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The Role of Exercise in the Alleviation of Neuropathic Pain Following Traumatic Spinal Cord Injuries: A Systematic Review and Meta-analysis

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Objective: The objective of this systematic review and meta-analysis was to assess the efficacy of exercise in neuropathic pain following traumatic spinal cord injuries.
Methods: The search was conducted in MEDLINE, Embase, Scopus, and Web of Science by the end of 2022. Two independent researchers included the articles based on the inclusion and exclusion criteria. A standardized mean difference was calculated for each data and they were pooled to calculate an overall effect size. To assess the heterogeneity between studies, I^2 and chi-square tests were utilized. In the case of heterogeneity, meta-regression was performed to identify the potential source.
Results: Fifteen preclinical studies were included. Meta-analysis demonstrated that exercise significantly improves mechanical allodynia (standardized mean difference [SMD], -1.59; 95% confidence interval [CI], -2.16 to -1.02; $p < 0.001$; $I^2 = 90.37\%$), thermal hyperalgesia (SMD, 1.95; 95% CI, 0.96–2.94; $p < 0.001$), and cold allodynia (SMD, -2.92; 95% CI, -4.4 to -1.43; $p < 0.001$). The improvement in mechanical allodynia is significantly more in animals with a compression model of SCI (meta-regression coefficient, -1.33; 95% CI, -1.84 to -0.57; $p < 0.001$) and in mild SCI ($p < 0.001$). Additionally, the improvement was more prominent if the training was started 7 to 8 days postinjury (coefficient, -2.54; 95% CI, -3.85 to -1.23; $p < 0.001$) and was continued every day (coefficient, -1.99; 95% CI, -3.07 to -0.9; $p < 0.001$). Likewise, voluntary exercise demonstrated a significantly more effect size (coefficient, -1.45; 95% CI, -2.67 to -0.23; $p = 0.02$).
Conclusion: Exercise is effective in the amelioration of neuropathic pain. This effect in mechanical allodynia is more prominent if voluntary, continuous training is initiated in the subacute phase of mild SCI.

Keywords: Exercise therapy, Neuropathic pain, Allodynia

INTRODUCTION

Injuries or functional disorders of the nervous system can lead to neuropathic pain, causing a persistent hypersensitivity to innocuous stimuli (allodynia) or an exaggerated response to nociceptive stimuli (hyperalgesia). Depending on the site of injury, neuropathic pain can have a central or a peripheral origin.[1] Spinal cord injury (SCI) is a pathological condition in which cascades of inflammatory and immunologic responses lead to improper neuroregeneration in the central nervous system (CNS) and cause subsequent sensorimotor deficits.[2] Patients with SCI commonly suffer from debilitating chronic pain that can range in severity. The overall prevalence of chronic pain is estimated to be around 68% in SCI patients, immensely affecting the patient's quality of life and psychological well-being.[3] Chronic pain is hard to treat, and management is generally limited to pharmacological treatments and lifestyle modifications for temporary relief.[4,5]

Long-term analgesics use is common in patients with chronic pain, resulting in dependence and tolerance over time.[6] Accordingly, researchers have focused on alternative treatment strategies that could be more effective in this setting. For instance, novel molecular therapies such as gene therapy and the use of viral vectors for the exclusive delivery of biological analgesic molecules have been developed recently.[7,8] Recent studies have shown that nonpharmacological approaches such as dermal skin stimulation, intracranial magnetic stimulation, acupuncture, and exercise therapy are also reasonably effective in the management of neuropathic pain.[9-11]

Physical exercise is an essential part of a healthy lifestyle and is known to have a multitude of benefits for the body. Exercise improves cardiovascular health, enhances muscle strength and endurance, and reduces the risk of various chronic diseases.[12-14] Additionally, recent studies have shown that exercise can also benefit individuals who suffer from neuropathic pain. Exercise can help alleviate pain by increasing the blood flow and oxygen supply to the injured tissues, reducing inflammation and hence improving neuronal function.[15,16] Moreover, the release of endorphins during physical exercise, reduces anxiety, improves patients' mood, and ultimately contributes to the amelioration of pain.[17-19] Studies have demonstrated a variety of exercise techniques that can be used to alleviate neuropathic pain, including aerobic exercises such as walking, jogging, cycling, or swimming, strength training, and stretching exercises.[20,21]

Clinical studies have shown that even light exercise can alleviate pain in conditions such as cancer, musculoskeletal disorders, diabetes, and SCI.[22-25] Despite these findings, there is still a lack of a comprehensive consensus on the role of different exercise protocols in the treatment of neuropathic pain following SCI. Therefore, this systematic review and meta-analysis were conducted to evaluate the efficacy of active exercise in the amelioration of neuropathic pain following traumatic SCI.

MATERIALS AND METHODS

1. Study Design

The objective of this systematic review and meta-analysis was to assess the efficacy of exercise as a therapeutic intervention for neuropathic pain following traumatic SCI. The present study employed 3 strategies for selecting keywords, including the use of MeSH (in the MEDLINE database) and Emtree (in the Embase database) to find related entries, consultation with experts in the field, and a review of the related articles. Based on the selected keywords, an exhaustive search was conducted in the electronic databases of MEDLINE, Embase, Scopus, and Web of Science by the end of 2022 to identify relevant articles. Search strategies were based on keywords related to exercise, SCI, and pain (Supplementary Material 1).

2. Inclusion Criteria

The definition of PICO was as follows: The population (P) of the included articles were humans or animals (rats or mice) with compression, transection, hemisection, or contusion models of SCI. The intervention (I) was the use of any active exercise technique to alleviate neuropathic pain. The comparison (C) was made with a control group that did not receive the intervention or received standard treatment. The outcomes (O) were the reported rating scales of pain perception in humans and allodynia and hyperalgesia in animals. Accordingly, we excluded studies that did not execute an active exercise program as the intervention, incorporated only assisted or combinative exercise programs, case reports, case series, studies without a control group, human studies that were not designed as randomized clinical trials, pre- posttest studies, studies without an SCI model, studies on transgenic animals, protocols, studies not reporting a desired outcome or lacking the sufficient data, studies that evaluated nonneuropathic pain, follow-up studies, and reviews.

