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Andrée-Anne Ledoux

Nicholas J Barrowman

Kathy Boutis

Adrienne Davis

Sarah Reid

See next page for additional authors

Authors

Andrée-Anne Ledoux, Nicholas J Barrowman, Kathy Boutis, Adrienne Davis, Sarah Reid, Gurinder Sangha, Ken J Farion, Kevin Belanger, Mark S Tremblay, Keith Owen Yeates, Carol DeMatteo, Nick Reed, and Roger Zemek

Multicentre, randomised clinical trial of paediatric concussion assessment of rest and exertion (PedCARE): a study to determine when to resume physical activities following concussion in children

Andrée-Anne Ledoux,[1] Nicholas J Barrowman,[1] Kathy Boutis,[2] Adrienne Davis,[2] Sarah Reid,[1,3] Gurinder Sangha,[4] Ken J Farion,[1,3] Kevin Belanger,[1] Mark S Tremblay,[1] Keith Owen Yeates,[5] Carol DeMatteo,[6] Nick Reed,[7] Roger Zemek,[1,3] Pediatric Emergency Research Canada PedCARE team

[1]Children's Hospital of Eastern Ontario Research Institute, Ottawa, Canada
[2]Department of Pediatrics, Hospital for Sick Children, Toronto, Canada
[3]Department of Pediatrics, Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, Canada
[4]Pediatric Emergency Medicine, Children's Hospital London Health Sciences Centre, London, Ontario, Canada
[5]Department of Psychology, Alberta Children's Hospital Research Institute, University of Calgary, Calgary, Canada
[6]School of Rehabilitation Science, McMaster University, Hamilton, Canada
[7]Holland Bloorview Kids Rehabilitation Hospital, Toronto, Canada

Correspondence to
Dr Roger Zemek, Children's Hospital of Eastern Ontario Research Institute, 401 Smyth Road, Ottawa, ON K1H 8L1, Canada; rzemek@cheo.on.ca

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ABSTRACT

Introduction Rest until symptom-free, followed by a progressive stepwise return to activities, is often prescribed in the management of paediatric concussions. Recent evidence suggests prolonged rest may hinder recovery, and early resumption of physical activity may be associated with more rapid recovery postconcussion. The primary objective is to determine whether the early reintroduction of non-contact physical activity beginning 72 hours postinjury reduces postconcussive symptoms at 2 weeks in children following an acute concussion as compared with a rest until asymptomatic protocol.

Methods and analysis This study is a randomised clinical trial across three Canadian academic paediatric emergency departments. A total of 350 participants, aged 10–17.99 years, who present within 48 hours of an acute concussion, will be recruited and randomly assigned to either the study intervention protocol (resumption of physical activity 72 hours postconcussion even if experiencing symptoms) or physical rest until fully asymptomatic. Participants will document their daily physical and cognitive activities. Follow-up questionnaires will be completed at 1, 2 and 4 weeks postinjury. Compliance with the intervention will be measured using an accelerometer (24 hours/day for 14 days). Symptoms will be measured using the validated Health and Behaviour Inventory. A linear multivariable model, adjusting for site and prognostically important covariates, will be tested to determine differences between groups. The proposed protocol adheres to the RCT-CONSORT guidelines.

Discussion This trial will determine if early resumption of non-contact physical activity following concussion reduces the burden of concussion and will provide healthcare professionals with the evidence by which to recommend the best timing of reintroducing physical activities.

Trial registration number Trial identifier (Clinicaltrials.gov) NCT02893969.

INTRODUCTION

Background information and scientific rationale

Concussion is defined as a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces.[1] Paediatric concussion is an important and rapidly increasing health problem in the paediatric population,[2–5] accounting for more than 95% of all traumatic brain injury (TBI) cases.[6] Compared with adults, children and adolescents are at higher risk of concussion and take longer to recover.[2 7] In fact, 30% of the paediatric population will suffer from persistent postconcussion symptoms at 1 month postinjury.[8] Persistent postconcussive symptoms (PPCS) is a potentially disabling condition defined as persistence of somatic (eg, headache, dizziness and fatigue), cognitive (eg, forgetfulness and inattention) and other physical, psychological and behavioural changes lasting beyond 1 month[9] and persisting for months or years.[2 7 10–16] Persistence of these symptoms negatively affects the quality of life of both patients and their families.[5 11 17] Having PPCS may reduce school attendance, academic performance and social encounters with peers due to removal from sports and recreational activities.[11 18–21]

With the hope of reducing the risk of PPCS, a widely used practice in paediatric concussion management is to prescribe cognitive and physical rest.[7 22–32] However, recently updated guidelines (2017)[1 33] recommend 24–48 hours of rest period before reintroducing gradually cognitive and physical activities in the child's routine.[1 33 34] Despite these new recommendations, little evidence beyond expert opinion exists to guide healthcare professionals on how and when to best reintroduce physical activity to promote recovery and reduce the burden of PPCS for children and families.[22 31 35–38] The lack of evidence-based studies on rest and exertion may explain the wide practice variation by professionals in the management of paediatric concussion.[22 36 37 39–42]

Although evidence confirms that rest is important,[43] recent studies have begun to suggest that protracted rest (ie, rest until full resolution of symptoms) may in fact negatively affect concussion recovery[44 45] and lead to secondary symptoms of fatigue, depression and physiological deconditioning.[46] A recent randomised controlled trial (RCT) demonstrated that strict cognitive rest for 5 days postinjury predisposed to worsening symptoms and delayed recovery as compared with 1–2 days cognitive rest followed by gradual return to normal cognitive activity.[44] For physical rest, no

comparative studies have been performed. Based on animal studies, early physical rehabilitation may enhance function and accelerate recovery following brain injury, depending on the intensity, frequency and type of activities.[45 47] Pilot evidence from symptomatic individuals supports the benefits from gradual resumption of aerobic exercise for symptom recovery, provided there is no increased risk of further head trauma.[48–50] A recent cohort study suggests that children who resume physical activity at 1 week postinjury are at lower risk of PPCS compared with children who abstained from physical activity for longer periods.[51]

Although early resumption of light physical activity, without concomitant risk of reinjury, may be beneficial following concussion, further research is needed to clinically confirm these results and to determine the best timing of initiation.[33 52] The purpose of this randomised clinical trial is to investigate whether early reintroduction of physical activity can reduce PPCS in a paediatric population. Determining if earlier resumption of non-contact physical activity is associated with superior recovery may significantly affect the well-being of millions of children and families worldwide and cause a paradigm shift in concussion management, while at the same time mitigating the undesirable effects of deconditioning associated with rest until full resolution of symptom recommendations.

