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Symptom Exacerbation and Adverse Events During a Randomized Trial of Early-Stage Rehabilitation After Sport-Related Concussion: Safety Outcomes From the Active Rehab Study

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Context: Authors of few studies have used randomized controlled trials (RCTs) to quantify clinical intervention safety of rehabilitation after sport-related concussion across sport levels.

Objective: Describe symptom exacerbation and adverse events (AEs) associated with two concussion rehabilitation interventions.

Design: Cluster RCT (NCT02988596)

Setting: Sports medicine clinic and field settings.

Patients or Other Participants: The RCT enrolled 251 concussed athletes (median age = 20 years; female, n = 48) across 28 sites from New Zealand professional rugby (n = 31), Canadian professional football (n = 52), US/Canadian colleges (n = 128) and US high schools (n = 40).

Interventions: Two medically supervised interventions: (1) enhanced graded exertion (EGE): international return-to-sport strategy and sport-specific activities only (EGE only, n = 119); and (2) multidimensional rehabilitation (MDR) followed by EGE: early symptom-directed exercises once symptoms were stable, followed by EGE after symptoms resolved (MDR + EGE, n = 132).

Main Outcome Measure(s): Primary outcomes were intrasession total symptom severity score exacerbation and significant intersession (increase 10+ severity points) sustained total symptom severity exacerbation, each measured with the Postconcussion Symptom Scale (132 total severity points on scale). Reported AEs were also described. Activity-based rehabilitation sessions (n = 1437) were the primary analysis unit. Frequencies, proportions, medians, and interquartile ranges were calculated for outcomes by treatment group.

Results: The 251 postinjury participants completed 1437 (MDR + EGE = 819, EGE only = 618) activity-based intervention sessions. A total of 110 and 105 participants contributed data (those missing had no documented session data) to at least 1 activity-based session in the MDR + EGE and EGE-only arms, respectively. Intrasession symptom exacerbations were equivalently low in MDR + EGE and EGE-only arms (MDR + EGE:

16.7%, 95% CI = 14.1%, 19.1%; EGE only: 15.7%, 95% CI = 12.8%, 18.6%). In total, 9/819 MDR + EGE sessions (0.9%) and 1/618 EGE-only sessions (0.2%) resulted in a presession to postsession symptom exacerbation beyond a 10+ severity point increase; 8/9 resolved to <10 points by the next session. Two study-related AEs (1 in each arm) were reported.

Conclusions: Participants in MDR + EGE and EGE-only activities reported equivalently low rates of symptom exacerbation.

Key Words: early activity, traumatic brain injury, return to sport

Key Points

- The early introduction of symptom targeted exercises (multidimensional rehabilitation) and standardized return-to-sport strategy (enhanced graded exertion only; based in international recommendations from 2017) demonstrated similar safety results.
- The multidimensional rehabilitation and enhanced graded exertion and the current return-to-sport strategy (enhanced graded exertion only), when clinically monitored, resulted in few significant symptom exacerbations and few overall safety concerns.

Previously, concussions were often managed by using a relatively unchallenged rest-and-wait approach.[1] Authors of emerging research suggests active rehabilitation may provide an advantageous and more contemporary approach to treating athletes with concussion.[2] Specifically, data from various protocols suggest benefits of early aerobic activity after concussion as well as aerobic activity in those with prolonged symptoms, which is a significant change in management strategy since 2012.[3–10] Additionally, more specific and targeted strategies such as cervical or vestibular rehabilitation provide recovery benefits for those with deficits in these areas, in various age groups.[11–13] The benefits across the various studies include faster time to clinical recovery, improved quality of life, and improved clinical outcomes.[11] Furthermore, patients seen earlier after injury (within 7 days of injury) may have a faster recovery time than those seen later (8–20 days postinjury).[14] Authors of this emerging literature mostly focused on adolescent and pediatric populations, with few focused across different age groups.[15] Despite this evidence, the clinical question often remains: Is early, active rehabilitation of concussion safe?