3. Data Gathering

The results of the systematic search in electronic databases were collected in the 20th version of the Endnote program. In the initial screening process, 2 independent researchers assessed the titles and abstracts of the obtained articles and selected the potentially relevant studies. Then, the full text of the selected articles was reviewed, the inclusion and exclusion criteria were applied, and articles meeting the criteria were included. A search in the grey literature (Google, Google Scholar, and the thesis section of the ProQuest database) was conducted to avoid any

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missing articles. Data were summarized in a checklist based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[26] The obtained data included information regarding the study design, the sample size and characteristics, the SCI injury model and severity, the interval from SCI to the initiation of exercise, the exercise protocol, the interval to outcome assessment, and the outcome measurement test. If multiple articles were based on the same data, we included the article with the largest sample size or the longest follow-up interval. For data that were not presented in the article, we contacted the corresponding author. For articles in languages other than English, the data were extracted with the help of a translator fluent in both languages. Any disagreements were resolved through discussions with the third reviewer.

4. Quality Control and Certainty of Evidence

The risk of bias in animal studies was evaluated using SYRCLE's risk of bias assessment tool[27] and a traffic light plot with a summary figure was created using the Robvis visualization tool[28] (Supplementary Material 2). The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was used to evaluate the certainty of evidence[29] (Supplementary Material 3). In the case of a disagreement, the conflict was resolved through discussions with a third researcher.

5. Statistical Analyses

The statistical analyses were conducted using Stata 17.0 (StataCorp LLC, College Station, TX, USA). The included studies were classified and summarized according to the classification of the reported neuropathic pain. A standardized mean difference (SMD) with a 95% confidence interval (95% CI) was calculated for each sample and they were pooled to calculate an overall effect size. It should be noted that meta-analysis was only performed if data were reported by at least 3 separate analyses. If a study used a scale in which a higher efficacy was observed with a lower score on the index scale, the absolute SMD value was inserted into the analysis. In this study, a random or fixed effect model was chosen based on the presence or absence of heterogeneity. To assess the heterogeneity between studies, I^2 and chi-square tests were utilized. In the case of heterogeneity, subgroup analyses, and meta-regression were performed to identify the potential source. Subgroup analyses were performed on different animal species, levels of SCI, models of SCI, severities of SCI, SCI to exercise timing, the duration of exercise protocol, number of days in the week that the animals were trained, and whether exercise was conducted voluntarily. Sensitivity analyses were performed to evaluate the robustness of the findings. Additionally, publication bias was reported with a funnel plot using the modified Egger's test proposed by Doleman et al.[30]

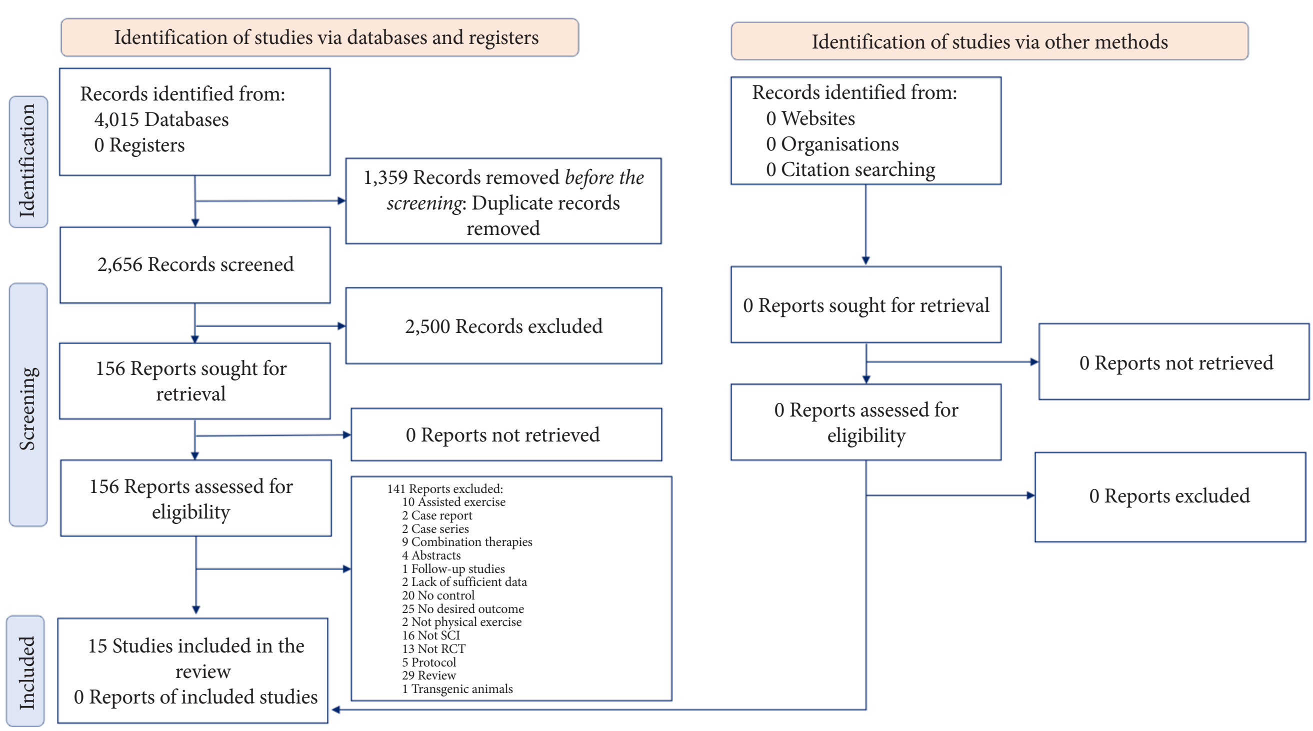

Fig. 1. PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow diagram of the screening process.

