effects of hypothermic therapy on concussion focused on college-aged athletes.[27] Because the recovery trajectory is different among children,[1–3] there is a need to evaluate hypothermic therapy among younger populations. To investigate the efficacy of hypothermia in the treatment of acute concussion in a pediatric population, we tested the feasibility of head and neck cooling when applied within 8 days of sustaining a concussion in adolescent athletes aged 12 to 17 years.

MATERIALS AND METHODS

Study Design and Setting

This prospective pilot, single-center, randomized, nonblinded, dual-arm (treatment n = 28, control n = 27) comparative study was approved by the Akron Children's Hospital's Institutional Review Board. Written informed consent was obtained from parents or guardians of study participants. Written assent was obtained from patients because all were younger than the age of 18 years. Study participants scheduled for an initial visit (henceforth referred to as the post-injury assessment visit) at the Sports Medicine Clinic were identified by study personnel through a review of the appointment schedule in the electronic medical record system, the day before their postinjury assessment visit and were invited to participate in the study. The control group received the standard treatment, whereas the treatment group received both the standard treatment and head and neck cooling therapy using the Pro-2cool device (Tec Traum, Inc, Cleveland, OH). The Pro-2cool device is a noninvasive hypothermic therapy device that provides localized cooling of the head and neck. This is achieved through a water and isopropyl alcohol mixture that is cooled to 6°C by a chiller assembly and then circulated through a cooling garment to create conductive heat transfer from the scalp and carotid arteries, thus achieving cooling of the head and neck and eventually the brain. Figure 1 shows an outline of the study visits and participant flow from the postinjury assessment visit to the end of study.

Study Participants

Students (men and women aged 12-17 years) participating in sporting activities in year 2017 to 2019, including men's football, baseball, basketball, soccer, lacrosse, hockey, swimming and diving, track and field, cross country, wrestling, women's softball, basketball, soccer, volleyball, lacrosse, swimming and diving, track and field, cross country, cheerleading, and gymnastics and who presented with sports-related concussion within 8 days of injury were included in the study.

Sport-Related Concussion and Eligibility Criteria

Adolescent athletes who presented to the Sports Medicine clinic within 8 days of injury and were diagnosed with a sports-related concussion were enrolled in the study. Sports-related concussion was defined as a traumatic impulsive force to the head or body during one of the sporting activities listed above. Patients were also required to have a minimum total symptom severity score that is greater than their reported preinjury score, as indicated at the beginning of their post-injury Cleveland, OH). The a serious traumatic brain injury, as evidenced by worsening symptoms, seizure, hospitalization, or existing positive diagnostic testing as determined by the provider, which had not resolved within 72 hours of injury were excluded from the study. In addition, patients who sustained another head or neck injury at the time of concussion that required medical treatment were also excluded from the study. Other exclusion criteria included (1) history of a serious medical or psychiatric disorder as determined by the principal investigator, (2) history of Raynaud's disease, (3) cold agglutinin disease, (4) cryoglobulinemia or cryofibrinogenemia, (5) previous diagnosis of a cerebrovascular disorder, and (6) enrollment in another investigational research study that may confound the results of this study.

Randomization

Study participants were assigned to study arm based on a block randomization schedule using SAS 9.4/14.2. Once enrolled, study participants were given an identification number (ID) for enrollment (1, 2, 3, etc.). Corresponding IDs on randomization schedules were used to identify whether subject is in the intervention arm or standard of care arm. A randomization schedule was completed for the study participants in blocks of 4 to promote size equality and comparability of groups.

Self-Reported Symptom Severity Assessment

Sport Concussion Assessment Tool 5 (SCAT5) symptom severity score assessment[7] was the primary outcome and was completed by treatment and control study participants at the post-injury assessment visit, before and after Pro-2cool treatment or standard treatment (0-8 days post-concussion); at 72 hours, before and after Pro-2cool treatment or standard treatment (±24 hours of post-injury assessment visit); 10 days (±3 days of post-injury assessment visit) and 4 weeks (28 days ± 7 days of post-injury assessment visit) post-treatment. The SCAT5 symptom severity score is part of the commonly used tool (SCAT5) to diagnose concussion on the sidelines. Only the symptom severity score was completed for outcome assessment. This section of the tool consists asking adolescent athletes to rate 22 symptoms on a scale of 0 to 6, with 0 being no symptoms and 6 being severe symptoms. To measure the effects of the treatment, the total symptom severity score was calculated as the sum of how the adolescent athlete rated each symptom. The SCAT5 raw scores were used to create the difference scores from the post-assessment visit to see if there is a reduction over time for those who received the intervention compared with those who did not receive the intervention.