Study objectives

Primary research objective

The purpose of this study is to investigate whether early reintroduction of non-contact, physical activity at 72 hours postinjury reduces the degree of PPCS at 2 weeks in children aged 10 through 17.99 years following an acute concussion as compared with a rest until symptom resolution protocol, defined as stepwise resumption of activity only once fully asymptomatic, as per the Zurich consensus return-to-play protocol.[7]

Secondary research objectives

In this group of children, among those initiating physical activities at 72 hours versus rest until symptom resolution, we will examine the following:

1. Differences between groups in symptoms at 1 and 4 weeks follow-up
2. Differences between groups in health-related quality of life (including school and sports participation) and functional outcomes at 2 and 4 weeks
3. Differences between groups in adverse events (eg, total number)
4. Differences between groups in sleep variables (eg, duration)
5. Intensity, duration and type of physical activity associated with recovery (in all patients)
6. Long-term healthcare use (using linked provincial health administrative data)
7. Incidence and risk factors for long-term concussion-related comorbidities (using linked provincial health administrative data)

Hypothesis

Non-contact, aerobic physical activities resumed in a standardised, incremental fashion at 72 hours postinjury are hypothesised to result in superior recovery following paediatric concussion as compared with a rest until resolution protocol (graduated return-to-play initiated only after full symptom resolution).

METHODS

Trial design

The proposed study is a multicentre, equal randomisation, parallel-group study conducted in Canada (three sites). Two groups will be studied: (1) intervention (early physical activity) group: early gradual resumption of non-contact, aerobic physical activity initiated 72 hours postinjury even if children are experiencing symptoms; and (2) rest until symptom resolution group: graduated return to physical activity initiated only after full resolution of symptoms based on the Zurich return-to-play guidelines.[7] A schematic diagram of the trial design, procedures and stages, can be viewed in figure 1; the proposed protocol adheres to the RCT-CONSORT research methods and the SPIRIT checklist.

Study setting

This study will include three Pediatric Emergency Research Canada (PERC) network hospitals: Children's Hospital of Eastern Ontario (Ottawa; coordinating centre), The Hospital for Sick Children (Toronto) and Children's Hospital London Health Sciences Centre (London). These centres constitute 3 of the 12 paediatric hospitals in Canada that are active PERC members and have a strong clinical research infrastructure with experience in recruiting patients for large clinical trials.[53 54] Research ethics boards (REB) have provided written approval from all three sites.

Eligibility criteria

Inclusion criteria

Participants presenting to one of the study hospital emergency departments after sustaining a direct or indirect head injury will be eligible if they (1) are aged 10 through 17.99 years; (2) are diagnosed with a concussion, defined by Berlin consensus statement; (3) sustained the injury in the previous 48 hours; and (4) are proficient in English or French.

Exclusion criteria

Participants will be excluded if they present with traumatic head injuries with any of the following: emergency department (ED) Glasgow Coma Scale (GCS) score ≤13; abnormality on standard neuroimaging studies,[7] including positive head CT findings (neuroimaging is not required, but may be performed if clinically indicated); neurosurgical operative intervention, intubation or intensive care required; multisystem injuries with treatment requiring hospital admission, operating room or procedural sedation in ED (hospital admission for observation or management of ongoing concussion symptoms is not an exclusion criteria); severe, chronic neurological disorder or developmental delay resulting in communication difficulties; intoxication at the time of ED presentation as per clinician judgement; no clear history of trauma as primary event (eg, seizure, syncope or migraine); inability to resume physical activities (eg, fractured extremity or other concomitant injuries); inability to obtain a proper written informed consent/assent (eg, language barriers, absence of parental authority, developmental delay, intoxication, patient too confused to consent); or legal guardian not present (certain forms need to be completed by parents/legal guardians).

Intervention protocols

Experimental group description: intervention (early physical activity) group

The intervention group and the control group differ in two important ways: (1) timing of the reintroduction of physical activities and (2) accommodation of ongoing symptoms for