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6. Ethic's approval

This research has been approved by Tehran University of Medical Sciences and Health Services and Iran Ministry of Health and Medical Education.

RESULTS

1. Preclinical Studies

1) Characteristics of the included studies

The systematic search resulted in 2,656 nonduplicate records, of which the full text of 167 was reviewed in detail. Finally, 15 animal interventional studies met the inclusion criteria (Fig. 1).[31-45] Notably, the search in human studies resulted in no eligible articles. In the included preclinical studies, 11 wielded strains of rats and 4 wielded mice. Eleven studies used the contusion model of SCI (9 moderate and 2 severe) and 4 used the compression model (1 mild and 3 moderate). The time interval between the induction of SCI and the initiation of exercise varied from 1 to 42 days postinjury; in 2 studies exercise was initiated in the first 5 days postinjury, 4 initiated the exercise protocol in 7 to 8 days postinjury, and in 6 studies exercise was initiated after the first 14 days. In 3 articles the interval from SCI to training was a combination of the aforementioned timelines. Twelve studies used a quadrupedal training program (running wheel, treadmill, exercise ball), 1 study used a bipedal gait training exercise and 2 studies used both quadrupedal and bipedal training. Apart from 1 study that continued the intervention for 2 years, the duration of exercise varied between 2 to 12 weeks. All exercise protocols were carried out 5–7 days per week. In 3 studies, animals were allowed to move freely during the exercise protocol, while in others each session lasted between 20 to 58 minutes. The last follow-up was immediately postintervention in all articles, except for one, that reported the outcome in 1 week and 2 weeks postintervention. All articles evaluated mechanical allodynia, 10 evaluated thermal hyperalgesia, and 4 evaluated cold allodynia. The results were separately reported for the contralateral or ipsilateral side of the injury in 3 articles (Table 1).

2. Meta-analysis

1) The effect of exercise on mechanical allodynia

Categorizing the effect of exercise on mechanical allodynia into ipsilateral, contralateral, and bilateral mechanical allodynia, 31 separate analyses were included in this meta-analysis. Pooled data analysis demonstrated that exercise significantly improves bilateral mechanical allodynia (SMD, -1.43; 95% CI, -2.17 to -0.7; $p < 0.001$; $I^2 = 89.86\%$). Moreover, pooled data analyses in the contralateral side exhibited meaningful improvement in mechanical allodynia following exercise (SMD, -1.9; 95% CI, -3.42 to -0.39; $p = 0.014$; $I^2 = 92.53\%$). The results were similar on the ipsilateral side (SMD, -1.76; 95% CI, -3.03 to -0.49; $p = 0.007$; $I^2 = 91.39\%$). In total, exercise therapy significantly improves mechanical allodynia in animals (SMD, -1.59; 95% CI, -2.16 to -1.02; $p < 0.001$; $I^2 = 90.37\%$) (Fig. 2).

2) Subgroup analyses for mechanical allodynia

Subgroup analyses and meta-regressions were performed to detect sources of heterogeneity. The improvement in mechanical allodynia was significant in almost all subgroups, except for animals with thoracolumbar SCI, which was investigated only in 3 distinct experiments. Performing a subgroup analysis was not methodologically feasible due to the low number of included experiments for animals that were trained 6 days per week. In the next step, meta-regressions demonstrated that the extent of improvement is significantly more in animals with a compression model of SCI (meta-regression coefficient, -1.33; 95% CI, -1.84 to -0.57; $p < 0.001$), while less improvement was evident in both moderate SCI (meta-regression coefficient, 2.95; 95% CI, 1.61–4.29; $p < 0.001$) and severe SCI (meta-regression coefficient, 3.67; 95% CI, 2.24–5.11; $p < 0.001$). Moreover, meta-regression showed a meaningful relationship between the effect size of improvement in mechanical allodynia and the SCI to training interval of 7 to 8 days (coefficient, -2.54; 95% CI, -3.85 to -1.23; $p < 0.001$) and also with animals that were trained every day (coefficient, -1.99; 95% CI, -3.07 to -0.9; $p < 0.001$). The improvement in mechanical allodynia was significantly more in animals that were in a voluntary exercise setting (meta-regression coefficient, -1.45; 95% CI, -2.67 to -0.23; $p = 0.02$) (Table 2). Determining the level of evidence in the pain-ameliorating effects of exercise on mechanical allodynia revealed a moderate level of evidence using the GRADE framework (Supplementary Material 3).

3) The effect of exercise on thermal hyperalgesia

In thermal hyperalgesia, 17 separate analyses were included. Pooled data analysis showed a significant improvement of thermal hyperalgesia reported on both sides following exercise (SMD, 1.95; 95% CI, 0.96–2.94; $p < 0.001$; $I^2 = 91.37\%$). Meta-analysis also demonstrated a meaningful improvement of thermal hyperalgesia on the contralateral (SMD, 3.03; 95% CI, 2.3–3.77; $p < 0.001$; $I^2 = 0\%$) and ipsilateral side (SMD, 2.38; 95% CI, 1.73–3.03; $p < 0.001$; $I^2 = 0\%$). In total, exercise therapy had a mean-

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Table 1. Characteristics of the included preclinical studies