Head and Neck Cooling Therapy Using the Pro-2cool Device

Treatment with the Pro-2cool device (Figure 2) was performed for a maximum of 30 minutes for the study participants in the treatment group at the post-injury assessment and 72-hours visits. Before treatment, post-injury assessment visit levels for temperature and other physiological measurements, such as blood pressure and heart rate, were recorded to monitor any adverse effects. The Pro-2cool device was fitted to the subject by an appropriately trained professional. Once the headpiece was properly donned, the chiller unit was set to 6°C. The chiller was set to the "cool down" mode for 10 minutes, providing the subject with the optimal temperature acclimation period. Once the desired treatment temperature was reached, the trained

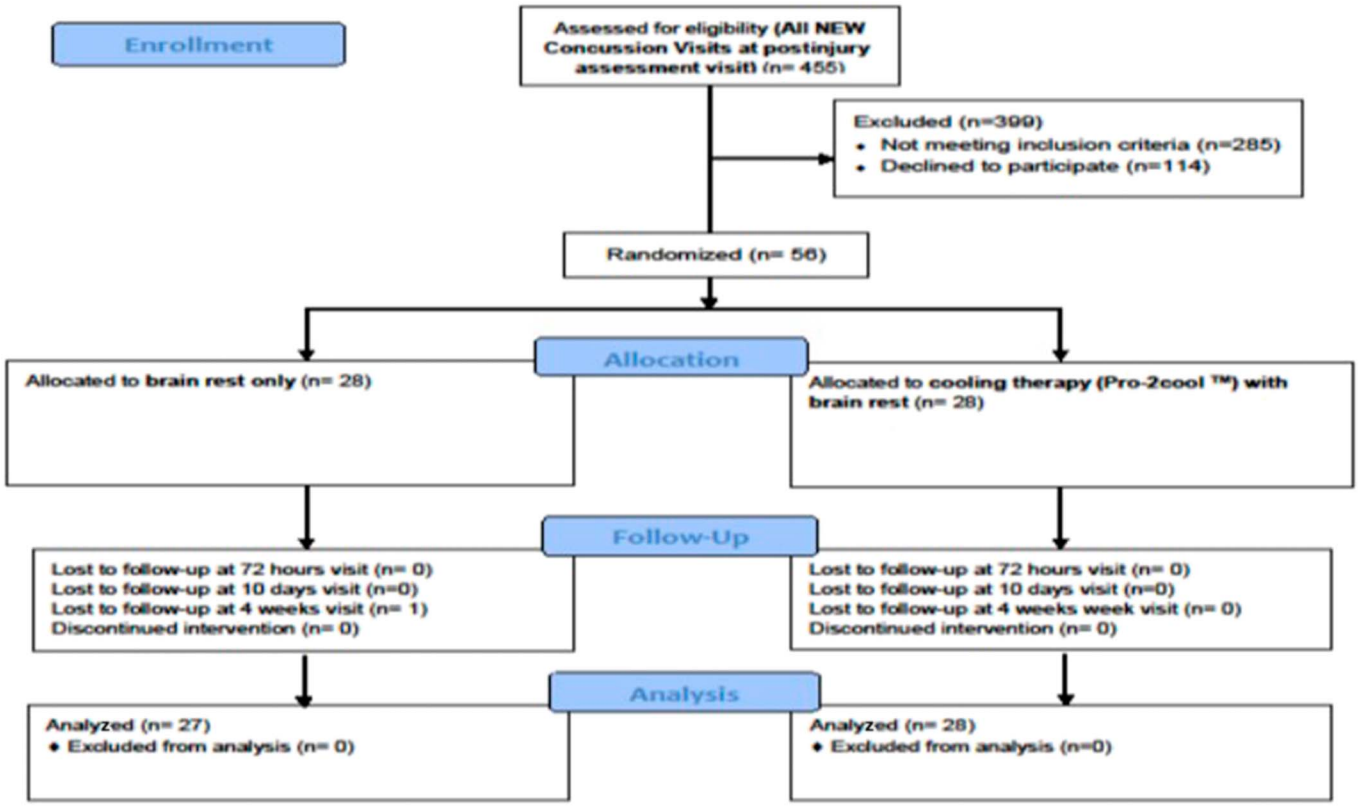

Figure 1. A CONSORT flow diagram outlining the flow of patients through the Pro-2cool pilot study according to the criteria recommended in the CONSORT Guidelines.

professional started the timer and treatment began. During the treatment, the SCAT5 symptom severity score was assessed every 15 minutes (ie twice in the 30-minutes treatment) to monitor for any adverse events. Treatment was limited to 30 minutes (±5 minutes) after which the device headpiece was removed, and vital signs were repeated (within 5 minutes of treatment completion). Study participants were then discharged to the care of a parent or legal guardian with study follow-up instructions.