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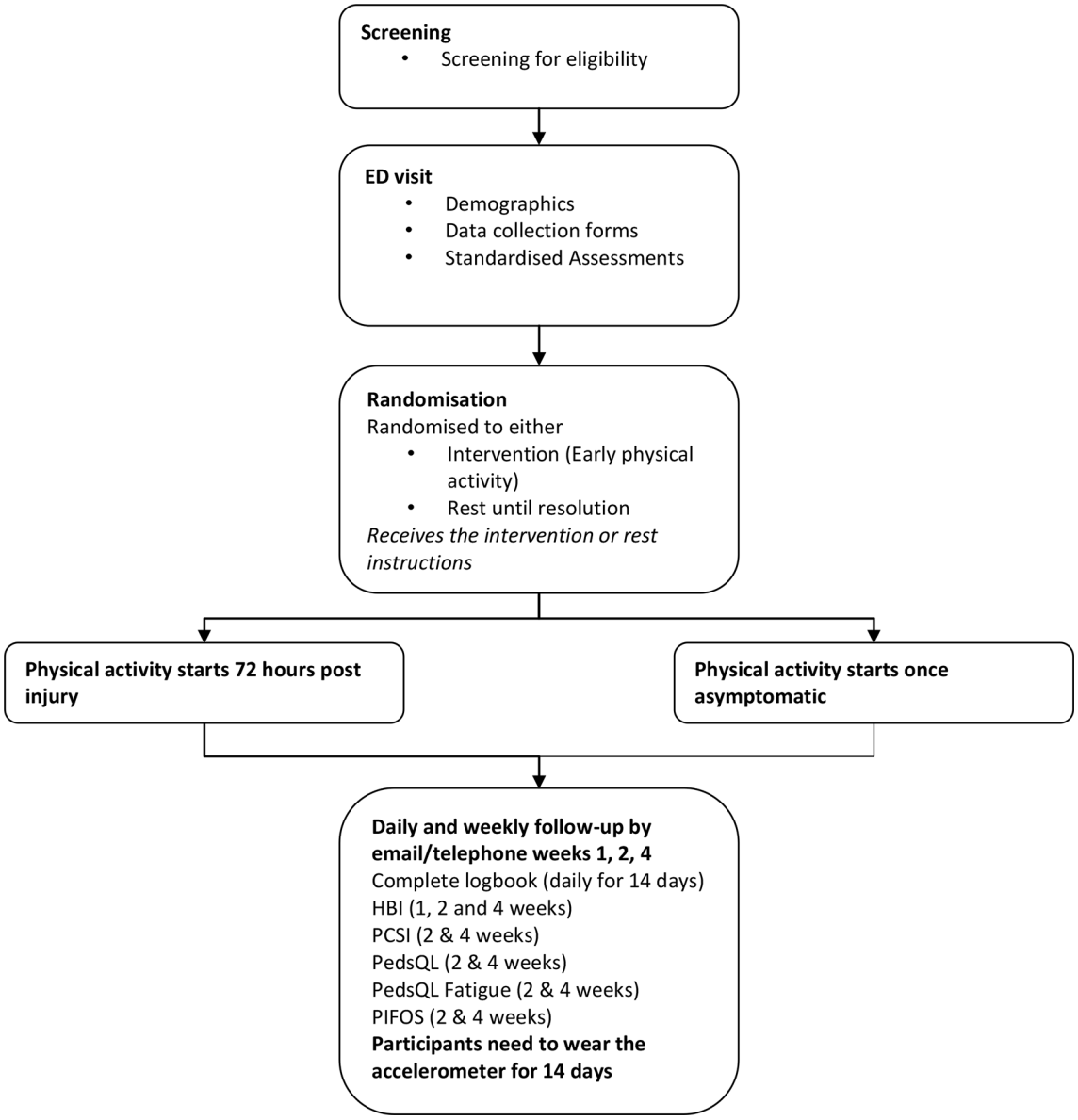

Figure 1 Study Procedure Flow Diagram. ED, emergency department ; HBI, Health and Behaviour Inventory; PCSI, Post-Concussion Symptom Inventory; PedsQL, Pediatric Quality of Life Inventory; PedsQL Fatige, PedsQL Multidimensional Fatigue Scale; PIFOS, Pediatric Injury Functional Outcome Scale.

both initiation and progression of return-to-play protocols. The experimental intervention (table 1) is based on the model for multimodal activity-exertion symptom management in children with concussion.[55] After an initial period of full physical rest (stage 0), patients allocated to the intervention group will initiate light aerobic exercise (eg, 15 min walk; step 1) 72 hours postinjury (table 1). Physical activity will be introduced in a systematic and progressive manner, even if children are experiencing symptoms, starting at a low level of intensity such that it does not significantly increase symptoms and that the symptoms remain tolerable as per patient report.

A symptom-limited approach will be used to progressively increase activity duration and intensity as long as symptoms are well tolerated, with a minimum of 24 hours between each step. Patients will document the type of activity, its duration and intensity level [using the Pictorial Children's Effort Rating Table (PCERT)],[56] along with preactivity/postactivity symptom severity. If symptoms become intolerable during or within 30 min following exercise (defined as much worse on the fifth and sixth questions of the logbook survey), children should return to the last well-tolerated level the next day and only attempt activity progression again after 24 hours. If children are unable to tolerate the initial step of the progression (15 min walk), they will be encouraged to attempt the walk again the next day.

Control group description: physical activity following symptom resolution (rest until symptom resolution) group

Children allocated to the control group will be assigned to a rest until symptom resolution protocol (table 2). Based on the Zurich return-to-play guidelines, children will refrain from any physical activity until full resolution of all concussion symptoms (stage 0).[7 22–30] When asymptomatic, children may initiate walking (stage 1). If asymptomatic, activity intensity and duration will be increased in a stepwise fashion, with a minimum of 24 hours between each stage. If symptoms develop at any stage of the

Table 1 Interventional (early physical activity) group protocol

Stage	Description	Functional exercise	Objective	Criteria to move to next stage
0	No physical activity	Symptom limited physical rest.	Recovery–72 hours postinjury	
1	Walking	Walking for 15 continuous minutes once a day at low intensity [level three on the Pictorial Children's Effort Rating Table (PCERT)]. No resistance training, weight lifting or activities risking collision or falls.	Initiate movement Level of physical activity: very, very easy to easy	To move to stage 2: You have reached level 3 of the PCERT
2	Light aerobic exercise	Progression of activities using one of the following of your choice per day: •Type (eg, walking up and down the stairs, jogging/running, swimming, stationary cycling). No resistance training, or activities risking collision or falls.	Increase heart rate Level of physical activity: easy to just feeling a strain	To move to stage 3: You have reached level 4 of the PCERT
3	Higher intensity/sport-specific exercise	Skating drills in ice hockey, running drills in soccer. No activities risking collision or falls.	Increase movement Level of physical activity: starting to get hard to getting quite hard	To move to stage 4: You have reached level 6 of the PCERT
4	High-intensity exercise/non-contact training drills	When sport-specific exercises are well tolerated, progression to more complex training drills (eg, passing drills in football and ice hockey). Maximum level eight on the PCERT. May start progressive resistance training.	Increase exercise and improve coordination The level of physical activity is hard to very hard	To move to stage 5: You have reached level 8 of the PCERT AND you have been cleared by a doctor
Visit medical provider for clearance when asymptomatic at intensity level eight or higher, only progress to step five if medical clearance has been obtained and you are fully back at school				
5	Full-contact practice	Participate in normal training activities	Restore confidence and assess functional skills by coaching staff	To move to stage 6: Fully back to preinjury performance
6	Return to full competition	Normal game play		