Study	Year	Animal	Species	Sex	Age (day)	Weight (g)	Sample size	SCI level	SCI model	SCI severity	Antibiotic	Injury to training	Exercise	Exercise protocol	Trained limbs	F/U (day)	Assessed limb
Brown et al.[31]	2011	Rat	SD	M	90–110	350–400	18	Thoracic	Contusion	Moderate	Penicillin G	1 & 8 Days	Exercise ball	Free, every day, 14 days	All	7 & 14	Both hindpaws
Cheng et al.[33]	2022	Rat	SD	F	Adult	250–300	84	Cervical	Compression	Mild	Ampicillin	7 Days	Running wheel	Free, every day, 21 days	All	Immediate	Contra/ipsilateral hindpaws
Cheng et al.[32]	2023	Mice	C57BL/6	F	56–70	19–20	95	Thoracic	Contusion	Moderate	Ampicillin	7 Days	Running wheel	Free, every day, 21 days	All	Immediate	Both hindpaws
Chhaya et al.[34]	2019	Rat	SD	F	Adult	225–250	23	Cervical	Contusion	Moderate	Cefazolin	5 Days	Running wheel	20 min, 5 days a week, 28 days	All	Immediate	Ipsilateral forepaw
Detloff et al.[35]	2016	Rat	SD	F	Adult	225–250	162	Cervical	Contusion	Severe	Ampicillin Cefazolin	14 & 28 Days	Running wheel	20 min, 5 days a week, 35 days	All	Immediate	Contra/ipsilateral hindpaws
Dugan and Sagen.[37]	2015	Rat	SD	M	N/R	150–200	72	Thoracic	Compression	Moderate	N/R	5 & 21 Days	Treadmill	40 min, 5 days a week, 84 days	All	Immediate	Both hindpaws
Dugan et al.[36]	2020	Rat	SD	M	Adult	250–300	48	Thoracic	Compression	Moderate	N/R	7 & 35 Days	Treadmill	40 min, 5 days a week, 70 & 77 days	All	Immediate	Both hindpaws
Dugan et al.[38]	2021	Rat	SD	M	Adult	250–300	24	Thoracic	Compression	Moderate	N/R	28 Days	Treadmill	40 min, 5 days a week, 700 days	All	Immediate	Both hindpaws
Hutchinson et al.[39]	2004	Rat	SD	F	Adult	250–300	47	Thoracic	Contusion	Moderate	Gentocin	4 Days	Stand, swim, treadmill	20 min, 5 days a week, 49 days	All & hindpaws	Immediate	Both hindpaws
Li et al.[40]	2020	Rat	SD	F	Adult	250–300	64	Thoracic	Contusion	Moderate	N/R	8 Days	Treadmill	40 min, 5 days a week, 28 days	All	Immediate	Both hindpaws
Nees et al.[41]	2016	Mice	C57BL/6	F	56–70	20–25	41	Thoracic	Contusion	Moderate	Ampicillin	7 Days	Treadmill	30 min, 5 days a week, 25 days	All	Immediate	Both hindpaws
Sliwinski et al.[42]	2018	Mice	C57BL/6	F	56–84	20–25	53	Thoracic	Contusion	Moderate	Ampicillin	42 Days	Treadmill	30 min, 5 days a week, 25 days	All	Immediate	Both hindpaws
Tashiro et al.[43]	2018	Mice	C57BL/6	F	56–63	18–22	55	Thoracic	Contusion	Severe	Ampicillin	42 Days	Bipedal gait training	20 min, 5 days a week, 42 days	Hindpaws	Immediate	Both hindpaws
Ward et al.[45]	2014	Rat	Wistar	M	60–70	160–180	16	Thoracic	Contusion	Moderate	Penicillin/Gentamicin	14 Days	Quadrupedal gait training	58 min, every day, 84 days	All	Immediate	Both hindpaws
Ward et al.[44]	2016	Rat	Wistar	M	60–70	300	38	Thoracic	Contusion	Moderate	Penicillin/Gentamicin	14 Days	Treadmill	30 min, 6 days a week, 42 days	All & forepaws	Immediate	Bilateral trunk

SCI, spinal cord injury; F/U, follow-up; SD, Sprague-Dawley; N/R, not reported.

