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Reduced Concussion Symptom Burden in Early Adolescent Athletes Using a Head–Neck Cooling Device

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Abstract

Objective: To determine whether an investigational head–neck cooling device, Pro2cool, can better reduce symptom severity compared with standard postconcussion care in early adolescent athletes after a sports-related concussion. **Design:** Prospective, longitudinal, randomized trial design conducted over a 28-day period. **Setting:** Six pediatric medical centers in Ohio and Michigan. **Participants:** The study enrolled 167 male and female 12- to 19-year-old athletes who experienced a sports-related concussion within 8 days of study enrollment and registering a Sports Concussion Assessment Tool 5 (SCAT5) composite score >7. **Interventions:** Pro2cool, an investigational head–neck cooling therapy device, was applied at 2 postinjury time points compared with postconcussion standard of care only. **Main Outcome Measures:** Baseline SCAT5 composite symptom severity scores were determined for all subjects. Sports Concussion Assessment Tool 5 scores for concussed athletes receiving cooling treatment were analyzed across 6 independent postenrollment time points compared with subjects who did not receive cooling therapy and only standard care. Adverse reactions and participate demographics were also compared. **Results:** Athletes who received Pro2cool cooling therapy (n = 79) experienced a 14.4% greater reduction in SCAT5 symptom severity scores at the initial visit posttreatment, a 25.5% greater reduction at the 72-hour visit posttreatment, and a 3.4% greater reduction at the 10-day visit compared with subjects receiving only standard care (n = 88). Overall, 36 adverse events (increased blood pressure, decreased pulse, and dizziness) were reported, with 13 events associated with the device, of which 3 were classified as moderate in severity. **Conclusions:** This study demonstrates the efficacy and safety of head and neck cooling for the management of concussion symptoms in adolescent athletes of an age group for which little to no prior data are available.

Key Words: concussion, head-neck cooling, symptom severity

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Dr. M. Smith contributed to the analysis and interpretation of data, drafted the initial manuscript, and critically reviewed and revised the manuscript. N. McNinch and L. Shauver performed the initial data analysis and interpretation, contributed to the study design, and provided manuscript edits. D. Chaney, T. Murray, P. Kline, and A. Lesak coordinated and performed the data collection. Drs. L. Scott, K. Logan, I. Ichesco, C. Liebig, and Mrs. L. Franco-MacKendrick contributed to the study design, coordination, and assisted in data interpretation and editing of the manuscript. Dr. J. Congeni conceptualized and designed the study, coordinated all aspects of the study, and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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INTRODUCTION

Concussions remain a significant public health problem in the United States, particularly in children aged 12 to 17 years.[1] The majority (~80%-90%) of sports-related concussions in pediatric/adolescent populations produce symptoms that resolve within 17 to 28 days, which is longer than the 7- to 10-day recovery time observed in adults.[2–4] Evidence suggests that the initial symptoms after a concussion are caused by a combination of functional and acute structural deficits to neural circuity within the brain. Although the exact mechanisms underlying these changes remain poorly understood, a combination of metabolic alterations, changes in cerebral blood flow, and neuroinflammatory mediators are likely drivers that correlate with an increase in core body and brain temperature after injury.[5–8] Accordingly, reducing body and/or brain temperature postinjury has evolved as a potential strategy to improve immediate postinjury symptoms, shorten recovery time, and reduce the risk of developing postconcussion syndromes.

Postinjury cooling interventions in animal and in vitro models have demonstrated neuroprotection by reducing synaptic transmission efficiency, lowering the cerebral metabolic rate, and preventing neuronal loss[9–12] and cognitive decline.[13–15] However, the clinical translatability of these cooling protocols is debated given poor safety profiles associated with a 'whole-body' cooling approach. As such, more selective approaches focused on providing cooling restricted to the head and/or neck are primarily explored in human subjects' research due to improved safety profiles and ease of use in clinical settings.[16–19]

Results from human studies using selective cooling methods are limited by their predominant use in patient populations with moderate-to-severe brain injury, lack of consistency in timing/use of devices, and the selective use of college-aged or adult subjects. We began to address this gap by exploring the clinical utility and therapeutic efficacy of selective surface cooling after mild brain injury in an adolescent population, which is important given that the concussion recovery trajectory differs in children versus adults.[20–22] Our preliminary findings from Congeni et al[23] showed promise in the ability of Pro2cool to reduce symptom severity with little adverse effects. However, as a pilot study, results were limited due to a small sample size.