The existing literature exploring the safety of the abovementioned protocols is emerging.[16] Safety of such protocols is important, given the focus earlier interventions have on improving outcomes sooner after injury. These safety concerns should be responsibly balanced against significant symptom exacerbation after activity.[17] Clinical uptake of the evidence concerning earlier activity and exercise postconcussion may be slowed, as data are very limited on potential and likely transient symptom exacerbations occurring during rehabilitation. Understanding significant symptom exacerbations and adverse events (AEs; eg, emergency department visits, sustained significant symptom increases) surrounding these interventions is critically needed to inform clinical expectations.

While authors of studies addressed overall safety of early, active concussion intervention protocols, these data do not generalize well across different age groups and sport populations.[15,16,18,19] Therefore, our study purposes were to examine intrasession and significant intersession symptom exacerbations associated with rehabilitation sessions and to examine reported AEs associated with 2 concussion rehabilitation intervention strategies among professional, college, and high school athletes. The intervention strategies consisted of (1) an early active rehabilitation protocol or (2) a standardized return-to-sport progression. We hypothesized the 2 interventions would be equally safe such that symptom exacerbations and possible study-related AEs would be similar across the 2 intervention types.

METHODS

Study Design and Setting

In the current study, we employed a pragmatic, unblinded, cluster-randomized controlled trial (RCT) design applied across different strata of athletes. Sites were randomized to 1 of 2 study arms before their initial season of participation via stratified (cohort) site randomization (schools for interscholastic and college or university, and teams for professional cohorts). Site (or cluster) randomization was chosen over individual participant randomization given the care delivery model in the sports setting occurs at the team or school level. Individual randomization would not be pragmatically feasible in this context. The 4 separate cohort participant groups included athletes from high school (8 sites), college or university (6 sites), professional football (9 sites), and professional rugby (5 sites). The total site × arm distribution included 15 multidimentional rehabilitation plus enhanced graded exertion (MDR+EGE) sites (contributing 132 participants with concussion) and 13 EGE-only sites (contributing 119 participants with concussion). The study settings were sports medicine clinics and field sites (including team headquarters). All procedures were conducted in conjunction with normal care delivery for participants at each site. Additional design and randomization process specifics were described previously.[20] Institutional review board approvals (Prime IRB 16-1228) were obtained before study initiation, and clinical trial registration was completed before enrolling the first participant (NCT02988596). All participants completed written and informed consent for the study.

Participants

The 3511 participants were rostered athletes from enrolled sites or teams that completed written and informed consent (and assent or parental consent when applicable) during preseason baseline assessments. From this participant pool, 305 were diagnosed with sport-related concussion, and of these, 251 athletes were eligible and elected to continue for enrollment in the postinjury protocol per their site's respective arm. Injured participants were not eligible for postinjury enrollment if they had (1) already been previously enrolled

in the postinjury protocol, (2) abnormal neuroimaging related to the injury, or (3) an injury diagnosed as moderate to severe traumatic brain injury.[20] Participants were enrolled in the intervention from April 2017 to May 2019.