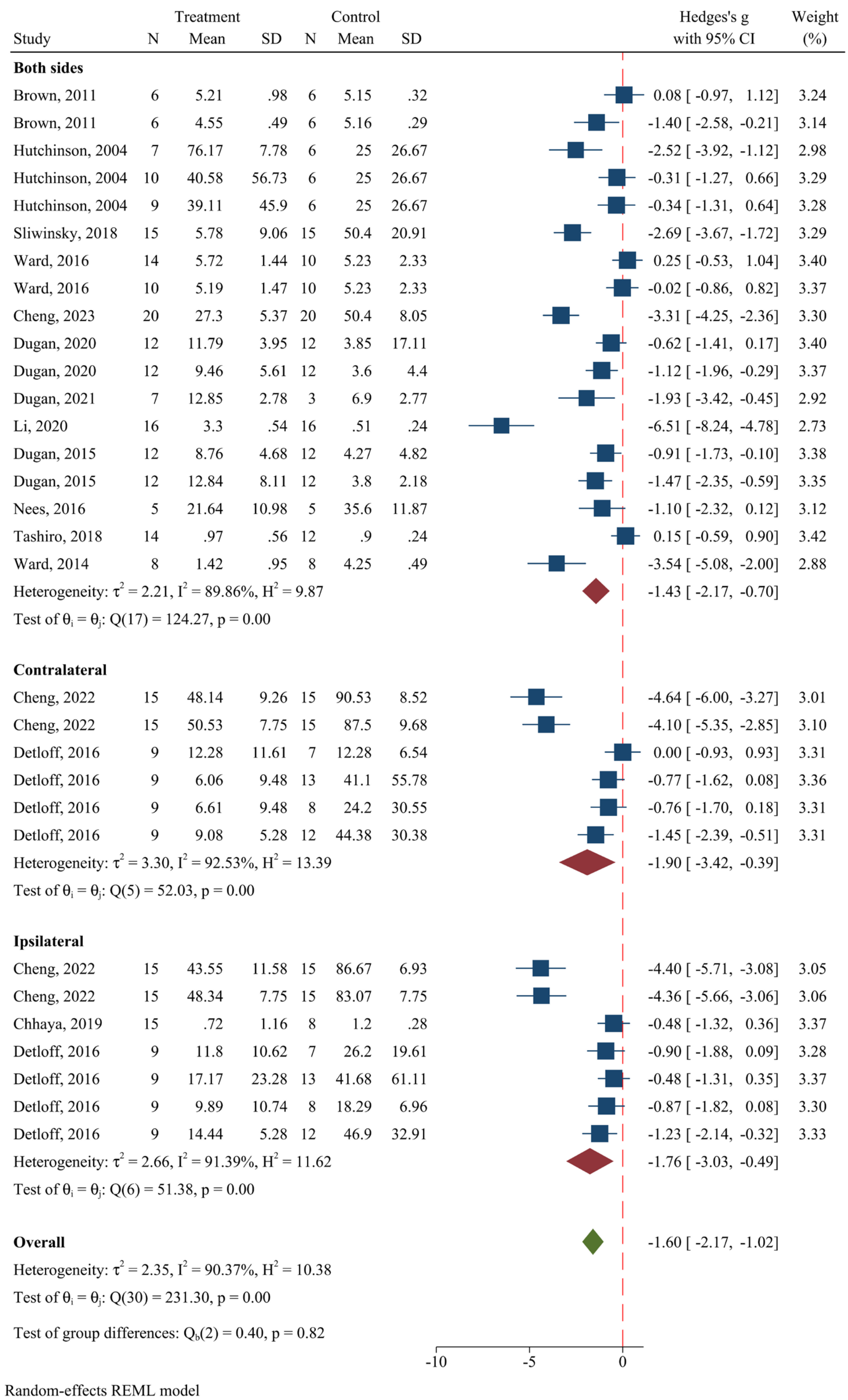

Fig. 2. The forest plot for the efficacy of exercise in mechanical allodynia. SD, standard deviation; CI, confidence interval; REML, random-effects meta-analysis.

ingful effect on the amelioration of thermal hyperalgesia in animals (SMD, 2.38; 95% CI, 1.73–3.03; $p < 0.001$; $I^2 = 88.72\%$) (Fig. 3).

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Table 2. Subgroup analyses and meta-regressions for different variables in mechanical allodynia and thermal hyperalgesia

Variable	No. of experiments	Subgroup analysis			Meta-regression	
		SMD (95% CI)	p-value	I^2 (p-value)	Coefficient (95% CI)	p-value
Mechanical allodynia						
Animal						
Mice	4	-1.73 (-3.30 to -0.16)	0.031	90.78 (< 0.001)	Reference	
Rat	27	-1.58 (-2.21 to -0.95)	< 0.001	90.64 (< 0.001)	0.151 (-1.57 to 1.87)	0.864
Level of SCI						
Cervical	13	-1.82 (-2.75 to -0.89)	< 0.001	91.28 (< 0.001)	Reference	
Thoracic	15	-1.57 (-2.44 to -0.70)	< 0.001	91.73 (< 0.001)	0.24 (-0.98 to 1.48)	0.691
Thoracolumbar	3	-0.77 (-1.69 to 0.16)	0.103	48.43 (0.145)	1.01 (-1.08 to 3.11)	0.343
Model of SCI						
Contusion	22	-1.20 (-1.80 to -0.60)	< 0.001	87.99 (< 0.001)	Reference	
Compression	9	-2.55 (-3.67 to -1.43)	< 0.001	90.32 (< 0.001)	-1.33 (-2.52 to -0.14)	0.02
Severity of SCI						
Mild	4	-4.36 (-5.01 to -3.71)	< 0.001	0.00 (0.956)	Reference	
Moderate	18	-1.47 (-2.18 to -0.75)	< 0.001	89.17 (< 0.001)	2.95 (1.6–4.29)	< 0.001
Severe	9	-0.67 (-1.03 to -0.31)	< 0.001	31.97 (0.179)	3.67 (2.24–5.11)	< 0.001
SCI to exercise						
≤ 5 Days	6	-0.64 (-1.18 to -0.11)	0.019	44.32 (0.073)	Reference	
7–8 Days	9	-3.32 (-4.58 to -2.05)	< 0.001	90.37 (< 0.001)	-2.54 (-3.85 to -1.23)	< 0.001
≥ 14 Days	16	-0.96 (-1.42 to -0.51)	< 0.001	74.08 (< 0.001)	-0.29 (-1.45 to 0.87)	0.624
Exercise duration						
No. of days	N/A	N/A	N/A	N/A	-0.0002 (-0.007 to 0.006)	0.943
No. of days in week						
5 Days	21	-1.15 (-1.63 to -0.66)	< 0.001	81.55 (< 0.001)	Reference	
6 Days	2	Insufficient data			Insufficient data	
7 Days	8	-3.18 (-4.37 to -1.99)	< 0.001	86.88 (< 0.001)	-1.99 (-3.07 to -0.90)	< 0.001
Exercise type						
Forced	23	-1.19 (-1.68 to -0.69)	< 0.001	83.78 (< 0.001)	Reference	
Voluntary	8	-2.71 (-4.14 to -1.28)	< 0.001	92.61 (< 0.001)	-1.45 (-2.67 to -0.23)	0.02
Thermal hyperalgesia						
Animal						
Mice	3	0.69 (-0.33 to 1.72)	0.186	75.18 (0.01)	Reference	
Rat	14	2.42 (1.61–3.23)	< 0.001	87.15 (< 0.001)	1.7 (-0.035 to 3.44)	0.055
Level of SCI						
Cervical	4	2.67 (2.18–3.16)	< 0.001	0.00 (0.545)	Reference	
Thoracic	12	2.05 (0.98–3.12)	< 0.001	92.13 (< 0.001)	-0.7 (-2.5 to 1.1)	0.446
Thoracolumbar		Insufficient data			Insufficient data	
Model of SCI						
Contusion	8	1.84 (0.21–3.48)	0.027	94.90 (< 0.001)	Reference	
Compression	9	2.40 (1.86–2.93)	< 0.001	58.16 (0.014)	0.71 (-0.76 to 2.18)	0.343