Table 2 Rest until symptom resolution group protocol

Rehabilitation stage		Functional exercise	Objective	Criteria to move to the next stage
0	No physical activity	Symptom limited: physical rest	Recovery	To move to stage 1: no more symptoms
1	Walking	Walking for 15 continuous minutes once a day at low intensity [level three on the Pictorial Children's Effort Rating Table (PCERT)]. No resistance training, weight lifting or activities risking collision or falls.	Initiate movement Level of physical activity: very, very easy to easy	To move to stage 2: No more symptoms If you have symptoms, go back to stage 0. Only progress when you have been asymptomatic for 24 hours.
2	Light aerobic exercise	Walking, swimming or stationary cycling keeping intensity to level 1, 2 or 3 of the PCERT. No resistance training.	Increase heart rate Level of physical activity: easy to just feeling a strain	To move to stage 3: No symptoms If you have symptoms, go back to stage 1. Only progress when you have been asymptomatic for 24 hours.
3	Higher intensity/sport-specific exercise	Skating drills in ice hockey, running drills in soccer. No activities risking collision or falls.	Increase movement Level of physical activity: starting to get hard to getting quite hard	To move to stage 4: No symptoms If you have symptoms, go back to stage 2. Only progress when you have been asymptomatic for 24 hours.
4	High-intensity exercise/non-contact training drills	Progression to more complex training drills, for example, passing drills in football and ice hockey. May start progressive resistance training.	Increase exercise and improve coordination The level of physical activity is hard to very hard	To move to stage 5: No symptoms and medical clearance is needed If you have symptoms, go back to stage 3. Only progress when you have been asymptomatic for 24 hours.
Visit medical provider for clearance when asymptomatic at intensity level eight or higher, only progress to step five if medical clearance has been obtained and you are fully back at school				
5	Full-contact practice	Participate in normal training activities following medical clearance	Restore confidence and assess functional skills by coaching staff	To move to stage 5: No symptoms If you have symptoms, go back to stage 4. Only progress when you have been asymptomatic for 24 hours. Fully back to preinjury performance
6	Return to play	Normal game play		

protocol, children should drop back to the previous asymptomatic stage and try to progress again after having been asymptomatic for 24 hours.

Common protocol description

Children in both groups must refrain from any activities that increase the risk of reinjury (drills with body contact or that risk falls) until fully asymptomatic and cleared by their primary care or other medical provider. Finally, children will be counselled to follow the cognitive rest recommendations based on the Zurich Acute Concussion Evaluation (ACE) return-to-learn guidelines[7] and recommendations provided by Iverson and Gioia.[57] Briefly, this is a six-stage model where participants return gradually to school with proposed accommodations (ie, no return to school, at home; return to school with partial day (1–3 hours); full day with maximal support needed through the day; full day with moderate support; full day with minimal support; and full return with no supports needed).

Participant compliance with the study intervention

Compliance to the treatment will be measured objectively with an activity monitor device (Actical Accelerometer; Phillips Respironics, Bend, Oregon, USA). The device monitors movement (ie, frequency and intensity) in selected time-stamped epochs of 1 min and will be worn by all participants 24 hours a day for 14 days following enrolment. Final data points will be collected on day 14. Child and/or caregiver logbook report (telephone/survey) will serve as the primary source of documentation.

Outcomes

Primary outcome and primary outcome measure

The primary aim of this randomised clinical trial is to evaluate whether early reintroduction of physical activity reduces the degree of postconcussive symptoms at 2 weeks. Symptoms will be measured using the Health and Behaviour Inventory (HBI).[9] The HBI has been adopted as a core measure in the NIH Common Data Elements for Paediatric Traumatic Brain Injury.[58] This measure is a 20-item self-report questionnaire using a four-point Likert scale rating of symptom frequency, yielding separate scores for cognitive and somatic symptom scales and a total score ranging from 0 to 60. The scale has good construct validity, reliability and was validated for children and adolescents 8–15 years of age.[9]

Patients in the experimental group are hypothesised to have a 20% lower total HBI score when compared with those in the control group at 2 weeks.

Secondary outcomes and secondary outcome measures

Several secondary outcomes are of interest:

- PPCS rates between the groups. The International Classification of Diseases, 10th Revision (ICD-10), defines PPCS as an increase from perceived preconcussion baseline of three or more concussion symptoms at 28 days following injury.[59] For the purpose of this secondary outcome, PPCS case will be defined as an increase from preconcussion baseline of ≥3 symptoms on both the HBI and the Postconcussion Symptom Inventory (PCSI), at 1, 2 and 4 weeks postinjury.
  a. The Retrospective Health and Behaviour Inventory (rHBI) will be used to collect preinjury symptoms, and the HBI will be used to collect the postinjury symptom score. The rHBI is a 20-item assessment answered by parents in the ED. These 20 items are exactly the same questions as within the HBI, except slightly worded differently. The assessment has good construct validity and good inter-rater reliability.[9]
  b. For confirmatory purposes, we will use another instrument, the PCSI,[60–62] to assess PPCS. The PCSI[60 63] is a validated, comprehensive, self-administered instrument, and only one of two measures applicable to younger children with published validity and reliability data.[60–62] For the purpose of this study, the PCSI preadolescent scale version (18-item, three-point scale), encompassing physical, cognitive, emotional and sleep domains will be used for all the children in the study. This specific version has demonstrated excellent internal consistency (r=0.87 for children aged 8–12 years). The assessment will be included in the second and fourth week follow-ups.
- Quality of life. Delayed recovery from concussion has been shown to affect the quality of life of the patient and the family.[11 18] To assess whether early reintroduction of physical activity can prevent declines in health-related quality of life, the Paediatric Quality of Life Inventory version 4.0 (PedsQL)[64 65] and PedsQL Multidimensional Fatigue Scale, will be used. Both assessments are reliable and valid measures of health-related quality of life in healthy children and adolescents and those with acute and/or chronic health conditions.[65–68] For this study, the child's version (ages 8–12 and 13–18 years) will be used and the two measures will be administered during second and fourth week of follow-up.
  a. The PedsQL is a 23-item, five-point scale, covering four domains: physical, emotional, social and school and takes approximately 4 min to complete.
  b. The PedsQL Multidimensional Fatigue Scale is an 18-item, five-point scale designed to measure fatigue in paediatric patients and comprises the General Fatigue Scale (six items), Sleep-Rest Fatigue Scale (six items) and Cognitive Fatigue Scale (six items).
- Functional outcome. The long-term effects of a concussion have been shown to affect both psychological and physical outcomes. Communication and self-care skills seem to be vulnerable to disruption after a concussion.[69] Academic performance is also hampered, with high rates of failure and need for academic support previously reported.[70–73] Thus, studying functional outcomes (motor, cognitive, communication skills, social-emotional, self-care and physical) postconcussion is important.
  a. The Pediatric Injury Functional Outcome Scale (PIFOS)[72] will be used to evaluate functional outcomes and determine if early physical activity can reduce the occurrence of poor functional outcomes. The PIFOS is a 26-item structured interview and is completed by caregivers. The assessment as good internal consistency (α=0.90-.93) and inter-rater reliability (α=0.90) for parents with children 3–15 years of age.[72] It elicits ratings of motor skills, daily living skills, communication skills, cognition, social-emotional functioning, physical changes and academic functioning.
- Physical activity. Exploratory research into the ideal duration, intensity and type of physical activity that reduces the risk of PPCS. Physical activity will be recorded using a logbook and objectively measured via accelerometer data.
  a. The patient will complete a daily logbook, the primary measure for assessing physical activity. This is a seven-item survey and questions relate to the child's concussion symptoms, daily physical activities (including type of activity, duration and intensity using the validated PCERT)[56], return to school progression and severity of