Study Intervention Arms

To enter the site-specific intervention, individuals were diagnosed with sport-related concussion by a qualified health professional (eg, physician, athletic trainer) using the study operational definition for concussion used by the CARE Consortium.[21] In the current study, we operationalized loss of consciousness (LOC) as well as dysfunction in this definition using current literature. The study definition is as follows: "a change in brain function following a force to the head, which may (or may not) be accompanied by temporary loss of consciousness (if LOC, temporary is defined as <30 min based on the Mayo TBI severity guidelines), but is identified in awake individuals with measures of neurologic and cognitive dysfunction, as indicated by 1 or more of the 22 symptoms from the Sport Concussion Assessment Tool symptom checklist."[20(p3)] Both intervention arms included postinjury education, and participants completed clinical assessments, in addition to the safety measurements included in this study at the same study-designated points. Additionally, both arms began their general postinjury protocols at their initial postinjury visit. The participants in the EGE-only arm were guided to complete the International Concussion in Sport Group's Return to Sport Strategy from the Berlin (2016) Consensus Conference (in which stage 2 is initiated once an individual becomes asymptomatic) with a specific focus on sport-specific activity, guided by site clinicians as deemed appropriate.[1] Activity beyond stage 1 began once an athlete was deemed clinically asymptomatic (eg, no more than 15% greater symptom burden than baseline) for the EGE-only arm. In the MDR + EGE arm, participants began study-prescribed activity as soon as symptoms were stable. We operationally defined *symptom stability* as symptom severity total not increasing by 10+ total symptom severity points on the Postconcussion Symptom Scale (PCSS; 132 total severity points) from first evaluation to the next, driven by their chief symptom complaints and directed by clinicians at their study site.[22] Once an individual was deemed clinically asymptomatic by a site clinician, the MDR progression was integrated with the 2016 International Concussion in Sport Group's Return to Sport Strategy with a focus on sport specifics as deemed appropriate by site clinicians.[1] Study intervention arms were previously described in detail along with exercise prescription progression examples.[20] For both arms, *clinically asymptomatic* was defined as no more than 15% greater symptom burden than baseline, and clinical recovery was determined by provider medical clearance for full return to sport.[20]

Procedures and Measures

Activity Sessions. After diagnoses, participants began the postinjury protocol for their respective sites as directed by their site clinicians. Intervention start time was recorded. Participants and their respective site clinicians (athletic trainer, athletic therapist, physiotherapist, physician, or combination) completed rehabilitation session logs as part of study documentation specific to each site's respective protocol arm.[20] These logs were completed during each specified MDR + EGE or EGE-only session based on study protocols and clinical expertise. Each session log also included a presession and postsession 22-item PCSS (with each symptom scored 0–6, yielding a hypothetical range for the summed symptoms scores of 0–132).[22] Additionally, these logs included information about number and types of activity, stages of rehabilitation and EGE, as well as overall perceptions of the session by the athlete and the clinician. Stopping a session was up to clinician and patient discretion, which was often informed by the determination of any significant symptom increases. Training was provided for all study site clinicians to enhance fidelity across sites and providers.

Table 1. Overview of Safety Definitions

Term	Definition
Intrasession symptom exacerbation	Determined as within a single session, postsession symptom severity score minus presession symptom severity score >0
Significant intrasession symptom exacerbation	Determined as an intrasession symptom exacerbation ≥10
Sustained (next session) significant symptom exacerbation	Determined from those with a substantial intrasession symptom exacerbation that remained substantial (≥10 points) when comparing the presymptom severity score of a subsequent session minus the presymptom severity score of the previous session; this included only those with a significant intrasession exacerbation in a session
Study-related adverse event	Event that caused adverse symptoms or outcomes was possibly related to the study (eg, hospital visit or stay, emergency room visit)
	Any significant intrasession symptom exacerbation that remained substantially elevated at the subsequent session (sustained intrasession symptom exacerbation above)

Symptom Exacerbations and AEs. General safety and AE definitions are outlined in Table 1 and in the published study methods.[20] Quarterly safety reports were reviewed by an independent safety monitor (a sports medicine physician with extensive clinical and research experience in the field of sport-related concussion) that included study enrollments, recovery outcomes, as well as significant intrasession and intersession symptom spikes, and AEs (emergency department visits or significant symptom exacerbations persisting across sessions). Secondarily, we also examined intersession symptom exacerbations (from one session to the next). Site personnel completed standardized forms to document AEs. These AEs were also reviewed by the respective institutional review boards. Study personnel followed up with sites to obtain details and resolutions concerning AEs.

Statistical Analyses

Demographic information was summarized using descriptive statistics. Statistical analyses included descriptive reporting of AEs and symptom exacerbations with a particular interest in intrasession symptom increases (exacerbations). Valid total symptom severity scores were defined as having information for at least 21/22 symptoms on the checklist. Given the large proportion of sessions (95% across both arms) that included valid total symptoms severity scores, we elected to use the total number of sessions overall as the denominator.

