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 longer1–3 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)2–7; 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 al10 showed that short-term brain rest followed by early symptomatic exercise result in a quicker recovery in adolescent who sustained a sport-related concussion.

Hyperthermia is a therapeutic approach that has shown promising outcomes for brain injury.11 Induced mild-to-moderate hyperthermia 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 hyperthermia in patients with severe traumatic brain injury.17 Hyperthermia 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 level18–20 by 2 mechanisms: (1) by improving neuronal function through reducing apoptosis and decreasing metabolic rate21 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...
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 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 assessment visit (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 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
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.

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

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**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.

**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.
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 \( \chi^2 \) or Z test for proportions. A repeated measures analysis of variance 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,
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: \( 0.9 \pm 14.2 \) (post-injury assessment visit post-treatment), \( -2.6 \pm 9.6 \) (72 hours post-treatment), \( -3.7 \pm 12.7 \) (72 hours post-treatment), \( -13.9 \pm 14.9 \) (10 days post-treatment), and \( -22.7 \pm 20.3 \) (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: \( -13.2 \pm 13 \) (post-injury assessment visit post-treatment), \( -11.8 \pm 12.1 \) (72 hours pre-treatment), \( -19.2 \pm 14.0 \) (72 hours post-treatment), \( -19.8 \pm 13.6 \) (10 days post-treatment), and \( -23.4 \pm 17.3 \) (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 period.

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

| Treatment Arm | Previous Hospitalizations | Migraine | Learning Disabilities | Depression | Anxiety | ADHD | Others* | Medications |
|---------------|---------------------------|----------|-----------------------|------------|---------|------|---------|-------------|
| Control, n (%)| 1 (4)                     | 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.
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.26 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. Postconcussion 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, and others.32 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.

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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