symptoms during and postactivity.

b. Actical accelerometer model z (Philips Respironics, Bend, Oregon, USA) will be used. The Actical provides an objective measurement of movement and sedentary time demonstrated by the participant. The device is capable of measuring or calculating raw acceleration, activity counts, energy expenditure and physical activity intensity. The device can store up to 32 MB of data (ie, 194 days on the Epoch mode of 1 min). The battery provides power for 180 days. The Actical accelerometer provides valid and reliable measures of movement behaviours.[74 75] Data collection and preprocessing (ie, cleaning and reduction) will follow established procedures for wear time criteria.[76 77]

c. Safety. We will examine the safety of early resumption of physical activity. Three extra questions will be added to the daily activity logbook survey (longer version), for the 1, 2 and 4 week follow-up. These safety questions address participants current versus preinjury activity levels, whether they have played contact sports since their injury, and if they have had any adverse events (ie, unscheduled visit to the ED or your primary provider due to exacerbation of symptoms).

- Long-term outcome. Concussion affects the overall health of individuals for years to come. To better understand the health-related and economic effect of paediatric concussions, the long-term healthcare use of study participants will be investigated in a future substudy. Using the Institute for Clinical Evaluative Sciences (ICES) Linkage services and Ontario Health Insurance Plan (OHIP) number, long-term healthcare use (ie, health information from healthcare services that the patient has used over the years) will be collected. These variables will help determine risks for concussion-related comorbidities, the effect of concussions on school performances, and help establish the economic effect of paediatric concussions. All legal residents of the province of Ontario with an Ontario health card are contained and tracked within health administrative data. These health administrative databases are maintained by ICES through a comprehensive data sharing agreement with the Ontario Ministry of Health and Long-Term Care. ICES take several steps to ensure that all collected personal health information remains secure, confidential and safeguarded. Personal health information can be collected from multiple sources under this clause: health information custodians including doctors, hospitals, long-term care facilities, community care access centres, pharmacies, laboratories/specimen collection centres, ambulance services, special care services and community health/community mental health programs, among others.

Please refer to table 3 for the specific time points of each outcome measure.

ED visit measurements

Case report forms

Information about children's injuries will be collected from medical records and medical personnel using a standardised case report form. Details regarding the injury and acute signs and symptoms of concussion (ie, loss of consciousness; GCS scores; mechanism of injury; neurological status, and other clinical features) will be collected by research assistants (RA), with clarification by physicians as necessary. Data will be verified by the site investigator.

Demographic data (such as household annual income and education level) will be used as a measure for socioeconomic status (SES). SES will be collected to assess whether randomisation is equally distributed in both groups. If SES is not equally represented in the sample, it will be controlled for in our

Table 3 Schedule of enrolment, interventions and assessments.

			Study period				
ED			Postallocation				
Time point	**Enrolment**	**Allocation**	**Day $_{1–6}$**	**Day $_{7}$**	**Day $_{8–13}$**	**Day $_{14}$**	**Day $_{28}$**
Enrolment:							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
Interventions:							
Physical activity			◆—	—	—◆		
Rest until symptom resolution			◆—	—	—◆		
Assessments:							
Case report (acute signs and symptoms)		X					
Physical activity		X					
BESS		X					
rHBI		X					
HBI		X		X		X	X
PCSI						X	X
PedsQL						X	X
PedsQL Fatigue Scale						X	X
PIFOS						X	X
Activity logbook			X	X	X	X	X
Accelerometer (Actical)			X	X	X	X	

BESS, balance error scoring system; HBI, Health and Behaviour Inventory; PCSI, Postconcussion Symptom Inventory; PedsQL, Paediatric Quality of Life Inventory; PedsQL Multidimensional Fatigue Scale; PIFOS, Paediatric Injury Functional Outcome Scale; rHBI, Retrospective Health and Behaviour Inventory (rHBI).

analysis with the household annual income and educational level variables.

Balance error scoring system

Balance will be evaluated by the RA using the Balance error scoring system (BESS),[78] a widely used instrument in the field of sports concussion[79] for objective assessment of postural stability. Two stances will be used: narrow double leg stance and tandem stance (hard surface only). Each stance is held, with hands on hips and eyes closed, for 20 s. Error points are given for specific behaviours, including opening eyes, lifting hands off hips or stepping, stumbling or falling. The BESS has shown satisfactory reliability in children and adolescents.[80]

Physical activity questionnaire

Preconcussion information on physical activity and sedentary habits will be assessed with selected questions from the Physical Activity and Children's Physical Activity surveys from the Canadian Health Measures Surveys (CHMS). The CHMS is a validated, reliable, standardised and comprehensive direct health measurement survey.[81 82] These selected questions will provide a baseline measure of physical activity and sedentary behaviour habits, as these are possible confounding variables. Thus, the data collected with this assessment will be used to assess whether randomisation adequately accounts for potential differences in preconcussion activity levels. If physical activity habits are not adequately represented in the sample, it will be controlled for in our proposed analyses. In addition, by collecting this information, we will have the potential of comparing the results to a representative Canadian paediatric population from the CHMS.

