Critique author	Linda Metzger

Bibliographic Data	
Authors	Topcuoglu A, Gokkaya NKO, Ucan H, and et al.
Title	The effect of upper-extremity aerobic exercise on complex regional pain syndrome type I: a randomized controlled study on subacute stroke.
PMID	25943440
Citation	Topics in Stroke Rehabilitation, 2015; 22:4, 253-261.
Other information if relevant	No trial registration

Methods	
Aim of study	To compare the clinical, functional, and psychosocial effects of upper extremity aerobic exercise with conventional physiotherapy in patients with complex regional pain syndrome (CPRS) type I following stroke.
Design	Single -blind randomized clinical trial

Participants	
Population from which participants are drawn	Hemiplegic patients were recruited who were admitted for an comprehensive subacute inpatient stroke rehabilitation program from acute care units at Ankara Physical Medicine and Rehabilitation Education and Research Hospital in Turkey from March to September 2009.
Setting (location and type of facility)	hospital
Age	adults 35 to 80 years of age, mean age 66.7 years
Sex	22 men, 18 women, total 40
Total number of participants for whom outcome data were reported	At the primary endpoint of 4 weeks (end of treatment), 40 reported outcome data and completed follow-up.
Inclusion criteria	1) Diagnosis with hemiplegia associated with a cerebrovascular event that took place 1-6 months prior to the study 2) Diagnosis of CRPS on the hemiplegic side. 3) 35 to 80 years of age
Exclusion criteria	1) uncontrolled hypertension 2) uncontrolled ischemic heart disease 3) cognitive impairment 4) unwillingness to take part in the study 5) aortic stenosis 6) history of hand surgery 7) aphasia, 8) serious mental disorder, 9) a disease that could hinder the aerobic exercise program to be carried out with upper-arm ergometry such as fracture, surgery to the extremity, serious restriction of joint motion, serious cardiovascular disease or pressure sores, 10) a history of fracture accounting for CRPS, 11) those with whom no cooperation could be established, 12) those without sitting balance for 20 minutes.

Other information if relevant	There were no significant differences between groups in participants' baseline sociodemographic or clinical characteristics, outcome measures or duration of illness. The mean duration of illness was 75.30 days in the exercise group and 81.40 days in the control group.

Intervention Groups

Group 1	
Group name	Aerobic exercise group
Number in group	20 at baseline
Description of intervention	The aerobic exercise program consisted of using an arm crank ergometer, also known as cycling with the arms. The exercise group exercised aerobically using the Monark arm crank 5 days a week, 30 minutes a day, for a period of 4 weeks. This ergometry device has a 35-cm diameter, adjustable resistance as well as timing, and the ability to be used as an arm cycle by both arms reciprocally. Unclear if just the hemiplegic arm or both arms were exercised.
Duration of treatment period	4 weeks of exercise 5 days a week, 30 minutes a day.
Co-interventions if reported	The conventional standardized **CPRS type I physiotherapy program** included TENS on the shoulder-hand region for 20 min/day, cold-pack for 20 minutes/day, retrograde massage, and contrast baths. The **medical treatment** involved NSAID medication, diclofenac Na twice a day, and paracetamol 4 times a day. The **comprehensive stroke physiotherapy program** consisted of therapeutic exercises, neurophysiological exercises, postural exercises, balance and coordination exercises, and exercises of activities of daily living.
Additional information if relevant	No information was provided on the frequency and the daily time spent for either the standard CPRS or stroke physiotherapy programs.

Group 2	
Group name	Physiotherapy group (control)
Number in group	20 at baseline
Description of intervention	This group also received the same conventional standardized **CPRS type I physiotherapy program** which included TENS on the shoulder-hand region for 20 min/day, cold-pack for 20 minutes/day, retrograde massage, and contrast baths.
Duration of treatment period	4 weeks
Co-interventions if reported	This group also received the same **medical treatment** involving NSAID medication, diclofenac Na twice a day, and paracetamol 4 times a day. The **comprehensive stroke physiotherapy program** was also the same and consisted of therapeutic exercises, neurophysiological exercises, postural exercises, balance and coordination exercises, and exercises of activities of daily living.
Additional information if relevant	No information was provided on the frequency and the daily time spent for either the standard CPRS or stroke physiotherapy programs.

