Intensive Training for Stroke: Evidence of Safety from Meta-analysis and Systematic Reviews

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Abstract [**Objectives**] To investigate the safety of intensive training for stroke recovery. [**Methods**] A systematic electronic search was conducted up to December 1st, 2022, and the number of falls and fall-related injuries, as well as other adverse events, were extracted. Odds ratios (ORs) were calculated to assess the two intervention methods, and a 95% confidence interval (95% CI) was calculated for each of them to ensure the statistical accuracy of the results. The heterogeneity of the included studies was also tested. [**Results**] Five moderate to high quality studies comprising a total of 184 participants were included in this review. All five randomized controlled trials reported adverse events, including falls that did not result in injury, pain in the joints, back, muscle, or chest, and skin injuries such as cuts, bruises, and scrapes. The pooled analysis of these trials showed no statistically significant differences between the intensive training and control groups in terms of falls ($P = 0.35$), pain ($P = 0.07$), or skin injuries ($P = 0.90$). [**Conclusions**] This review provides good evidence to suggest that intensive training is safe and feasible as a novel intervention during the stroke recovery.

Key words Stroke, Intensive training, Safety, Meta-analysis

1 Introduction

Stroke is the second leading cause of death globally, with 6.5 million people dying from stroke each year, next to ischemic heart disease (IHD)[1]. About half of stroke patients experience hemiplegia or weakness on one side of the body, and their sedentary lifestyle results in changes in body structure and function that further limit their mobility and cause functional disabilities[2]. Moreover, post-stroke fatigue and cognitive impairment impede their recovery process. Research shows that stroke patients walk an average of 79% fewer steps per day than healthy older adults[3], which is far below the recommended daily step count of 5 000 steps. An observational study found that hospitalized stroke patients spend 76% of their time in bed and only 23% of their time standing and walking[4]. The lack of necessary activity increases the incidence and mortality of stroke, hinders the recovery of motor function, and leads to stroke recurrence[5], while increasing the risk of cardiovascular disease[6]. Therefore, it is necessary to apply more effective exercise interventions to alleviate the health burden of stroke patients.

It has been reported that moderate to high-intensity rehabilitation training can alleviate the motor function disabilities of stroke patients[7-8]. In recent years, intensive training has gradually been applied in the rehabilitation of cardiovascular diseases[9], diabetes and other conditions, aiming to control infections and chronic inflammation, repair damaged tissues, increase walking speed, and improve walking function. Although intensive training has been proven to be an effective clinical rehabilitation strategy in some literature, related safety studies are very limited[10]. The incidence of various cardiovascular events (such as myocardial infarction, arrhythmias) and injuries (such as falls, ankle sprains) increases rapidly during intense exercise. Therefore, the safety risks of intensive training cannot be ignored. Thus, our review aimed to explore the safety of intensive training during stroke recovery.

2 Methods

2.1 Search strategy The review and meta-analysis were conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[11]. English literature was searched in databases such as the Cochrane Library, PubMed, Web of Science, and EMbase. The literature search was conducted between the date of database establishment and December 1st, 2022, using a combination of subject terms and free words. The English searching formula was: (Stroke [Mesh] OR "cerebrovascular accident" OR "cerebrovascular disorder" OR "ischemic stroke") AND ("intensive training" OR "intensive exercise" OR "high intensity training" OR "high intensity exercise).

2.2 Inclusion and exclusion criteria Inclusion and exclusion criteria: Inclusion criteria were: (i) Study Participants: The study participants were individuals who were either in the acute, sub-acute, or chronic stages of stroke recovery and were 18 years of age or older, without mixed diagnoses; (ii) randomized controlled trials (RCTs); (iii) intervention group receiving intensive training, and control group receiving usual physical activities or sham exercises; (iv) outcome measures including number of falls and fall-related injuries, or other adverse events. Exclusion criteria were: (i) reviews, conference abstracts, case reports, animal

Received: May 20, 2023 Accepted: July 8, 2023
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experiments; (ii) unclear outcome measures or incomplete data; (iii) studies that combined training with another intervention; (iv) inability to contact the authors or obtain relevant data or full text.

2.3 Methodological quality assessment The methodological quality of the literature and the statistical methods were evaluated according to the Cochrane protocol and the Quality of Reporting of Meta – Analyses (QUOROM) guidelines. Two researchers independently evaluated the quality of the included studies according to the specific items in the guidelines and cross-checked their evaluations. In case of any disagreement, a third researcher was consulted for arbitration. The assessment tool consists of two parts. The first part evaluates seven specific domains, namely sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other issues. The second part assigns a judgment relating to the risk of bias for each domain, which includes "low risk" of bias, "high risk" of bias, or "unclear risk" of bias.