Our current study aimed to validate and expand on our preliminary findings in the study by Congeni et al, vetting the safety and efficacy of a newly developed head–neck cooling device (Pro2cool) in reducing postconcussion symptom severity in a previously unreported age group of pediatric/adolescent patients.

MATERIALS AND METHODS

Study Participants

One hundred sixty-seven female and male patients (aged 12-19 years) who presented to participating pediatric hospitals in Ohio and Michigan from 2017 to 2021 for sports-related concussion within 8 days of injury were included in the study. The mean age of the study participants in the control group was 15.1 ± 1.6 years and that of treatment groups was 15.2 ± 1.5 years. Patients participated in a range of sporting activities, with most reported injuries stemming from soccer- and football-related activities. Regardless of clinical site, all patients were either referred (through Emergency Department, by primary care physician, or athletic trainer or coach) or entered by direct appointment (self or via parent/guardian) to the respective hospital's affiliated primary care sports medicine clinic. Participants were identified using eligibility criteria (Table 1) by study personnel via review of electronic medical record system appointment scheduling and included all genders, race/ethnicities, and socioeconomic levels. All experimental procedures were approved by the Institutional Review Board of Akron Children's Hospital; the complete study protocol and potential risks were presented to all participants upon which assent/consent was determined. For a complete list of enrollment distribution across sites, see Table 2.

TABLE 1. Summary of Participant Enrollment Eligibility

Inclusion Criteria	Exclusion Criteria
Males and females, ages 12-21 yrs	Has a SCAT5 symptom score of <7 or was cleared to return to play at the initial visit
Confirmed concussion diagnosis from sporting activities	Suffers a *serious* traumatic brain injury as evidenced by worsening symptoms, specifically: a. Seizure b. Hospitalization c. Existing positive diagnostic testing that includes radiology scans that indicate brain bleed d. Slurred speech, which has not resolved within 72 hours of mild traumatic brain injury injury
Initial provider visit is within 8 days of injury	Sustains another head or neck injury at the time of mild traumatic brain injury injury that requires medical treatment
Has a symptom score of at least 7 (analogous of the SCAT5 symptoms score)	History of a serious medical or psychiatric disorder that include suicide attempt in the last 6 months; unmanaged depression or anxiety; hospitalization in the last 6 months for psychiatric treatment; history of Reynaud disease or phenomenon, cold agglutinin disease, cryoglobulinemia, or cryofibrinogenemia; previously diagnosed with a cerebrovascular disorder
In generally good health as confirmed by medical history and as determined by the site investigator	Known or disclosed pregnancy or breast-feeding
	Non–English-speaking subjects and parents/legal guardians

TABLE 2. Summary of Subject Demographics

Demographic	Control Group (n = 88)	Treatment Group (n = 79)	*P*
Enrollment by site (n)			NA
Akron Children's Hospital (main campus)	46	40	
Mahoning Valley	10	7	
Warren	1	0	
Cincinnati Children's Hospital	8	8	
University of Michigan	19	19	
Dayton Children's Hospital	4	5	
Age at consent			0.533
Mean (STDEV)	15.1 (1.6)	15.1 (1.6)	
Range	15.0–19.0	15.0–19.0	
Sex, n (%)			0.089
Male	37 (42)	45 (57)	
Female	51 (58)	34 (43)	
Race/ethnicity, n (%)			0.667
White	79 (89.8)	77 (90.6)	
African American	6 (6.8)	4 (4.7)	
Other	3 (3.4)	2 (1.2)	
Hispanic/Latino	2 (1.2)	3 (1.8)	
Non-Hispanic/Latino	84 (97.7)	80 (96.6)	
Mean height (inches)	66.5	67.3	0.111
Mean weight (kg)	67.5	68	0.858
Sporting activity, n (%)			
Soccer	26 (14.9)	28 (16.1)	NA
Football	14 (8.1)	18 (10.3)	
Basketball	12 (6.9)	8 (4.6)	
Softball	8 (4.6)	3 (1.7)	
Wrestling	4 (2.3)	6 (3.5)	
Lacrosse	5 (2.9)	5 (2.9)	
Volleyball	5 (2.9)	4 (2.3)	
Hockey	2 (1.2)	3 (1.7)	
Cheerleading	3 (1.7)	1 (0.6)	
Baseball	2 (1.2)	1 (0.6)	
Track/field	0 (0)	1 (0.6)	
Other	7 (4.0)	8 (4.6)	