Table 2. Participant Demographics (N = 251)

	MDR + EGE (n = 132)	EGE Only (n = 119)
Age, y, median (interquartile range)	20 (18, 25)	20 (18, 22)
Cohort, No. (%)		
Professional football	31 (23)	21 (18)
Professional rugby	22 (17)	9 (8)
College or university	57 (43)	71 (60)
Interscholastic	22 (17)	18 (15)
Gender, No. (%)		
Male	106 (80)	96 (81)
Female	26 (20)	23 (19)
Sport, No. (%)		
Male baseball	2 (2)	0 (0)
Male basketball	2 (2)	2 (2)
Male football[a]	24 (18)	45 (38)
Male ice hockey	2 (2)	11 (9)
Male lacrosse	5 (4)	5 (4)
Male professional football	31 (23)	21 (18)
Male professional rugby	22 (17)	9 (8)
Male soccer	5 (4)	1 (1)
Male volleyball	5 (4)	0 (0)
Male rugby	0 (0)	1 (1)
Male wrestling	8 (6)	1 (1)
Female basketball	1 (1)	3 (3)
Female ice hockey	0 (0)	5 (4)
Female field hockey	1 (1)	0 (0)
Female lacrosse	4 (3)	3 (3)
Female rugby	3 (2)	9 (8)
Female soccer	11 (8)	3 (3)
Female volleyball	4 (3)	0 (0)
Female wrestling	2 (2)	0 (0)

Abbreviations: EGE, enhanced graded exertion; MDR, multidimensional rehabilitation.
[a] Canadian college and US college or high school football programs included.

Table 3. Total and Median Number of Activity-Based Rehabilitation Sessions

	Total No. Documented Sessions[b]	Median Sessions per Participant (IQR)[b]
MDR + EGE (n = 132 injuries)[a]	819	6 (5, 9)
Professional football (n = 31)	182	6 (4, 9)
Professional rugby (n = 22)	150	6 (5, 7)
College or university (n = 57)	317	6 (4, 9)
Interscholastic (n = 22)	170	7 (6, 9)
EGE only (n = 119 injuries)[a]	618	5 (4, 6)
Professional football (n = 21)	133	5 (4, 7)
Professional rugby (n = 9)	48	5 (5, 6)
College or university (n = 71)	352	5 (4, 6)
Interscholastic (n = 18)	85	4.5 (4, 5.5)

Abbreviations: EGE, enhanced graded exertion; IQR, interquartile range; MDR, multidimensional rehabilitation.
[a] Number of injuries in each arm and cohort.
[b] A total of 110 and 105 participants contributed data to at least 1 activity-based session in the MDR + EGE and EGE-only arms, respectively.

Confidence intervals that did not overlap for a specific variable of interest (proportion of sessions with exacerbation) between groups were deemed significant for intrasession (with sessions as the unit of analysis) exacerbations across both study arms. We reported descriptive statistics for all reported AEs and proportion of individuals contributing to the sessions resulting in symptom exacerbations.

RESULTS

The study intervention participants included 251 athletes diagnosed with a sport-related concussion who met our study inclusion criteria for the postinjury protocol (EGE-only, n = 119; MDR + EGE, n = 132; Table 1). Most participants were male (80%) and competed at the college level (51%). Of the enrolled participants, 89.6% (105 EGE only, 110 MDR + EGE) contributed at least 1 activity-based session (those missing had no documented session data), such that a total of 1437 activity-based sessions were conducted (EGE only = 618, MDR + EGE = 819). Of those, 584 (94.5% of sessions) in the EGE-only arm and 785 (95.8% sessions) in the MDR + EGE arm had valid presession and postsession total symptom severity scores recorded. Sample and session descriptives are provided in Tables 2 and 3.