Sample size

The sample size calculations for this trial were informed from unpublished data of the HBI assessment. Based on the parental HBI report, the head injury group had an HBI retrospective mean of 14.90; a 1-month HBI mean of 15.85 (SD=9.83) and a 12-month HBI mean of 13.22 (representing a return to normal). In the orthopaedic group, the retrospective parent-report mean was 13.38, the HBI parental-report mean at 1 month was 13.29 and the HBI parental-report mean at 12 months was 11.64. Considering these results, the experimental group is expected to demonstrate a 20% decrease in total symptom score at 2 weeks postinjury (ie, HBI M=12.68). Fixing the probability of type-I error at 5%, assuming an SD of 9.83, a sample size of 152 per group would give 80% power to detect a 20% absolute difference in HBI total scores between the study arms. Accounting for an anticipated 15% loss in the follow-ups, a sample size of 175 per group is required (total number of 350).

PROCEDURE

Data collection methods

When a child with head injury presents to ED triage, the nurse will triage the child as per the existing protocol at each site. If the child has suffered symptoms possibly consistent with concussion, a member of the ED clinical team will inform the family that there is a study on children who have head injuries and ask if they are interested in learning more about the study. If so, the charts of potentially eligible patients will be flagged and the research team will be notified.

In families that agree to learn more about the study, the RA will introduce the study and complete a brief screening questionnaire. Patients who are not eligible based on initial screening will be thanked for their time. Eligible and willing parents, along with children and adolescents capable of consenting on their own behalf, will be asked for written informed consent; children aged 10 years or older unable to consent on their own behalf will be asked for assent. Subsequently, RAs will begin assessments and interventions. RAs will complete the screening and assessment questionnaires on a tablet for all potentially eligible patients who present to the ED during the study enrolment hours.

ED visit and randomisation

Description

Once consent is obtained, RAs will enrol patients and assign patient ID numbers by clinical sites. Subsequently, the RA will collect contact information and the demographic, injury and symptom information. Afterwards, participants will be tested with the BESS, rHBI, HBI and five selected questions from the physical activity and sedentary behaviours questionnaire.

Physician management and prognostications

The treating physician will assess the child as per the normal operating procedures of the ED. Once a patient has given consent to participate in the study, the RA will liaise with the treating physician to notify them that the patient is enrolled in the study. The child will remain in the normal treatment queue, and participation in this study is not anticipated to lengthen their ED visit. The physician will complete a brief electronic survey on the same tablet computer to provide data about presenting symptoms and the physical examinations (eg, mental status change, neurological deficits and ED GCS).

Randomisation, blinding and allocation

RAs will log into the Research Electronic Data Capture (REDCap) to randomise the patient to the experimental or control group, via a randomisation table. The randomised sequence was created using R V.3.1.1 software and was stratified by sites and sex, with a 1:1 allocation using random blocks. Only the RA recruiting and evaluating the participant will be unblinded; other researchers will be blinded to the allocated intervention protocol. The intervention plan to which participants are randomised will be a hidden field within the database; unblinding will be permissible if serious adverse events occur.

Subsequently, RAs will provide patients with physical rest recommendations (either experimental or control), cognitive rest recommendations as per the Zurich ACE return-to-learn guidelines and verbal and written education materials for accelerometer use. A flow chart of the time sequence of events in the ED can be reviewed in figure 2.

Follow-up procedures

Telephone/survey communication

During the ED visit, caregivers will be asked their preferred method of communication, email or telephone. Following discharge, enrolled patients will either be entered into an automated follow-up web survey using REDCap[83] or be contacted by telephone. Follow-up will be daily for 14 days (including a longer survey at the first and second week postinjury) and at the fourth-week postinjury for further data collection of primary and secondary outcome measures. A standardised script and survey/data collection form will be employed. Follow-up surveys include a daily logbook survey, the HBI, PCSI, PedsQL and PIFOS.