Group Assignment and Randomization

An a priori power analysis based on prior pilot study data with a power of 90%, and a two-tailed alpha of 0.035, SD of 19.5 (10% adjustment to account for potential data attrition) yielded a minimum total sample size of 156 subjects or 78 subjects per group to achieve power for this study. At the start of the study, 174 patients were enrolled. Study participants were randomly assigned to 2 groups using a block randomization schedule created using SAS Software 9.4/14.2: 1) *control group* (n = 88), which received the standard of care (ie, physical and cognitive rest) without head–neck cooling and 2) *treatment group* (n = 86), which received both the standard care plus head–neck cooling therapy using the Pro2cool device (TecTraum, Inc., Cleveland, OH). Sex, race, or socioeconomic status had no bearing on group assignment. Seven patients within the treatment group were removed during the study because the initial severity of their symptoms was not significant enough to meet eligibility (SCAT composite score < 7), thus violating the inclusion criteria and reducing treatment sample size to 79.

Study Time Points and Outcome Measurements

Figure 1 provides an overview of the study events and the measurement time points. The Sports Concussion Assessment Tool 5 (SCAT5) was used as the primary outcome measure to assess symptom severity in study participants across both study groups.[24] The symptom severity subscore on the SCAT5 is a commonly used tool to aid in the diagnosis of concussion, which asks subjects to rate 22 signs and symptoms on a numeric scale ranging from 0 (no symptoms) to 6 (severe symptoms). Sports Concussion Assessment Tool 5 was administered during a scheduled office visit at 1 of the 6 sports medicine clinics or via telephone for the 10- and 28-day time points.

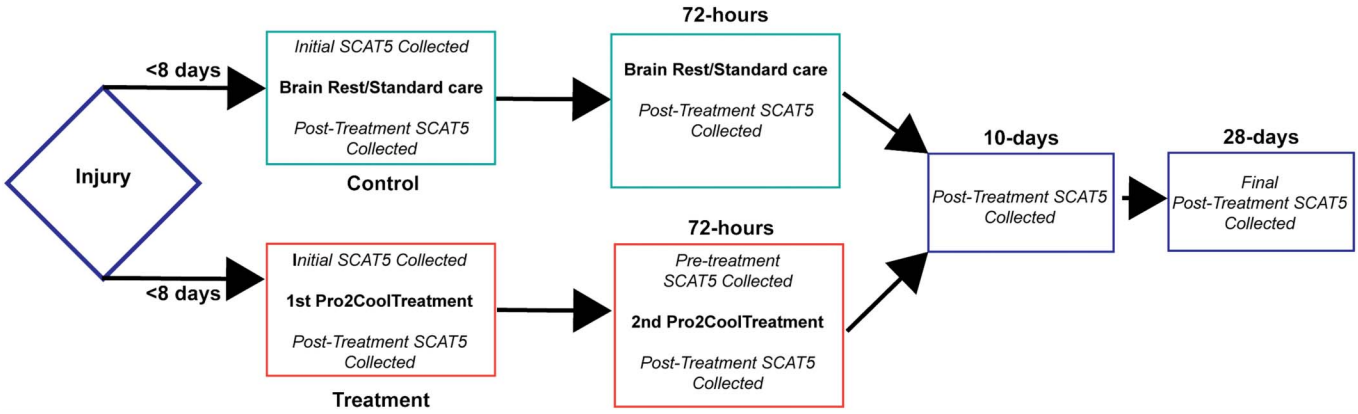

Figure 1. Study design. Flow diagram outlining the flow of patients through the Pro2cool study. Within 8 days after injury patients were evaluated for concussion, baseline/initial SCAT5 scores were collected, and eligibility was determined. If subjects met criteria for inclusion into study, subjects were randomized into either the control arm (turquoise) where they received standard care or the treatment arm (orange) where subjects received head–neck therapy via the Pro2cool device. In both cases, posttreatment SCAT5 scores were collected after standard or Pro2cool therapy. Seventy-two hours after initial intervention, subjects in the treatment group received a second treatment via the Pro2cool device, whereas the subjects in the control arm continued standard care. SCAT5 scores were derived before and after treatment only for the treatment group, whereas only a single SCAT5 was recorded from the control group at 72 hours. Ten and 28 days (blue) after the first treatment, study subjects across each group were contacted via telephone where the SCAT5 was evaluated once again.