Our treatment was designed based on the following: (1) length: previous similar studies suggest that a 30-minute cooling period was enough to impact brain temperature with mild hypothermia,[27–29] (2) time points: our treatment was combined with the standard treatment (brain rest), which is usually performed on the initial visit and 72 hours later, and (3) the 8 days post-injury was selected because it is the time that most patients are seen in our clinic if they visit the emergency room when they get injured. Since the 30 minutes 1-time treatment as described in Wang et al resulted in relief of symptoms,[27] we hypothesized that repeating the treatment at least once after 72 hours will be more effective in reducing symptoms.

Figure 2. A image showing the Pro-2cool device in use. Red arrow: Garments, black arrow: chiller with quick hose connect, blue arrow: power supply, *: Hood, and accessories: (A) garment transport cylinder, (B) disinfecting wipes and coolant solution, (C) head sleeve insulator, and (D) thyroid cartilage insulator.

Adverse Events

Adverse events were collected at each study visit. These included unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings), whether related to use of the investigational Pro-2cool device or not. Safety was evaluated by reporting adverse events by type and frequency throughout the study follow-ups for the treatment and control groups. To

TABLE 1. Patient Demographics at the Postinjury Assessment Visit

Total Number of Patients (n)	Control Group (n = 27)	Treatment Group (n = 28)	*P*
Age at diagnosis, years			
Mean ± SD	14.25 ± 1.4	14.7 ± 1.6	0.29
Range	12.0-17.0	12.0-17.0	
Sex, n (%)			
Male	14 (52)	14 (50)	0.89
Female	13 (48)	14 (50)	
Race/ethnicity, n (%)			
White	20 (74)	24 (86)	0.28
African American	5 (18)	3 (11)	0.41
Hispanic	1 (4)	1 (3)	0.97
Unknown	1 (4)	0 (0)	0.30
Height, cm			
Mean ± SD	167.9 ± 9.6	169.1 ± 9.2	0.5
Range	141.0-184.9	151.5-188.0	
Weight, kg			
Mean ± SD	66.9 ± 16.6	66.1 ± 17.6	0.61
Range	40.1-105	36.7-116.2	
Type of sport, n (%)			
Football	7 (26)	1 (4)	0.018*
Lacrosse	2 (7)	6 (21)	0.14
Soccer	5 (18.5)	3 (11)	0.41
Swimming	1 (4)	5 (18)	0.09
Volleyball	1 (4)	1 (4)	0.97
Wrestling	3 (11)	3 (11)	0.96
Basketball	4 (15)	2 (7)	0.36
Cheerleading	1 (3.7)	1 (4)	0.97
Other	3 (11)	6 (21)	0.52
Average days between injury and initial visit	4.5	4.14	0.39
Preinjury SCAT5 score			0.75
Mean ± SD	25.76 ± 19.76	27.4 ± 19.19	
Range	0-78	1-76	
post-injury SCAT5 score at the post-injury assessment visit			0.87
Mean ± SD	32.11 ± 20.5	32.28 ± 23.39	
Range	2-77	2-85	

** Denotes significance between control and treatment groups.*

prevent bias, adverse events were evaluated by a provider outside of the Sports Medicine Clinic with clinical knowledge of traumatic brain injury. Examples of side effects monitored in this study included: increase in systolic and diastolic blood pressure, decreased heart rate, decreased respiratory rate, decreased core temperature, headache or localized tingling, and discomfort.

Statistical Analysis

Statistical analyses were conducted using SAS 9.4/14.2 (SAS Institute, Cary, NC). Unless otherwise noted, all hypotheses testing was 2-tailed and evaluated at a type I error rate of 0.05, with *P*-values below that value deemed statistically significant. *P*-value for age, height, weight, and preinjury and the postinjury assessment visit SCAT5 total symptom severity score comparisons between treatment and control groups was calculated using the nonparametric Mann–Whitney *U* test. Categorical distributional equivalence comparisons were performed using χ^2 or Z test for proportions. A repeated measures analysis of varience followed by post-hoc pairwise analysis was conducted to assess for a potential treatment effect, time effect, interaction of treatment by time effect, as well as sport type and gender effects.