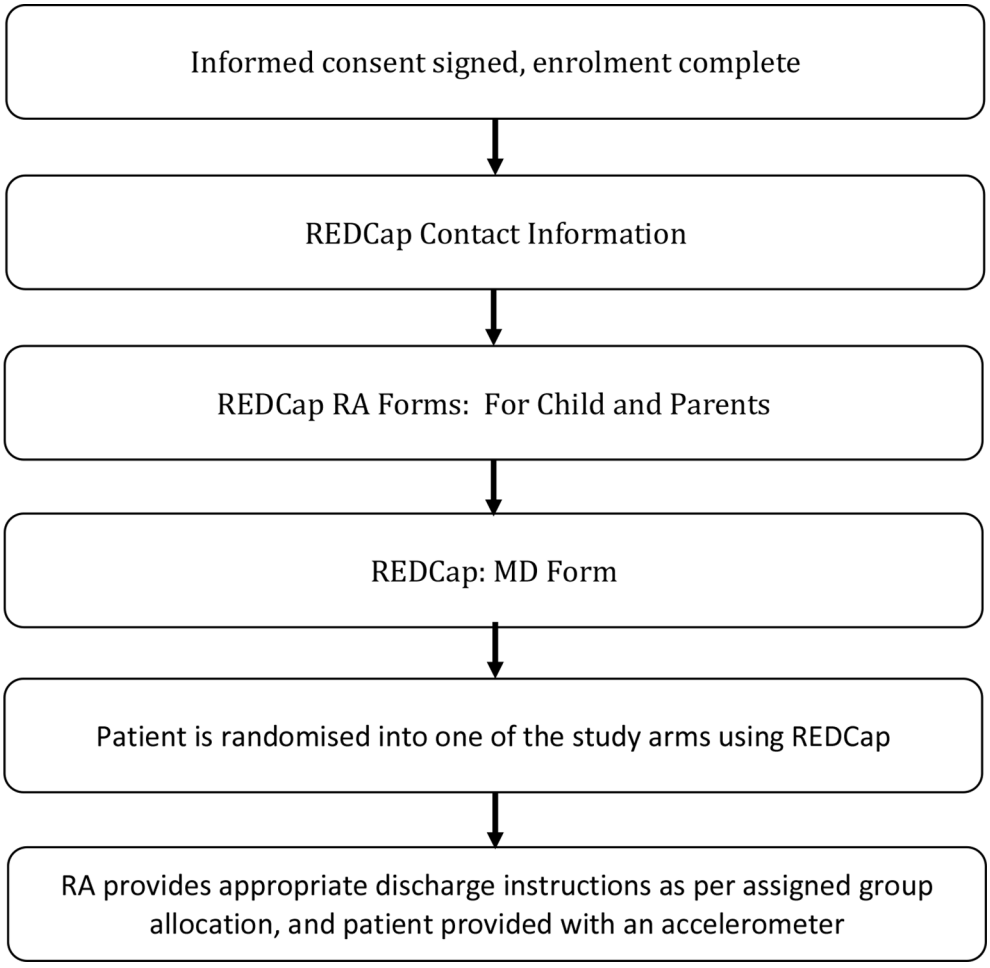

Figure 2 Flow chart of the sequence of event during the ED visit. ED, emergency department; RA, research assistant; REDCap, Research Electronic Data Capture.

Daily movement measurement

During the ED visit, all participants will be instructed on how to use the Actical accelerometer. All participants will be required to wear the accelerometer, for 14 consecutive days, 24 hours a day (removing only for water-related activities). To prevent reactivity to the measure, the device will be automatically activated at midnight. The accelerometer will be worn at the waist on an elasticised belt and positioned in line with the right mid-axillary line. Data will be collected at a sampling mode of 1 min. Data will be automatically stored in memory on the accelerometer. On the 15th day, participant will be instructed to return the Actical and belt via a courier service. Data will be downloaded directly into the REDCap database.

Data management

The Clinical Research Unit Data Coordinating Centre will be used as a central location for data processing and management, and data will be private and secured to industry standards for both clinical and patient sensitive data in Canada. Study data will be collected and managed using REDCap[83] electronic data capture tools hosted and supported by the CHEO Research Institute. REDCap is a secure, web-based application designed to support data capture for research studies.

Only members of the research team will be granted access to the database. Users will be assigned to 'Data Access Groups' that will restrict their rights to viewing and entering data for their site alone. For monitoring purposes, the study coordinator will be able to view data from all sites. Within the Data Access Group, user privileges will be designated by the study coordinator to ensure research team members have only the minimum required rights to perform their duties. All identifying information that is collected will be flagged in the database and removed from data export unless the identifying information is required for statistical analysis (eg, date of birth).

STATISTICAL ANALYSIS

Proposed analyses

All main efficacy analyses will be based on the intent-to-treat principle. We will perform per-protocol analyses for additional insight. All reports and publications will distinguish these analyses. Multiple imputation techniques will be employed to replace data missing at random.

Analysis of primary outcome

The primary outcome investigated is whether early resumption of physical activity can reduce ratings of the frequency of PPCS compared with rest until resolution of symptoms at 2 weeks postinjury. The primary outcome will be evaluated with a linear multivariable model, where the total score on the HBI will be the dependent variable and treatment the primary independent variable of interest. The model will be adjusted for site and prognostically important covariates derived from Zemek *et al*[8]: sex, age, prior concussion and symptom duration, migraine history, balance

error scoring, answering questions slowly, headache, sensitivity to noise and fatigue. Assessment of collinearity using the variance inflation factor (VIF) will be performed, and if VIF greater than five is detected, variables will either be removed from the model or combined. Finally, main effect results with two-sided p values less than 0.05 will be considered to be statistically significant.

Planned subgroups analyses

Four planned linear models will be generated for the subgroup analyses for the primary outcome. (1) treatment×sex predicting PPCS—while concussion incidence is greater in males (approximately 60%), evidence demonstrates a greater PPCS risk in females.[8 84] Since concussion affects both sexes differently, the interaction between sex and treatment will be analysed. (2) Treatment×age (10–12 years, 13–17 years) predicting PPCS—evidence from Zemek *et al*[8] demonstrated a greater PPCS risk in adolescents compared with younger children. To understand the optimal timing of reintroducing physical activities by age, the interaction effect between age and treatment will be investigated. (3) Treatment×severity of symptoms predicting PPCS—examining the relation between treatment and symptom severity predicting PPCS will be studied. (4) PPCS risk—a subgroup analysis stratified to PPCS risk using the PPCS prediction rule derived from the 5P study[8] to stratify risk will be performed. A small difference in physical activity between treatment groups is expected for children with a quick recovery; the largest treatment difference is expected in children with protracted symptom recovery (elevated PPCS risk). Tests related to all subgroup analyses will be conducted with adjusted significance levels in order to keep the overall type I error rate less than 0.05.

Analysis of secondary outcomes

Differences between the groups in health-related quality of life (PedsQL and PedsQL fatigue scale), functional outcome (PIFOS) and performance, sports/recreational participation and performance (data collection form collected in the ED), overall symptom burden (rHBI with HBI score at 1, 2 and 4 weeks and PCSI score at 2, 4 weeks), accelerometer data and adverse event rates will be analysed using parametric and non-parametric tests. We will also report observed differences in the secondary outcomes and corresponding 95% using the appropriate summary statistic. We will use Holm's correction, as necessary, to correct for multiple testing.

Analysis of secondary outcomes: ICES linkage

As part of this novel study, with data linkage through use of the patient's OHIP number (with consent to use), the long-term healthcare use of concussion of both groups as well as the risks for concussion-related comorbidities (eg, mental health) group differences will be analysed. Future opportunities exist for ICES linkage to educational databases; a metadata analysis will permit examination of effect on school performance. Finally, we will be able to establish the economic effect related to paediatric concussion through ICES analysis.