Initial pretreatment SCAT5 data were collected for all study participants within 8 days of injury at their initial visit to the sports medicine clinic; this time point is referred to as "**initial visit pre-treatment (IVPreT).**" This period was selected based on recent data suggesting that earlier intervention in clinical care is associated with faster recovery after concussion.[25] Immediately after the IVPreT SCAT5 evaluation, study participants received a 30-minute intervention with either (a) control treatment: standard care (controlled and gradual introduction of daily activity and subthreshold [nonstrenuous exercise] as tolerated) or (b) experimental treatment: standard care + head–neck cooling therapy via Pro2cool. After the 30-minute treatment period, SCAT5 assessments were completed again. This time point was referred to as the "**initial visit post-treatment (IVPostT)**" measurement. Seventy-two hours after the IVPreT, subjects were instructed to return to the clinic for a second intervention with a 30-minute Pro2cool treatment + standard care. Patients received the same treatment conditions assigned on the first visit. At the second visit, another SCAT5 preassessment "**72-hour pretreatment (72PreT)**" was completed, and again after the 30-minute treatment, "**72-hour posttreatment (72PostT)**" was completed. No further Pro2cool treatment was provided to the participants beyond this time point. Those in the control group received only 1 SCAT5 assessment at 72 hours. Additional SCAT5 assessments were taken at 10 and 28 days after the initial visit; these follow-up assessments were conducted via phone to prevent subjects from returning to the clinic to keep the attrition rate low.

For analysis, a composite symptom severity score was derived from each subject, which was the total of all scores across the 22 signs and symptoms in the SCAT5 assessment. These composite scores were used to calculate the difference between symptom severity at the **IVPreT** and symptom severity at subsequent posttreatment time points, as described above.

Figure 2. A picture showing the Pro2cool device in use. A, Individual device components. B, Example of device in use, patient fitted with head and neck cooling straps. Hood garment applied to patient to increase cooling surface area across head and neck (inset).

Head and Neck Cooling Therapy Using the Pro2cool

The Pro2cool device (Figure 2) is a noninvasive hypothermic therapy device that provides localized surface cooling of the head and neck. Pro2cool at the time of the study classified as an investigational product that had not yet been approved by the Food and Drug Administration (FDA) for any purpose. The device contained a water and isopropyl alcohol mixture that was 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, thereby dissipating heat from the head and neck.

At the designated treatment time points, participants assigned to the treatment group were fitted with a Pro2cool garment (Figure 2B) by a study investigator/clinical provider. Once fitted, the 30-minute treatment period began. Subjects were seated upright or allowed to recline (45 degrees), whichever was most comfortable for the subject, during the cooling procedure. After the 30-minute procedure, the Pro2cool garment was removed, and the posttreatment SCAT5 evaluation was completed. Additionally, vital signs and observation of adverse events (AEs) were conducted before fitting, during treatment (after ~15 minutes), and at the conclusion of treatment. Subject-reported adverse effects were also recorded as described during the treatment procedure. Given the design and physical requirements of the device, blinding of patients and investigators could not be implemented in this study. To minimize bias, data analysis was conducted by individuals who were blinded to the treatment group assignment.

Monitoring of Adverse Events

Adverse events (AE) were documented at each study visit beginning at the time of enrollment and included unintended disease or injury, or clinical signs (including abnormal laboratory findings), whether related to the use of the investigational Pro2cool device or not. Adverse events were documented based on type, frequency, and severity. Adverse events were further assessed based on possible relatedness to the device and classified by likelihood (not related, possibly related, likely related). Criteria used to determine if AEs were device related was based on the onset of AE and the weather onset only at the time of device use and replicated over multiple applications (ie, headaches appear only and each time device is used at several time points; preexisting headaches worsen only during device application and occurrence is replicated across multiple independent time points). Adverse events reported throughout all observation periods of the study by participants in both experimental and treatment groups were used to evaluate safety. To prevent bias, AE data were evaluated by a Medical Safety Officer, an independent physician not associated with the study, who adjudicated and classified reported AEs for seriousness, severity, and device relationship according to the provided written guidelines. Adverse events included: (1) any condition, signs, or symptoms that were not recorded as preexisting at baseline or a worsening of a prerecorded condition in nature, severity, or degree of incidence; (2) hospitalization for a new condition, with serious deterioration in health; (3) increase/decrease in heart rate, greater than 20% of baseline; (4) increase/decrease in respiratory rate, greater than 20% of baseline; (5) decreased systolic and diastolic blood pressure <100/70 mm Hg or increase 20% of baseline; (6) decreased core temperature but <96.8ºF or outside 20% of baseline; and (7) localized pain, tingling, or other discomfort prompting patient to withdrawal from treatment. Each AE was assessed for its severity, or the intensity of the event experienced by the subject, according to the Society of Interventional Radiology classification system for complications by outcome.