(*Continued*)

Table 2. Subgroup analyses and meta-regressions for different variables in mechanical allodynia and thermal hyperalgesia (Continued)

Variable	No. of experiments	Subgroup analysis			Meta-regression	
		SMD (95% CI)	p-value	I^2 (p-value)	Coefficient (95% CI)	p-value
Severity of SCI						
Mild	4	2.67 (2.18–3.16)	< 0.001	0.00 (0.545)	Reference	
Moderate	12	2.13 (1.13–3.13)	< 0.001	90.15 (< 0.001)	-0.62 (-2.27 to 1.03)	0.461
Severe		Insufficient data			Insufficient data	
SCI to exercise						
≤ 5 Days	4	1.81 (1.15–2.47)	< 0.001	28.42 (0.255)	Reference	
7–8 Days	7	2.90 (1.28–4.52)	< 0.001	93.91 (< 0.001)	1.00 (-0.92 to 2.93)	0.309
≥ 14 Days	6	1.48 (0.39–2.58)	0.008	86.86 (< 0.001)	-0.31 (-2.29 to 1.66)	0.756
Exercise duration						
No. of days			N/A		-0.001 (-0.009 to 0.005)	0.615
No. of days in week						
5 Days	12	2.06 (1.00–3.13)	< 0.001	91.79 (< 0.001)	Reference	
6 Days		Insufficient data			Insufficient data	
7 Days	5	2.29 (1.43–3.16)	< 0.001	74.58 (0.004)	0.27 (-1.40 to 1.95)	0.751
Exercise type		Insufficient data			Insufficient data	

SMD, standardize mean difference; CI, confidence interval; SCI, spinal cord injury; NA, not applicable since the data was included as continuous variable in the analysis.

4) Subgroup analyses for thermal hyperalgesia

Subgroup analyses demonstrated that exercise improved thermal hyperalgesia in rats, different levels of SCI, models of SCI, severities of SCI, intervals between SCI to exercise, and different groups of training durations in a week. However, meta-regressions showed that there were no significant differences in the effect sizes of different subgroups (Table 2). The level of evidence was demonstrated moderate using the GRADE framework (Supplementary Material 3).

5) The effect of exercise on cold allodynia

Cold allodynia was reported bilaterally in all included articles. Pooled data analysis on 6 separate analyses from 4 articles revealed that exercise significantly affected the improvement of cold allodynia (SMD, -2.92; 95% CI, -4.4 to -1.43; $p < 0.001$; $I^2 = 87.3\%$) (Fig. 4). The level of evidence was determined as moderate in the pain-ameliorating effect of exercise on cold allodynia (Supplementary Material 3).

6) Sensitivity analyses

We performed sensitivity analyses for mechanical allodynia and thermal hyperalgesia due to the sufficient number of included experiments to evaluate the robustness of our results. The findings of these analyses demonstrated that the efficacy of exercise in the amelioration of mechanical allodynia and thermal hyperalgesia is evident in all different sets of experiments (Supplementary Material 4).

3. Clinical Studies

1) Characteristics of the included studies

Even though our search resulted in no eligible studies on the human population for the aforementioned outcome, we summarized the obtained randomized controlled trials (RCTs) that evaluated the amelioration of chronic pain in SCI patients following active exercise protocols.[21,46-49] In this regard, shoulder pain and generally perceived pain were the 2 reported outcomes and were subsequently included in separate meta-analyses. Two articles evaluated the WUSPI (wheelchair user shoulder pain index), 2 reported the 36-item Short-Form survey (SF-36), and 1 reported both. All articles included chronic SCI patients. Three studies conducted a home-based exercise program whereas 2 articles conducted the exercise protocol in rehabilitation centers. All exercise protocols were for the upper extremities except for 1 study that exercised all limbs. The exercise duration ranged between 6 to 36 weeks, 2 to 4 days a week. Except for 1 article that only included resistance training, others included aerobic, stretching, and resistance training in their exercise protocol (Table 3).