Overall, similar proportions of sessions occurred for both arms, in which total symptom severity score intrasession exacerbations (EGE only [15.7%, 95% CI = 12.8%, 19.6%] versus MDR + EGE [16.7%, 95% CI = 14.1%, 19.1%]) and across sessions (EGE only [3.8%, 95% CI = 2.2%, 5.2%] versus MDR + EGE [4.8%, 95% CI = 3.3%, 6.2%]) were recorded. For those contributing at least 1 activity-based session, the intrasession exacerbations were reported by 45/105 (42.9%) EGE-only arm and 50/110 (45.5%) MDR + EGE arm participants, respectively (Table 4). Additionally, reports of symptom exacerbation across sessions (intersession; from one session to the next) in both arms were low, with 4.8% of MDR + EGE sessions (range in cohorts: 3.3%–6.0%) and 3.8% of EGE-only arm sessions (range in cohorts: 0.0%–5.3%).

The MDR + EGE group had a slightly higher proportion of sessions with a reliable and significant intrasession symptom exacerbation of 10+ total symptom severity score points than the EGE-only arm (EGE only: 1 session, 1 participant; MDR + EGE: 8 sessions, 5 participants; Table 4). The median significant intrasession symptom exacerbation for these 9 sessions was 13 points (interquartile range, 11–13). However, only 1 session (1 person) in the MDR + EGE arm had a significant intersession symptom increase that persisted at the beginning of the next session and constituted an AE (0 individuals with persisting symptoms in the EGE-only arm). The individual's symptoms were documented as returning to within 10 total symptom severity score points of his or her previous session at 3 days after the event. All individuals and their respective postinjury progressions were monitored by medical personnel throughout the study.

The 819 MDR + EGE and 618 EGE-only sessions were spread across the postinjury period. The overall proportion of sessions and proportion of sessions with symptom exacerbations within key recovery windows (0–3 days, 4–7 days, 8–14 days, and 14+ days) are outlined in Table 5. In the MDR + EGE arm, the proportions of sessions with an intrasession exacerbation were similar across all windows; however, in the EGE-only arm, a slightly higher proportion of exacerbations was seen in the 14+ window. The 8 significant intrasession exacerbations in the MDR + EGE arm were spread out across the recovery window (2 in 0–3 days, 1 in 4–7 days, 2 in 8–14 days, and 3 in 14+ days). The only significant intrasession symptom exacerbation that remained the next day (MDR + EGE arm) occurred in the 4–7-day period (see details below for specific symptoms for this participant).

Table 4. Frequency of Global Symptom Exacerbation, Significant Symptom Exacerbation, and Sustained Symptom Exacerbation[a]

	Sessions With Intrasession Symptom Exacerbation	Sessions With Significant Intrasession Symptom Exacerbation	Sustained Significant Symptom Exacerbation (AE)
MDR + EGE (n = 819 sessions)	136 (16.7%)	8 (1.0%)	1 (0.1%)
Professional football (n = 182)	23 (12.6%)	2 (1.1%)	1 (0.0%)
Professional rugby (n = 150)	32 (21.3%)	5 (3.3%)	0 (0.0%)
College or university (n = 317)	57 (18.0%)	1 (0.3%)	0 (0.0%)
Interscholastic (n = 170)	24 (14.1%)	0 (0.0%)	0 (0.0%)
EGE only (n = 618 sessions)	97 (15.7%)	1 (0.2%)	0 (0.0%)
Professional football (n = 133)	22 (16.5%)	0 (0.0%)	0 (0.0%)
Professional rugby (n = 48)	2 (4.2%)	0 (0.0%)	0 (0.0%)
College or university (n = 352)	67 (19.0%)	1 (0.3%)	0 (0.0%)
Interscholastic (n = 85)	6 (7.0%)	0 (0.0%)	0 (0.0%)

Abbreviations: AE, adverse event; EGE, enhanced graded exertion; MDR, multidimensional rehabilitation.
[a] See Table 1 for definitions.

Activities driving increases were varied from biking and squats to progression of intensity and duration of activities. The single significant intrasession exacerbation in the EGE-only arm occurred in the 14+ day period (but resolved by the next session) with biking reported as the primary driver of symptom exacerbation.