RESULTS

Study Population

A total of 55 participants were included in this study. About half of whom were male in each group. There were no statistically significant differences in the mean age, height,

TABLE 2. Patient Hospitalization, Comorbidities and Medical History at the Post-injury Assessment Visit

Treatment Arm	Previous Hospitalizations	Comorbidities						Medications
		Migraine	Learning Disabilities	Depression	Anxiety	ADHD	Others*	
Control, n (%)	1 (~4)	0 (0)	2 (8)	2 (8)	1 (4)	1 (4)	10 (37)	21 (78)
Treatment, n (%)	2 (7)	3 (11)	1 (3.5)	3 (11)	5 (18)	4 (14)	6 (21)	24 (86)
P-value	0.57	0.08	0.52	0.66	0.09	0.17	0.2	0.44

** Primarily included asthma and allergies.*
ADHD: attention deficit hyperactivity disorder.

weight, preinjury, and postinjury SCAT5 scores between the groups at the post-injury assessment visit. Most of our patients were white (74% and 86% in the control and treatment groups, respectively). In the control group, most injuries were from football (7 patients, 26%), whereas in the treatment group, most injuries were from lacrosse (6 patients, 21%) (Table 1). Participants' history including hospitalization, comorbidities, and medical history was similar between the 2 groups (Table 2). Our final analysis included only those participants who completed the study (there was 1 subject lost to follow-up in the standard group).

SCAT5 Assessment Analysis

Primary analysis of the absolute differences in SCAT5 total symptom severity scores from the post-injury assessment visit at the initial visit to follow-up scores revealed significant main effects (group and time, $P < 0.01$ for each), as well as interaction between time and group ($P = 0.017$). For the control group, the mean absolute difference of SCAT5 total symptom severity scores between post-injury assessment visit pre-treatment and that reported at the different follow-up time points were as follows: 0.9 ± 14.2 (post-injury assessment visit post-treatment), -2.6 ± 9.6 (72 hours pre-treatment), -3.7 ± 12.7 (72 hours post-treatment), -13.9 ± 14.9 (10 days post-treatment), and -22.7 ± 20.3 (4 weeks post-treatment). Whereas for the treatment group, the mean absolute differences of SCAT5 total symptom severity scores between post-injury assessment visit pre-treatment and the different time points were as follows: -13.2 ± 13 (post-injury assessment visit post-treatment), -11.8 ± 12.1 (72 hours pre-treatment), -19.2 ± 14.0 (72 hours post-treatment), -19.8 ± 13.6 (10 days post-treatment), and -23.4 ± 17.3 (4 weeks post-treatment) (Figure 3). The between groups mean differences (95% CI) at each of these time points demonstrated a significantly greater and earlier reduction in symptoms for the treatment group: initial visit post-treatment 14.1 (6.7-21.4), 72 hours visit pre-treatment 9.2 (−3.3-15.1), 72 hours visit post-treatment 15.5 (8.2-22.8), 10 days visit 5.8 (1.9-13.5), and 4 weeks visit 0.7 (−9.5-10.9).

Adverse Events

No significant adverse events were reported by any of the patients in any group.

DISCUSSION

In this pilot study, we showed that head and neck cooling could be used for the treatment/management of concussion in adolescent athletes within 8 days of sustaining an injury. Participants in the treatment group who received head and neck cooling had a significant reduction in the total symptom severity score at each time point over the 28 days treatment