Statistical Analysis

Statistical analyses were conducted using SAS 9.4/14.2 analytics software (SAS Institute, Cary, NC). Statistical significance was set at $P < 0.05$. Independent samples t tests were used to assess baseline differences in age, height, weight, and IVPreT SCAT5 total symptom severity scores between participants in each group. Chi-square (χ^2) Tests of Independence were used to determine baseline demographic and clinical characteristics and the occurrence of AEs by group. A repeated-measures factorial analysis of variance (ANOVA) was conducted to assess changes in the SCAT5 total symptom score across 6 time points (IVPreT, IVPostT, 72PreT, 72PostT, 10 days, and 28 days) as a function of treatment group (standard of care vs Pro2cool) and time. The interaction of time by trial arm was also assessed, followed by post hoc pairwise analyses to assess differences by time point using least squares (LS) means. The Greenhouse and Huynh–Feldt corrections were used to account for sphericity violations. Finally, the factorial repeated-measures ANOVA was repeated, adjusting for gender, sport type, and site.

RESULTS

Participant Demographics

A total of 167 participants (experimental treatment group, n = 79; control group, n = 88) fully met the inclusion criteria for the study. The retention rate was 100%, with no dropouts or losses to follow-up. The mean age of participants was 15.1 ± 1.6 years in the control arm and 15.2 ± 1.4 years in the treatment arm. The control arm sample was mostly female (57.8%), whereas only 44.3% of the treatment arm was female and did not differ significantly between groups: χ^2 (1, N = 167) = 3.1, $P = 0.078$, ns. Most participants in both arms of the study were identified as white (89.8% in the control arm; 89.7% in the treatment arm), black (6.82% in the control arm race, 5.18% in the treatment arm), and other (3.41% in the control arm; 2.56% in the treatment arm) and did not differ significantly between groups: χ^2 (1, N = 166) = 2.6, $P = 0.466$, ns. A complete list of the demographics is presented in Table 2.

Injury and Treatment Interval

The mean number of days from injury occurrence to treatment initiation did not differ between patients in the control (M = 4.3, SD = 1.6) and experimental treatment (M = 4.3, SD = 1.6) arms ($t_{165} = 1.1$, $P = 0.259$, ns). At the initial IVPreT, the SCAT5 total symptom score did not differ between patients in the control (M = 32.1 SD = 18.7) and treatment (M = 36.5, SD = 21.8) arms ($t_{165} = 1.4$, $P = 0.156$, ns).

Pro-2cool Hypothermic Therapy Reduces Symptom Severity after Concussion

A repeated-measures factorial ANOVA was conducted to assess for change over time in mean absolute difference SCAT5 symptom severity scores from IVPreT compared with IVPostT, 72PreT/PostT, 10 days, and 28 days across the control and Pro2cool treated groups. As presented in Figure 3, significant main effects were observed for the trial arm ($F_{1,165} = 9.1$, $P = 0.003$) and time ($F_{4,162} = 128.8$, $P < 0.001$), which were qualified by a significant group × time interaction ($F_{4,162} = 37.5$, $P < 0.001$). Post hoc comparisons by time point using LS means indicated significant group difference in absolute difference from baseline SCAT5 scores