Primary outcome	
Outcome name and criteria for definition	The primary outcome measures were improvement in pain scores, and CRPS clinic determinants including hyperesthesia, allodynia, pain on movements, edema in the hand, and range of motion of shoulder and wrist. Severity of pain was assessed on a 10 point visual analog scale for the shoulder and hand as day pain, night pain, and pain upon movement.
Time points measured and/or reported	At baseline, and at 4 weeks right after the last treatment by a blinded assessor.
Differences between groups	No statistically significant differences were found between the exercise group and the control group for hyperesthesia (P=0.464), allodynia (P=1.000), or hand edema (P=0.066). The exercise group was found to exhibit significantly less shoulder and hand pain upon movement (P=0.012, and P=0.001, respectively) compared to the control group. Improvement in the pain scores of the exercise group compared to the control group were found to be statistically significant for shoulder region day pain (P=0.027), hand day pain (P=0.007), and hand pain upon movement (P=0.013). There were no statistically significant differences in the improvement of the pain scores between the 2 groups for shoulder region night pain (P=0.776), shoulder pain upon movement (P=0.073), and hand night pain (P=0.165). Results for range of motion of the shoulder and wrist were not reported.
Additional information if relevant	Clinical adverse effects were not reported. Patients lost to follow-up were not reported.

Secondary outcomes	
Outcome name and criteria for definition	The secondary outcome measures were: the functional independence measure (FIM), Nottingham Health Profile (NHP), and the Beck Depression Scale scores.
Time points measured	At baseline, and at 4 weeks right after the last treatment by a blinded assessor.
Differences between groups	When the post-treatment FIM sub-scores for motor and cognitive were compared, there was a statistically significant difference between the groups (P=0.001 and P=0.006, respectively). The exercise group had higher FIM motor and cognitive sub-scores compared to the control group. For the Nottingham Health Profiles, the exercise group exhibited significantly less pain and fatigue after treatment (P=0.001 and P=0.000, respectively) than the control group. No statistically significant difference was found between the groups for all other NHP sub-categories including functioning (P=0.154), sleep (P=0.217), social isolation (P=0.147) and emotion (P=0.192). When the groups were compared in terms of Beck Depression Scale scores, there was a statistically significant difference between the treatment groups and the exercise group was less depressed when compared to the control group (P=0.005).
Additional information if relevant	

Conclusions	
Key Conclusions Of Study Authors	- This RCT found that the exercise group had better post treatment results than the control group in terms of hyperalgesia, metacarpophalangeal tenderness, tenderness to wrist extension, day pain, and pain upon movement in the shoulder and hand. The exercise group also had higher FIM sub-scores than the control group. When the groups were compared in terms of NHP total and subscores, the exercise group had less pain and fatigue symptoms. According to the Beck Depression Scale, the exercise group showed less depression than the control group. - The lack of any change in sensory changes, hyperpathia, allodynia, or hyperesthesia, which are associated with central sensitization, may suggest that aerobic exercise has no impact on this physiopathologic mechanism. The length of the exercise period may have been too short to be effective on these mechanisms. - The beneficial role of exercise, and specifically incorporating aerobic training, may be to facilitate neuroplasticity and improve motor learning. - The results of this study showed that aerobic exercise alleviates the clinical characteristics of CRPS due to its anti-inflammatory, mechanical, proprioceptive, neuromuscular, and reciprocal qualities. - Aerobic exercises should be prescribed in addition to the conventional treatment of CRPS in order to increase the functional independence of hemiplegic patients with CRPS, to improve their participation in the activities of daily life, to reduce their depressive symptoms, and to improve their general well-being.

Risk of bias assessment		
Domain	Risk of bias Low High Unclear	Comments
Random sequence generation *(selection bias)*	Low	Randomization was done using computer-generated numbers and the treatment group was assigned by the system.
Allocation concealment *(selection bias)*	Unclear	A second researcher proceeded with allocation.
Blinding of participants and personnel *(performance bias)*	High	Because of the nature of the interventions, it was not possible to blind participants or treatment provider.The lack of blinding does not prejudice the conclusions.
Blinding of outcome assessment *(detection bias)*	Low	Assessors blinded to group allocation obtained all outcome measures.