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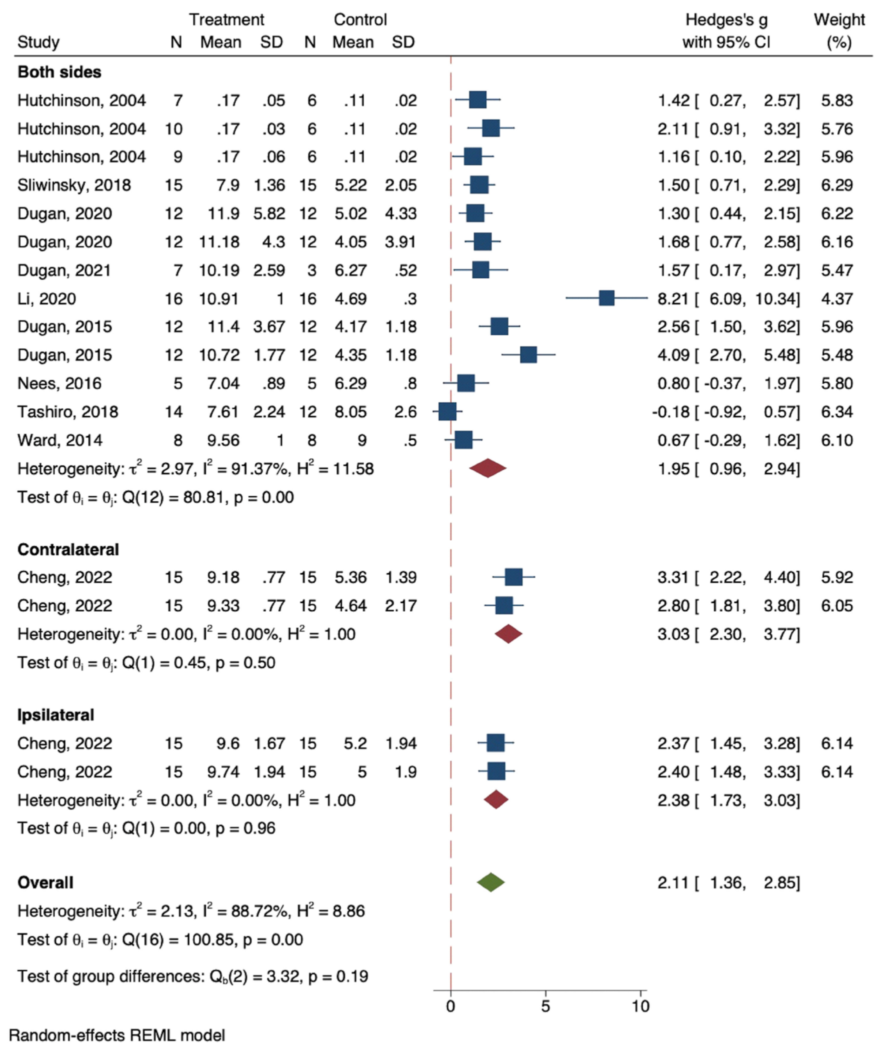

Fig. 3. The forest plot for the efficacy of exercise in thermal hyperalgesia. SD, standard deviation; CI, confidence interval; REML, random-effects meta-analysis.

4. Meta-analysis

1) The effect of active exercise on chronic pain following traumatic SCI

Pooled data analysis on 3 different samples demonstrated that exercise therapy significantly improved the general perception of pain in chronic SCI patients (SMD, -0.76; 95% CI, -1.14 to -0.37; $p < 0.001$; $I^2 = 0\%$). Conversely, the meta-analysis exhibited no significant improvement in shoulder pain following exercise (SMD, -0.43; 95% CI, -1.04 to 0.17; $p = 0.159$) (Fig. 5).

2) Quality control

In the included preclinical studies, all studies adjusted the experiment and the control groups at baseline for confounders. Randomization and its proper concealment were adequately applied. The risk of bias was unclear in the domain of random housing in all included articles. Drop-out animals were not adequately mentioned and imported in analyses of 4 studies (Supplementary Material 2).

In RCTs, the allocation concealment and the blinding of the participants were not adequately addressed in any of the included articles. The blinding of the study team and the outcome assessor were unclear in 3 articles. One article had incomplete outcome data. In total, the risk of bias in all RCTs was considered high (Supplementary Material 5).

3) Publication bias

No publication bias was observed in the articles reporting mechanical allodynia ($p = 0.288$), thermal hyperalgesia ($p = 0.163$), and cold allodynia ($p = 0.686$) (Supplementary Material 6). Due to the low number of included RCTs, publication bias assessment

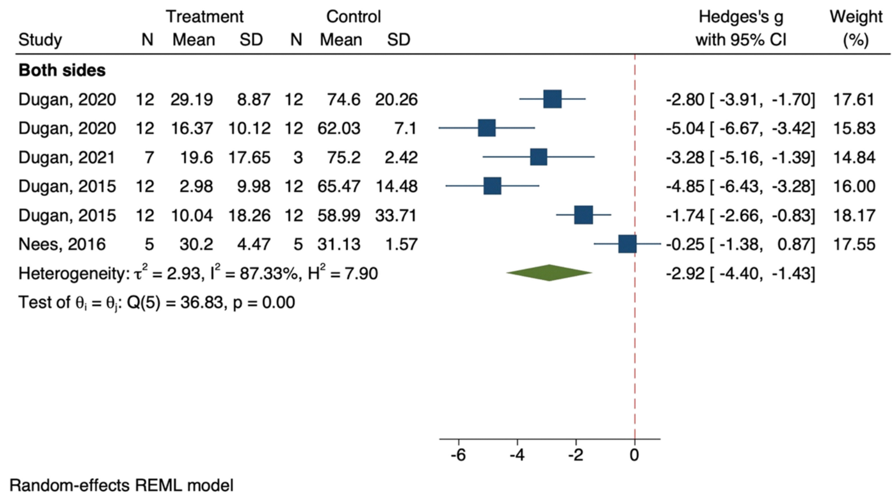

Fig. 4. The forest plot for the efficacy of exercise in cold allodynia. SD, standard deviation; CI, confidence interval; REML, random-effects meta-analysis.

Table 3. Characteristics of the included randomized clinical trials

Study	Year	Sample size	Age (yr)	Sample characteristics	Control characteristics	Injury level	Years post-SCI	Exercise type	Exercised limbs	Exercise protocol	F/U (wk)
Cardenas et al.[46]	2020	32	44.8 ± 12.5	Chronic SCI wheelchair users	Regular activity + education	N/R	19.4 ± 13.5	Home-based	Upper	3 Days in week, 12 weeks	4
Ginis et al.[47]	2003	34	38.6 ± 11.7	Traumatic chronic SCI	Regular activity	N/R	10.4 ± 11.7	Rehabilitation center	All	2 Days in week, 12 weeks	Immediate
Hicks et al.[48]	2003	34	N/R	Traumatic chronic SCI wheelchair users	Regular activity + education	C4–L1	N/R	Rehabilitation center	Upper	2 Days in week, 36 weeks	Immediate
Nightingale et al.[49]	2018	24	47 ± 8	Chronic SCI patients with shoulder pain	Regular activity	< T4	16 ± 11	Home-based	Upper	4 Days in week, 6 weeks	Immediate
Mulroy et al.[21]	2011	80	45 ± 11.2	Chronic SCI wheelchair users	Regular activity	< T2	20 ± 11	Home-based	Upper	3 Days in week, 12 weeks	4

SCI, spinal cord injury; F/U, follow-up; N/R, not reported.

ws not feasible in terms of methodology.