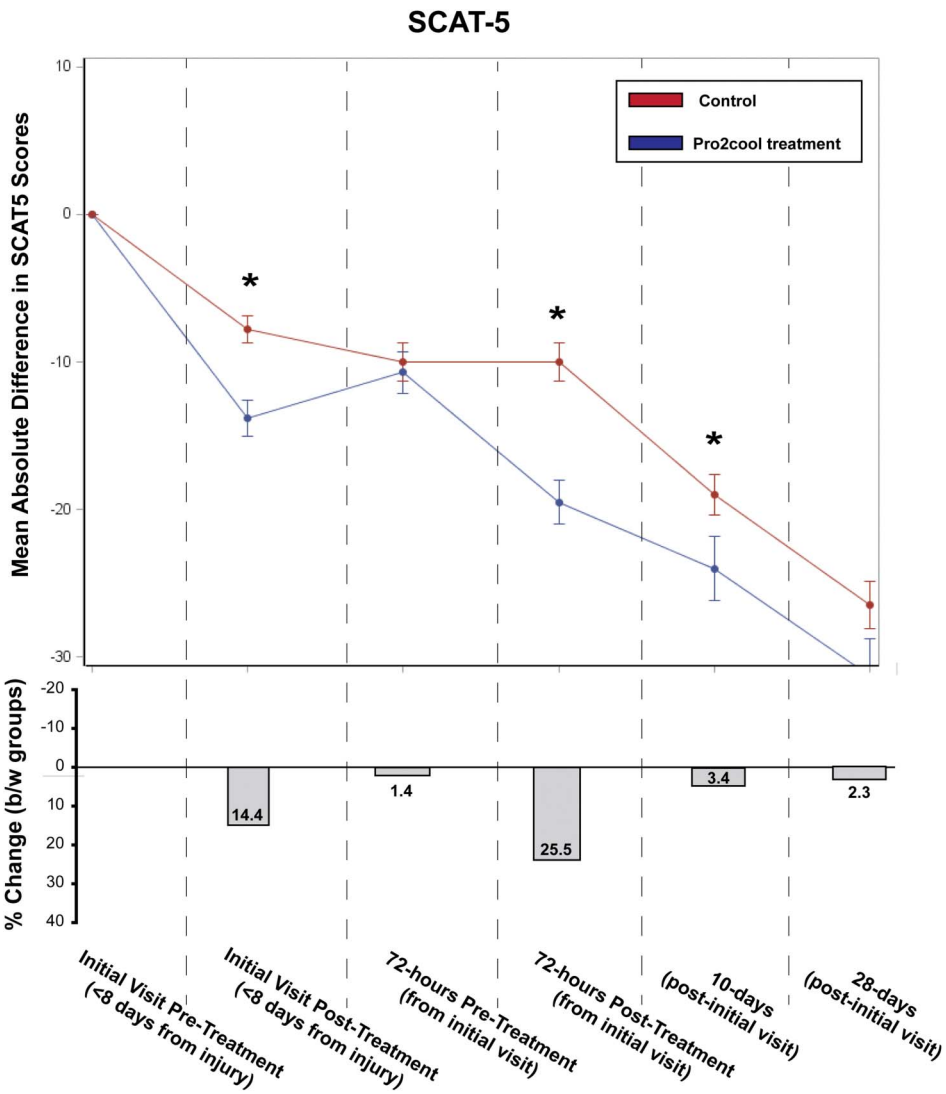

Figure 3. Comparison of absolute difference in SCAT5 scores between control (red) and Pro2cool treatment (blue) groups across time (*x* axis). Lower panel represents difference in percent change of SCAT5 score from baseline between Pro2cool treatment and control groups at each time point. The mean absolute value in SCAT5 scores was significantly lower for the Pro2cool treatment group at the initial visit after the first treatment, 72 hours after the second treatment, and at 10-day mark from the initial treatment. The greatest change in SCAT5 scores was seen at the 72-hour time point after the second treatment period with the Pro2cool device. *Indicates significance at $P > 0.05$.

favoring the Pro2cool treatment arm at the IVPostT [LS mean diff (95% confidence interval (CI)), 6.1 (3.2-9.0)], at 72PostT [LS mean diff (95% CI), 9.5 (5.6-13.4)], and at the 10-day visit [LS mean diff (95% CI), 5.0 (0.1-10.0)]. Significant differences were not seen at the 72PreT [LS mean diff (95% CI), 0.8 (−3.0 to 4.5)] or at the 28-day visit [LS mean diff (95% CI), 4.8 (−1.0 to 10.5)]. The results indicated that participants in the control group had significantly higher SCAT5 scores at each of these 3 time points compared with those in the experimental treatment group. Considering the data in terms of percent change in absolute difference of SCAT5 scores between groups across time, the Pro2cool group demonstrated a 14.4% (95% CI, 6.4-22.4) greater reduction in SCAT5 scores at IVPostT, a 25.5% (95% CI, 15.3-35.1) greater reduction at 72PostT, and a 3.4% (95% CI, −8.1 to 14.9) greater reduction at the 10-day visit compared with control subjects.