Only 2 possible study-related AEs were reported in the clinical trial. One in the MDR + EGE arm related to symptom provocation (significant intersession symptom increase as described above that did not return to <10 points by the next session; symptom severity scores pre = 0, post = 13; remained at 12 at the beginning of the next session). The symptoms remaining elevated were headache, pressure in head, sensitivity to light or noise, not feeling right, difficulty concentrating, and trouble falling asleep. The participant's symptoms as described above returned to within 10 points of the session increase at a documented sessions within 3 days and fully recovered after the event, as the symptoms were returned to within 85% of his or her baseline score (study definition of asymptomatic) at the beginning of a scheduled session at 8 days after the symptom exacerbation (symptom severity score = 3). The participant was withdrawn from the study by medical and research staff due to prolonged symptoms but recovered from the event as documented above with symptom tracking and per medical staff.

Also, 1 AE in the EGE-only arm was reported, in which a participant went to the emergency department due to headache on the evening after a session. During and immediately after the session, the participant did not have any reported symptom exacerbation; the symptoms worsened approximately 30–60 minutes postsession. The participant took time away from the clinic during recovery but followed up via text message during this time and was followed closely until clearance. Upon return to campus, the participant's symptoms were documented within 85% of his or her baseline symptom severity score (study definition of asymptomatic) at a documented session 18 days postexacerbation (symptom severity score = 3). The participant was deemed recovered from the event and cleared for return to sport as determined by site medical personnel. All AEs were reviewed by an independent safety monitor and the respective institutional review boards.

DISCUSSION

While clinicians can expect some mild symptom exacerbation to occur in both forms of exercise intervention (early activity and standard return-to-sport strategy) after sports-related concussion, our cluster-RCT safety data indicate the relative safety of both protocols when these interventions are clinically directed and supervised. These findings are in line with recent International Concussion Consensus recommendations that progression of activity after mild and brief symptom exacerbation is relatively safe.[2] Overall, both MDR + EGE and EGE-only management strategies, evaluated in a cluster-randomized design, indicate comparable levels of overall safety when evaluating symptom provocation and AE occurrence in a large generalizable population of athletes from a variety of sports, levels of participation, and age groups. Additionally, any AEs from MDR + EGE are rare, suggesting benefits of these early rehabilitation interventions may outweigh any concerns about the potential deleterious effects of early exercise intervention.[5,11,23] We advise caution when applying these results to other settings, as our data come from a highly standardized protocol in which clinicians were recording data on safety outcomes and symptom scores, and fidelity to intervention protocols was likely important to maintaining low AE rates.

Previous recommendations from 2012 raised caution about possible adverse outcomes arising from early interventions

Table 5. Frequency and Percentage of Sessions Overall and Sessions With Documented Intrasession Symptom Exacerbation by Postinjury Period

Arm	0–3 d Postinjury	4–7 d Postinjury	8–14 d Postinjury	>14 d Postinjury
Overall distribution of sessions (proportion of sessions in each arm within each period)[a]				
MDR + EGE	18.9%	33.7%	28.0%	19.4%
EGE only	6.1%	18.9%	25.2%	49.7%
Intrasession exacerbations (proportion of sessions in each arm within each period with an exacerbation)[a]				
MDR + EGE	24/155 (15.5%)	50/276 (18.1%)	35/229 (15.3%)	27/159 (17.0%)
EGE only	5/38 (13.2%)	8/117 (6.8%)	19/156 (12.2%)	65/307 (21.2%)

[a] Summed over both arms, 1437 documented rehabilitation sessions occurred; a total of 110 and 105 participants contributed data to at least 1 activity-based session in the MDR + EGE and EGE-only arms, respectively.