2.4 Statistical analysis The specific process of data statistical analysis and the results were presented using Review Manager Version 5.3. The odds ratios (ORs) value was used to compare and analyze the two intervention methods, and the 95% confidence interval (95% *CI*) was calculated for each of them, to improve the statistical results. The heterogeneity of the included studies was tested. If the heterogeneity was significant ($P \leqslant 0.1$ or $I^2 > 50\%$), a random-effects model was used for meta-analysis. If the heterogeneity was acceptable ($P > 0.1$ and $I^2 \leqslant 50\%$), a fixed-effects model was used for meta-analysis.

3 Results and analysis

3.1 Studies retrieved Literature screening results: Initially, 1 428 relevant articles were obtained from the search. After reading the titles and abstracts and excluding duplicates and articles without full text, 453 articles remained for further screening. Upon reading the full text and excluding articles that did not meet the inclusion criteria in terms of study participants, intervention measures, and outcome measures, a total of 19 articles were obtained. After quality assessment and screening, 5 articles[10-22] were ultimately included. See Fig. 1 for the flowchart of literature screening.

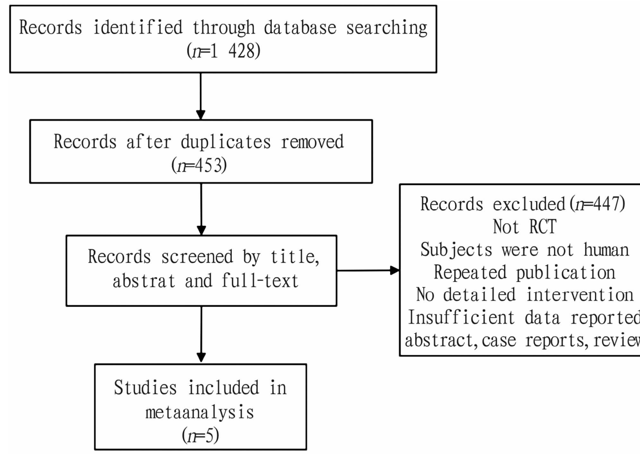

Fig. 1 PRISMA flowchart diagram of the search process

3.2 Characteristics of included studies There were 5 RCTs involving 184 participants. The intensity and duration of exercise varied greatly between studies, with an exercise intensity range of 70% – 80% HRR, a total time range of 25 – 40 min, and most training lasting 30 – 40 min. Weekly frequency ranged from 3 – 5 times, with most participants training 3 times per week. The intervention period in studies ranged from 4 – 24 weeks. In the control group, participants performed aerobic exercise such as underground walking, stretching exercises, and usual physical therapy for a duration of 28 – 45 min, at intensities below 50% HRR. Table 1 summarizes the descriptive characteristics of the studies that met inclusion criteria for the review.

Table 1 Characteristics of the studies included in this review

Author, year	Sample size, study design	Mean age years old	Control	Intervention		Frequency
				Intensity	Time//min	
Boyne *et al.* [12] 2016	nE = 11, nC = 5, RCT	E: 59/C: 57	25 min at 45% – 50% HRR	30 s at maximum safe speed	25	3 d weekly for 4 weeks
Hornby *et al.* [13] 2016	nE = 15, nC = 17, RCT	E: 57/C: 60	30% – 40% HRR	70% – 80% HRR	40	4 – 5 d weekly for 100 weeks
Leddy *et al.* [14] 2016	nE = 21, nC = 12, RCT	E: 55/C: 61	30% – 40% HRR	70% – 80% HRR	40	10 weeks
Pang *et al.* [15] 2005	nE = 32, nC = 31, RCT	E: 65.8/C: 64.7	Seated upper extremity program	70% – 80% HRR	30	3 d weekly for 19 weeks
Tang *et al.* [16] 2014	nE = 22, nC = 25, RCT	E: 65.9/C: 66.9	<40% HRR	70% – 80% HRR	30 – 40	24 weeks

Note: E. experimental; C. control; RCT. randomized controlled trial; HRR. heart rate reserve.

3.3 Adverse events and acceptability There were 19 studies that reported the safety of exercise, with most studies reporting no adverse events (*e. g.* orthopedic injury, cardiac symptoms) occurred by the patients during the training sessions in all group ($n = 16$). Three studies reported slight adverse events, including non-injurious falls, skin breakdown and slightly higher rates of hypertension. In addition, 5 studies reported the acceptability of high intensity intervention, with 2 studies reporting that all subjects well tolerated the training and 3 studies reporting that subjects seemed satisfied with the therapy, followed by increased confidence and enjoyment of high intensity training.

3.4 Main analysis Overall, 16 studies reported the safety after intensive training, with most studies reporting no adverse events (*i.e.*, orthopedic injury, cardiovascular events) ($n=6$) and no serious adverse events noted ($n=10$) in any participants during or after the training sessions. Only 5 RCTs detailed adverse events, including non-injurious falls; pain in joint, back, muscle or chest; and skin injuries (*i.e.*, cuts, bruises, scrapes). The pooled analysis of the RCTs failed to showed significant differences between the intensive training and control groups in falls ($n=184$, *RD* 0.06 [95% *CI* −0.06; 0.18], $P=0.35$, $I^2=0\%$, Fig.2), pain ($n=74$, *RD* 0.16 [95% *CI* −0.01; 0.33], $P=0.07$, $I^2=0\%$, Fig.3), and skin injuries ($n=56$, *RD* 0.01 [95% *CI* −0.20; 0.23], $P=0.90$, $I^2=0\%$, Fig.4).