A factorial repeated-measures ANOVA was implemented to assess differences in SCAT5 scores across time points as a factor of gender, sport type, and site. These covariates were

TABLE 3. LS Means for SCAT5 Scores Across Study Endpoints Adjusting for Gender, Site, and Sport Type

	Gender (LS Mean [CI])	Site (LS Mean [CI])	Sport Type (LS Mean [CI])
Initial visit, posttreatment score	6.5 [3.6, 9.4]	6.1 [3.2, 9.1]	6.1 [3.1, 9.1]
72 hours, pretreatment score	1.00 [−2.8, 4.8]	0.65 [−3.2, 4.4]	0.78 [−3.1, 4.6]
72 hours, posttreatment score	9.8 [5.9, 13.8]	9.3 [5.3, 13.22]	9.4 [5.4, 13.4]
10-day visit	5.0 [−0.06, 10.0]	5.3 [0.29, 10.4]	5.5 [0.6, 10.5]
28-day visit	4.9 [−0.88, 10.7]	4.9 [−0.85, 10.8]	4.3 [−1.5, 10.1]

chosen based on their potential to alter symptomology after concussion. The calculated LS means did not alter the significant main effects described between the control and treatment groups across time points. Significant differences in symptom severity scores between the control and treatment groups were still observed at the IVPostT, 72PostT, and at the 10-day visit when controlling for sex, site, and sport. See Table 3 for a summary of LS means for gender, site, and sport across the study time points.

Limited Adverse Events After Pro2cool Treatment

There were 36 AEs (n = 11 control, n = 25 device). There is evidence of a significant association between the experimental group and AEs χ^2 (1, 167) = 8.97, P = 0.003) with ~69% of the events occurring in the treatment arm (Figure 4). Subjects in the Pro2cool treatment group were approximately 3.2 times more likely to experience an event than those in the control group (odds ratio = 3.2, 95% CI = 1.5-7.1). There were 31 mild events (n = 9 control, n = 22 device) and 5 moderate events (n = 2 control, n = 3 treatment). Completion of Fisher's exact test (P-value = 0.631) suggests that there is no evidence of a significant association between the experimental group and the severity of the event. Thirteen events were possibly related to the device and 23 were unrelated to the device, Fisher's exact test (P-value = 0.003). There is evidence of a significant association between the experimental group and the relationship between event and device. The most commonly reported device-related AEs were increased blood pressure (4 out of 13 total events), heart rate fluctuations (4 of 13 total) events, and dizziness (3 of 13 total events). Table 4 summarizes the type and distribution of reported AEs across groups.

TABLE 4. Type and Distribution of Reported AEs Across Groups

AE	# Cases (Control/Treatment/Device Related)
Increased blood pressure	0/4/4
Decreased blood pressure	0/1/1
Increased heart rate	0/3/3
Decreased heart rate	2/2/2
Headache	3/2/1
Dizziness	0/3/3
COVID infection	2/2/0
Upper respiratory infection	0/1/0
Influenza	0/1/0
Anxiety attack	1/1/0
Somatic pain (neck, limb)	1/4/0
Brief episodes of shaking	0/2/0
Difficulty concentrating	1/0/0

DISCUSSION

Our results revealed a significant improvement in postinjury symptom severity via reduction in SCAT5 scores in patients who underwent selective head–neck surface cooling treatment using the Pro2cool. Although an improvement in SCAT5 score was observed in those receiving only standard care, a 14% greater reduction in SCAT5 score was attributed with Pro2cool use after first treatment at the initial visit. This effect was strengthened after the second Pro2cool treatment at 72PostT, where SCAT5 score was 25% lower than baseline in Pro2cool patients compared with those receiving standard care. Interestingly, SCAT5 scores increased in the Pro2cool subjects between the first and second treatment, observed at 72PreT. These data are consistent with the findings of similar studies and suggest that multiple treatments at additional postinjury time points using the Pro2cool may be necessary to maximize therapeutic impact.[25–27] Furthermore, given that the most significant effect on SCAT5 score followed the second Pro2cool treatment, it will be necessary to determine in future studies whether earlier treatment (intervention hours to <4 days postinjury) and/or more frequent treatments (>2 treatments) can produce even greater improvement in symptoms. Some examples in the literature support the former.[8,27,28]