after concussion and recommended further scientific study.[10] Over the past 10 years, research and clinical knowledge have adapted to this recommendation for further study. In the current study, our findings align with more recent and previous studies of early exercise and rehabilitation suggesting such interventions are relatively safe and therapeutic for brain recovery.[6,18,19] Furthermore, results from the current study suggest symptom changes are short lived, typically minor, and occur in a comparable range across early MDR + EGE versus typical activity progressions, when medically supervised. Authors of studies also suggested some mild symptom increases during exercise sessions may be experienced under normal exercise conditions in healthy participants but return over time to a relative baseline.[24,25] It is expected that symptom provocation may be greater in concussed individuals. The clinical concern occurs when intrasession symptom increases persist and only slowly return to a manageable presentation. Our data support very few significant intrasession exacerbations, and when they do occur, they dissipate relatively quickly. We also observed very few intersession (across) exacerbations. While slightly more significant intrasession symptom exacerbation sessions occurred in the MDR + EGE (n = 8) than the EGE-only (n = 1) arm, these events were rare in both arms, and only 1 event of these 9 remained significant at the next session. Additionally, we observed a similar proportion of any type of intrasession symptom exacerbations in both the MDR + EGE (16.7%) and EGE-only (15.7%) arms in the study.

The current data also highlight the proportions of sessions resulting in intrasession exacerbations are similar across all clinical time frames in the MDR + EGE arm but may be greater in the EGE-only arm in sessions 14+ days after injury. The slight differences in timing may be a result of those in the EGE-only arm having less exposure to activity until later in the protocol due to the nature of the return-to-sport progression. This may indicate a response to mild deconditioning, whereas those in the MDR + EGE arm were engaged in activity from the very beginning of the postinjury process. Our study findings have the benefit of being generated from a randomized trial with clinical supervision throughout the study, and the low AE outcome rates attained here may not apply in the absence of clinical supervision or monitoring. Nevertheless, our data have considerable significance, particularly as no other authors to date have examined the potential presence and timing of symptom exacerbation across multiple interventions. Timeframe data may be useful to clinicians in understanding when to expect symptom exacerbation along the recovery pathway based on activity decisions or rehabilitation progression. Future work is needed to better understand such factors and how this can inform policy and postconcussion decision making.

Overall, our findings suggest significant intrasession symptom exacerbations (10+ total symptom severity score points) during the study interventions were rare and did not remain over long periods of time, even when activity was introduced early in the recovery process. All cohorts, though not directly compared, also had similar proportions of sessions with significant symptom exacerbation. In the MDR + EGE arm (early activity), interscholastic and Canadian professional football had fewer intrasession exacerbations overall. More work is needed to compare cohorts and age groups to better understand implications for implementation across age groups. Overall, these findings suggest clinicians can expect symptom exacerbations in progression of activity, whether this activity is started earlier or later. Clinicians can expect relatively rare within-sessions significant symptom exacerbation regardless of intervention type. Additionally, our data support that mild and brief symptom exacerbations may occur and resolve quickly, supporting the recommendations of the most recent international consensus guidance.[2] It should be noted that our measurement of symptoms was more nuanced (specific symptoms and scores) than the general 0–10-point scale of overall well-being available now for measurement of brief and mild exacerbations. Additionally, we assessed sustained symptom exacerbations at the next rehabilitation session to ensure clinicians were present to determine next steps. Future researchers should also include additional symptom tracking and use ecological momentary assessments at various points across the day to better understand symptom trajectories with concussion-related interventions.

Our study is not without limitations. Given the pragmatic study design conducted in a clinical setting, it was unblinded, which could have resulted in performance or detection bias.[20] Additionally, our study sample included more males than females. Future work in female athletes is needed. Reasons for stopping sessions were also not fully captured, and future researchers would benefit from understanding session-stop reasons as well as the proportion of sessions stopped. However, the study was pragmatic and conducted in a real-world setting, providing greater study external validity and more generalizable information concerning these types of safety-related findings for clinicians.

CONCLUSIONS

The data from this prospective RCT provide an innovative contribution to the current literature on the safety of both (1) early, clinically directed multidimensional rehabilitation strategies (MDR + EGE) and (2) current return-to-sport interventions (EGE only). Both approaches resulted in few sessions with significant symptom exacerbations and a limited number of AEs, when following a clinically monitored intervention program in a controlled setting. These data provide further support that early and active rehabilitation is as safe as the traditional return-to-sport progression. Lastly, in the current study, we establish a safety framework to study the clinical efficacy of early, active intervention strategies to facilitate recovery after sports-related concussion.

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