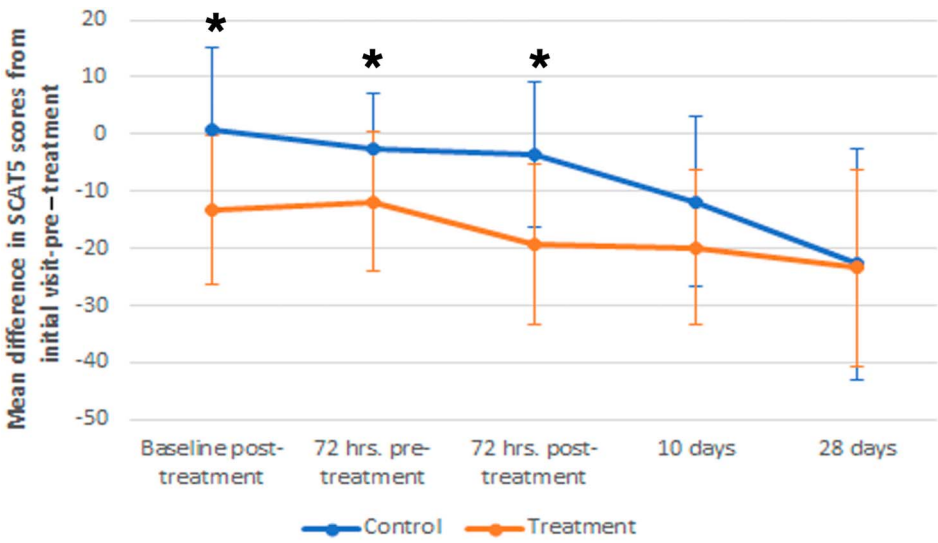

Figure 3. A line graph showing the mean absolute difference between SCAT5 scores from the post-injury assessment visit to follow-up visits (post-injury assessment visit post-treatment, 72 hours visit pre-treatment, 72 hours post-treatment, and 10 days and 28 days post-treatment). Repeated measures ANOVA followed by post-hoc pairwise analysis was used to determine the significance in treatment effect, time effect, and interaction of treatment by time effect. *$P < 0.05$ indicates a significant decrease in the absolute difference in the SCAT5 symptom severity score in each group compared with the post-injury assessment visit values. Values are shown as mean ± SD.

period compared with those who received the standard treatment. A multicenter study is currently underway to investigate the efficacy of the therapy using a larger sample size.

Cooling the head and neck may lead to cooling of the brain by reducing the intracranial pressure resulting in a neuroprotection mechanism and minimizing short-term and long-term cognitive and behavioral complications.[30] During the acute phase of sports-related concussions, head and neck cooling was reported to be effective in optimizing brain temperature by increasing the cerebral blood flow.[27] Cooling of the head and neck after concussion in pediatric patients described in this study may have led to cooling of brain through similar mechanisms. Studies are warranted to investigate the physiologic effect of head and neck cooling in this population.

Reducing concussion symptoms early in athletes is the primary goal for the management of brain injury. This clinical measure determines the return to play and helps prevent significant postconcussion syndrome (PCS) pathology. Post-concussion syndromes are those symptoms that persist—beyond 10 to 14 days in adults and 4 weeks in children—after a concussion and consist of deficits in attention or memory, headache, dizziness, fatigue, sleep disorders, irritability in addition to apathy, and changes in personality.[7,31] This study shows that head and neck cooling reduces symptoms in a time frame that is shorter than that of the standard treatment alone with post-concussion symptom severity scores approaching similar values at the 4-week visit. It is possible that the effect of the head and neck cooling treatment seen in this study is a temporary relief from physical symptoms as described in Walter et al study who also used head and neck cooling for relief of symptoms in patients with concussion,[27] but considering the differences between our study and Walter et al study (age of the patients and number of treatment sessions), we believe that this effect may not be temporary as shown in Figure 3, where the symptom score reduction was observed over time. Furthermore, our treatment was combined with the brain rest (standard treatment), which could have also helped with the relief of the symptoms. Longer longitudinal studies to see whether the symptoms are reduced further in the standard treatment followed by head and neck cooling therapy are warranted.

A major strength of this study was the use of a patient population that is younger (14 years average) than most previous studies.[27] However, the small sample size renders it too early to draw conclusions around the efficacy and clinical relevancy of the head and neck cooling therapy as an effective intervention for enhancing concussion recovery in this population. As shown in Figure 1, most of the new concussion patients who presented to the Sports Medicine Clinic were ineligible because of age and/or the injury being outside of the 8 days window. In addition, most patients declined to participate in the study for several reasons such as driving to the clinic multiple times because some of them lived too far away from the treating clinics (our main campus services 17 counties which some participants have to drive over an hour to be seen), and the visits were too long and parents did not want to spend a whole day in the clinic. We are in the process of evaluating efficacy and clinical relevancy of the head and neck cooling therapy in a larger, more geographically diverse population and anticipate a much larger sample size that will confirm the results reported herein. In addition, full inferential statistics are not reported (nor were alpha adjustments for multiple comparisons made) because the primary purpose of these analyses was to facilitate conduct of a sample size analysis in preparation for the pivotal multicenter study that includes additional measures for outcome assessment currently underway.

In conclusion, this study provides preliminary evidence of efficacy of early brain rest (24-48 hours) followed by head and neck cooling in the management of acute sports-related concussion. Clinicians may consider adding head and neck cooling therapy to the current standard treatment followed by light exercise to enhance the recovery process and shorten the return to play time period for adolescent athletes.

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