DATA SAFETY MONITORING

Data safety monitoring board

The independent data safety monitoring board (DSMB) will consist of an independent paediatric ED physician, two paediatric concussion experts and a statistician not involved in the project. The DSMB will be immediately advised of severe adverse events, and they will meet in the event of a serious adverse event. Given the low risk intervention and no intention to stop the trial for benefit/futility, only biannual meeting will be required.

Proposed frequency of analyses

In keeping with StaRChild Health guidelines,[85] the DSMB will, in collaboration with the trial steering committee, establish safety outcomes (including reinjury and PPCS rate and frequency rate at 4 weeks) and stopping rules prior to trial initiation. The DSMB will meet biannually to review enrolment, study procedures, form completion, data quality, loss to follow-up and interim safety results. Based on trends and adverse events, the DSMB may decide to meet sooner than planned using boundaries adjusted accordingly and may request unblinding if deemed necessary.

Potential harms

Safety outcomes include (1) repeated concussion or other exercise-related injuries within 4 weeks postinjury, (2) PPCS frequency rate at 4 weeks postinjury, (3) severe worsening of symptoms and (4) any symptoms requiring an unscheduled visit to the ED or primary care provider.

Although participants may experience an exacerbation of symptoms with increased activity, there are also risks associated with prolonged inactivity, including an increase in postconcussion symptoms. Participants in the experimental group will be instructed to progress with activity and exertion only if symptoms remain tolerable. Participants in the control group will be instructed to progress with activity and exertion only once asymptomatic. The activities undertaken in both groups are non-contact and as such pose little risk of head injury.

If concussion symptoms worsen during the treatment to the degree that the participant requires an unscheduled visit to the ED or primary care provider, then symptoms will be considered as an adverse event. Symptoms could develop into an adverse event if they become unbearable and the patient needs immediate medical attention. Patients will report adverse events through REDCap or the daily telephone survey. Daily reports will be monitored by RAs. In case of adverse events, site investigators will be notified in order to monitor the event and advise their respective REB, CHEO REB and DSMB.

ETHICS AND DISSEMINATION

Ethical considerations

The clinical trial study as received written approval from all sites REB. The study will be carried out according to the principles outlined in the Declaration of Helsinki,[86] Good Clinical Practices, within the laws and regulation of the Tri-Council Policy Statement and the institutional policies of the CHEO REB.

Informed consent will be sought from all parents and participants aged 16 years and older. In addition, informed assent will be sought from participants under the age of 16 years, or from those deemed by their physician and the RA to be cognitively unable to provide informed consent.

Confidentiality considerations

Research personnel will take all appropriate and customary steps to ensure that data remain secure and that patient privacy and confidentiality are maintained.

Dissemination

Results will be disseminated at international conferences and in manuscripts to peer-reviewed journals. A manuscript communicating the results of the primary objective will be published in a peer-reviewed journal. Separate manuscripts will be written on each of the subgroup analyses and on the secondary

objectives of the protocol, and these will also be submitted for publication in peer-reviewed journals. Finally, results will be integrated into concussion guidelines and shared with relevant key stakeholders (eg, public health agencies, education and sport ministries, sporting bodies, medical professional associations and foundations/associations encompassing sport and brain injury).

DISCUSSION

The proposed study is an innovative, large-scale, multicentre RCT, comparing two physical activity protocols: early resumption of non-contact aerobic physical exercise at 72 hours post-injury versus graduated return-to-play initiated only after full symptom resolution (rest until symptom resolution). The main objective of this study is to determine whether the early resumption of non-contact physical activity will yield superior recovery with a reduced degree of PPCS following a concussion. Secondary aims are to evaluate the effect of early reintroduction of physical activity on HRQoL, functional outcome, sleep and long-term use of healthcare services. Participants in the experimental group are expected to have a reduced risk of PPCS; they will also demonstrate better quality of life, functional outcomes and sleep compared with the control group. Finally, prospectively, participants in the experimental group are predicted to show reduced use of healthcare services compared with the control group.

International concussion experts participating in the Predicting and Preventing Postconcussive Problems in Pediatrics (5P)[8 51 87] study determined that 72 hours postinjury was an acceptable time to initiate physical activities in the experimental group, in terms of promoting recovery but doing so safely. In patients with a stroke (a severe TBI), fewer days from onset of stroke symptoms to the initiation of exercise programs have been consistently associated with improved functional outcomes and shorter rehabilitation, particularly in those with more severe symptoms[88 89] The 72-hour window allows time to begin recovery from metabolic and autoregulatory changes in the acute postinjury phase and was deemed safe to resume light non-jarring activities.

While we anticipate good adherence to the assigned protocol, the possibility of decreased compliance exists in both arms. In the experimental group, children and/or families may experience problems with resuming or progressing physical activities due to higher than anticipated symptoms. Alternatively, children in the control group may not fully refrain from physical activities until completely symptom-free, as currently recommended in return-to-play protocols. Both groups may not fully comply with the provided cognitive return-to-learn advice, although this should occur equally among both groups given the randomised design. Measures have been put into place to minimise compliance problems by (1) providing comprehensive educational materials on physical and cognitive rest at the time of study enrolment at the ED and (2) regular follow-up. Finally, the act of wearing an accelerometer may result in better adherence to the assigned protocol and will enable us to perform objective per-protocol analyses in addition to intention-to-treat analyses.

It is anticipated that the results from this study will provide healthcare professionals with evidence on when and how best to reintroduce physical activities in a patient's treatment plan. The knowledge gained from this randomised clinical trial will help guide paediatric concussion management by healthcare providers, families and educators/coaches and may positively affect patient-care and healthcare costs.

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Contributors RZ and NR conceived the study. AAL, RZ, NR, NB, CD, SR, KB, AD, GS, KJF, KB, KOY and MST contributed to the study design and contributed to the writing of the trial protocol. AAL and RZ prepared the first draft of the manuscript, AAL, NR, CD, SR, KB, AD, GS, KJF, KB, KOY and MST contributed to editing the manuscript and read and approved the final manuscript.

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Ethics approval CHEORI REB, SickKids REB and London Children Hospital REB.

Provenance and peer review Commissioned; externally peer reviewed.

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