Incomplete outcome data *(attrition bias)*	High	Loss to follow up was not mentioned.
Selective outcome reporting? *(reporting bias)*	High	The trial was not registered with clinicaltrials.gov. The authors failed to report the results of one listed primary outcome, and instead reported outcomes that were not defined as primary or secondary outcomes. The authors also reported the subscores of various scales instead of the total score, presumably to highlight the positive results.
Other bias		

Sponsorship if reported		
Study funding sources if reported	No funding received.	
Possible conflicts of interest for study authors	The authors have no conflicts of interest to declare.	
Notes:		

Comments by DOWC staff

- There were so many primary outcomes for the effect of aerobic exercise on CRPS, some positive and some negative. Without a designation of a primary outcome, it is impossible to determine if one intervention is better than the other. Therefore, no conclusions can be drawn.

- Primary and secondary outcomes were unclearly defined. The authors failed to report the results of 2 listed primary outcomes, range of motion of the shoulder and the wrist, and instead reported the results of many outcomes that were not defined as primary or secondary outcomes. The primary and secondary outcomes listed in the abstract and the text were conflicting, adding even more uncertainty to the numerous outcomes. The authors also reported the subscores of various scales instead of the total score, presumably to highlight the positive results. Furthermore, this trial was not registered with clinicaltrials.gov. This outcome sprawl leads one to be highly suspicious of selective outcome reporting.

- The quality of this study is very poor and does not meet the criteria for our standards for evidence. This RCT was poorly written with many typographical errors, and the results were poorly reported and unorganized. Many results were not reported in tables which would have made it easier for the reader to understand the results.

- Sample size calculations were not described. The underpowered sample size makes it impossible to declare that there is no difference between the interventions and one also cannot rule out that there is a difference between groups. This is an inconclusive small study.

- The interventions were inadequately described. For the aerobic exercise intervention, the authors failed to mention if one or both arms were exercised using the ergometer. No information was provided on the frequency and the daily time spent for either the standard CPRS or stroke physiotherapy programs. No description was given for the exercises included in the stroke physiotherapy program.

Comments by DOWC staff

- Many CRPS clinical signs and symptoms were assessed as outcome measures. No descriptions were provided of how such symptoms as hyperalgesia, hyperesthesia, allodynia, hand edema, etc. were measured.

- There is a major risk of bias imposed by the design of the study in that the groups were unbalanced in terms of time and attention of each intervention. The exercise group received added attention 5 days a week in the rehab unit performing their aerobic exercises compared to the control group resulting in a potential risk of attention bias. These non-specific effects of added provider attention in the exercise group could have influenced the results in favor of the exercise group that would overestimate the treatment effect sizes.

- This RCT provided unacceptable reporting of data and results. No baseline shoulder and wrist mean pain scores for each group were reported, so it is unknown how many VAS pain points each group improved. One cannot determine if the statistically significant improvements in pain scores were clinically meaningful without knowing the baseline scores. No mean differences or standardized mean differences are provided for the data. All results were merely reported as P values, so effect sizes for outcomes cannot be calculated.

- A statistically significant difference at baseline (pretreatment) was found between the groups in terms of day pain in the hand region. However, which group had more baseline hand daytime pain was never stated. The post-treatment results for this outcome should not even be reported unless statistical adjustments for this baseline imbalance are implemented. The groups are not comparable on this outcome measure.

- This study provided no long-term follow-up beyond the end of treatment. Long-term outcomes were not assessed, and it is not known whether the differences observed at post-treatment can be maintained over a long time period.

- Other limitations of the study include a short treatment period (4 weeks),participants were recruited from a single hospital which may decrease the generalization of the results, no reporting of adverse effects, and no reporting of drop-outs.

Assessment by DOWC staff	
Overall assessment as suitability of evidence for the guideline ☐ High quality ☐ Adequate ☒ Inadequate	This inadequate quality study provides no evidence that a 4-week upper-extremity aerobic exercise program is more effective in treating CRPS symptoms than a standard CRPS and stroke physiotherapy program immediately after the end of the interventions in people with CRPS.
If inadequate, main reasons for recommending that the article not be cited as evidence	Please see DOWC comments above.

Additional references if relevant