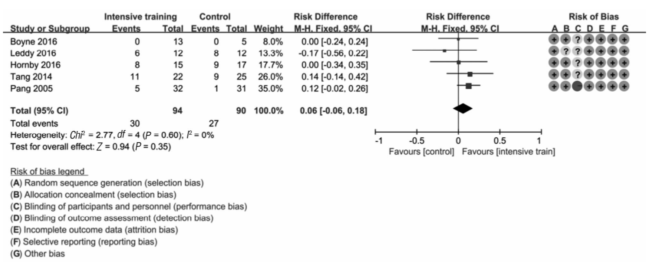

Fig.2 Summary effect sizes post-intervention for adverse events of falls

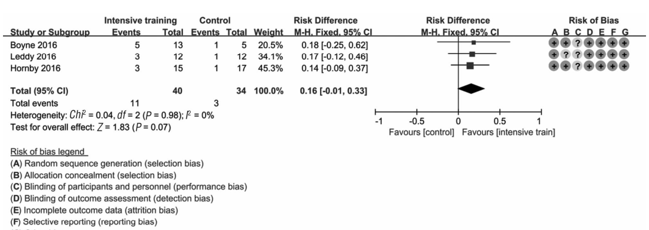

Fig.3 Summary effect sizes post-intervention for adverse events of pain

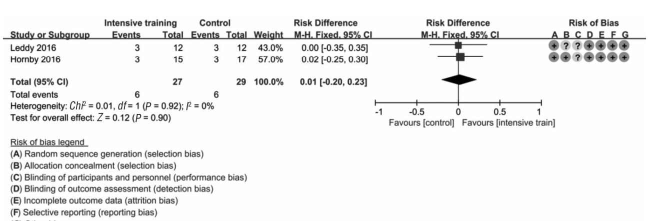

Fig.4 Summary effect sizes post-intervention for adverse events of injuries

4 Discussion

Intensive exercise has been increasingly recognized as a potential intervention for improving functional outcomes in stroke survivors[9]. Despite its benefits, concerns about the safety of intensive training in this vulnerable patient group remain. In the current review, most included studies did not report any serious adverse events during or after intensive training. Furthermore, the pooled analysis of randomized controlled trials did not show significant differences in falls, pain, and skin injuries between the intensive training and control group.

To provide a more comprehensive understanding of the safety profile of intensive exercise in stroke survivors, several studies have investigated the cardiac, orthopedic, and other potential risks associated with this type of training. Carl *et al.*[17] conducted a study in which they assessed safety by measuring electrocardiographic, blood pressure, heart rate, and orthopedic responses in participants with stroke who underwent 3 different high-intensity interval exercise protocols. The preliminary results showed that the HIIT protocols were safe and not associated with any signs of cardiac insufficiency, orthopedic injury, or symptomatic hypertensive/hypotensive responses.

Collectively, these findings suggest that post-stroke intensive training appears to be reasonably safe for further studies with appropriate screening, monitoring, and precautions. However, as the safety of intensive exercise in stroke survivors has not yet been fully established, it would be beneficial to conduct more randomized controlled trials to study the safety in a wider range of stroke survivors, such as those who are sub-acute or chronic, with and without comorbidities.

Based on the current evidence and previous studies, recommendations have been made to minimize the risks of orthopedic and cardiovascular events during intensive training in stroke survivors. To minimize the risk of orthopedic injury, excluding individuals with primary orthopedic diseases, such as injuries, joint replacement, lower limb fractures, severe dyskinesia, or active rheumatoid arthritis affecting gait, is recommended. Additionally, providing orthotic devices as needed to keep the knee and ankle stable, and using protective devices, such as an overhead harness system or safety strap, to prevent falls without adding body weight could be effective approaches.

To minimize the risk of cardiovascular events, excluding individuals with high-risk heart diseases (American Heart Association class C or D), or evidence of myocardial ischemia or significant arrhythmia on electrocardiographic exercise stress test, is recommended. It is also suggested to monitor potential hypotensive responses during training, such as heart rate, blood pressure, and cardiac symptoms, and to stop the training if the pulse rises to > 160 beats/min, or if the blood pressure rises to > 110 mm Hg diastolic or > 200 mm Hg systolic[18-20].

In conclusion, while extensive research has been conducted on the safety of intensive training in stroke survivors, more studies are needed to adequately establish the overall safety and potential risks associated with this type of intervention. By implementing appropriate screening, precautions, and monitoring, stroke survivors may be able to safely incorporate intensive exercise into their rehabilitation programs, thereby improving their functional outcomes and overall quality of life.

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