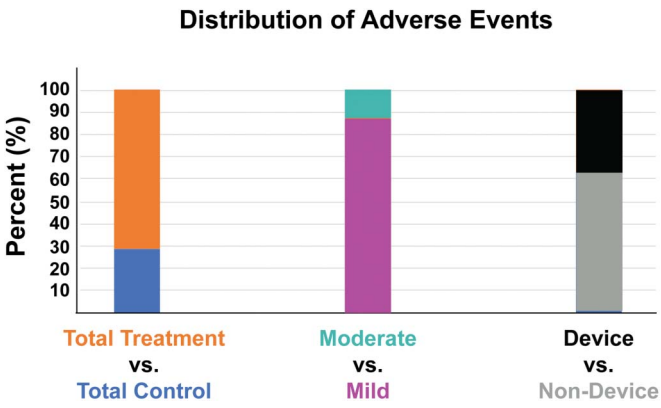

Figure 4. Distribution of AEs by group and event. Most AEs were reported from subjects in the treatment group; however, of the total number of events reported, the majority were classified as mild and were not related to the Pro2cool device.

Additional comparison of our findings with previous studies is difficult, given the significant differences in study design, outcome measures, and device design/protocols that vary greatly across the literature. In previous studies: (1) the use of treatment protocols where the treatment is delivered once and data are derived from 1 to 2 postintervention time points[8,25–27] and (2) subject cohorts typically comprised older adolescents (>17 years old) or adults. Our study diverges from previous studies, whereby we assessed effects of selective head–neck cooling in a randomized population of 12- to 19-year-old adolescent athletes using repeated treatment application to which data is derived from multiple posttreatment endpoints. The mean age at consent for both the study groups was 15 years. Given the neurobiological differences in brain development and recovery patterns after concussion, our data reflect a promising clinical benefit to an age group that is disproportionally impacted by concussion in incidence and recovery compared with adults and older adolescents.[2] Furthermore, extending our study to 28 days provided insight into whether the observed therapeutic effects were transient or sustained. The effects of the Pro2cool treatment were maintained after the second treatment; however, patients who received only standard care also showed a steady decline in the symptom severity over time.

Selective head–neck devices are linked to improved safety outcomes compared with whole-body approaches.[29] Here, Pro2cool use showed positive safety outcomes with only 13

AEs tied to device itself. Furthermore, all reported device-related events were characterized as mild and were mostly attributed to increases in dizziness or blood pressure, consistent with the reported safety profile of similarly designed surface-cooling devices.[30–32] It is unlikely that head–neck surface cooling could induce a significant thermal impact on deep brain structures or visceral organs, so more severe adverse reactions are not expected. However, we did not assess intracerebral temperature in the present study, so we cannot conclude whether any outcomes presented here were the direct results of a reduction in intracranial or intracerebral temperature.

Limitations

Although our data suggest that symptom burden is reduced after Pro2cool treatment without major adverse effects, the results should be interpreted cautiously. Despite showing a significant reduction in symptom severity scores, other outcomes such as "time to recovery" and "time to return to normal activity" were not assessed. Determining whether a 25% reduction in symptom severity scores correlates with more direct clinical outcomes is required to further validate and understand the clinical utility of Pro2cool use. Additionally, given the nature of the device application, subjects and the study personnel were not blinded to study conditions; therefore, subjects' perception of receiving treatment leading to improved symptom severity (placebo effect) could have contributed to study results. Future study designs using sham devices or devices providing warmer temperatures (cooling at subtherapeutic levels) may be considered. Efforts to improve neuroimaging and biomarker profiling for concussion are ongoing[33]; however, research efforts to understand how SCAT5 scores track internal physiological or molecular processes over the course of injury and treatment are needed. In the immediate term, it is necessary to further elucidate the "optimal" protocol such as temperature, duration, time of initial application, and device design, for maximum clinical benefit across age groups to ensure a more tailored personalized treatment strategy for each patient. This will best be achieved when there is a better understanding of the underlying neurophysiological mechanisms by which selected surface cooling interventions are acting to improve clinical outcomes and alleviate symptoms.

CONCLUSIONS

This study provides promising evidence for the efficacy and relative safety of Pro2cool use in the management of sports-related concussions in pediatric and adolescent patients; however, further investigation is needed before any recommendation for clinical use can be made.

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