DISCUSSION

The purpose of the present systematic review and meta-analysis was to gather current literature regarding the efficacy of exercise in the amelioration of neuropathic pain following traumatic SCIs. We demonstrated that exercise significantly improves mechanical allodynia, thermal hyperalgesia, and cold allodynia in rodent models of SCI. Meta-regressions showed a significantly more effect size for the amelioration of mechanical allodynia in compression models of SCI and mild SCIs. Likewise, the extent of this improvement was substantially more if the exercise protocol began in the subacute phase[50] of SCI, continued every day, and was voluntary.

The development of neuropathic pain is a consequence of nerve injury, either in the periphery or the CNS.[51] Even though a multitude of factors have been suggested to provoke the pathological pathways that lead to neuropathic pain, the distinct molecular and cellular alterations involved in the process remain understudied.[52,53] The underlying mechanisms of neuropathic pain can be categorized into the alterations of pain threshold in the primary afferent nociceptive neurons, activation of nonnociceptive receptors, changes in neurotransmitter transduction, and rewiring of neurons in the pain perception pathways of the CNS.[54,55]

As the resident immune cells in the CNS and the main modulators of neuroinflammation, microglia play an important role

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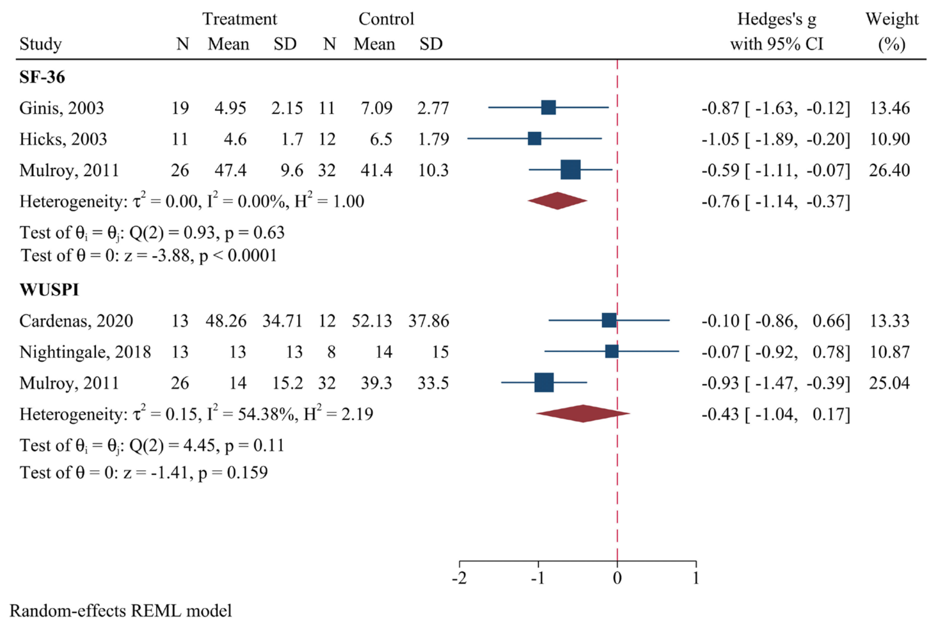

Fig. 5. The forest plot for the efficacy of exercise in the amelioration of chronic pain following traumatic spinal cord injury. SD, standard deviation; CI, confidence interval; SF-36, 36-item Short Form health survey; WUSPI, wheelchair user shoulder pain index; REML, random-effects meta-analysis.

in both central and peripheral mechanisms of mechanical allodynia.[56] Following an injury to the nervous system, microglia undergo activation and morphologic changes, exerting both beneficial and detrimental effects on the tissue healing process. One way the activation of these cells could contribute to the development of neuropathic pain is the activation of the ionotropic adenosine triphosphate receptor P_2X_4 which eventually leads to the release of brain-derived neurotrophic factor (BDNF), altering the pattern of excitability in the sensory and dorsal horn neurons.[57] Physical activity has been shown to exert an anti-inflammatory effect that suppresses microglia activation and thus improves neuro-inflammation.[58] With the role of BNDF being controversial in the pain perception pathways, the relationship between exercise and subsequent alterations in BDNF levels should be addressed in future studies.[59-62]

Furthermore, recent literature argues that high-intensity and interval training programs could promote oxidative stress and neuroinflammation, whereas low- to moderate-intensity and continuous exercises would exert more anti-inflammatory and neuroprotective properties.[63] In rodent models, it was previously reported that forced treadmill exercise contributed more to the production of proinflammatory molecules in comparison with voluntary wheel running.[64] Considering that different exercise programs influence the neuroplasticity of distinctive brain regions,[65-67] the present systematic review along with previous studies exhibited that continuous and voluntary exercise protocols are more beneficial in the amelioration of neuropathic pain.

We demonstrated that exercise—regardless of the timing of commencement after SCI—is effective for the amelioration of mechanical allodynia. However, the extent of this improvement is more if exercise is started in the subacute phase, and similar for both acute and chronic phases. We could explain this by increased neural plasticity involved in the acute and subacute phases of SCI. As reported previously, early therapeutic approaches in the management of SCI lead to better outcomes and fewer postoperative complications, both in clinical and preclinical evidence.[68-71]

Even though we aimed at summarizing the evidence from both animal and human populations, our search resulted in no clinical research that would meet our inclusion criteria. The chronic shoulder pain and generally perceived pain that was evaluated in previous RCTs could have etiologies other than neuropathic pain, and their inclusion is considered an ancillary analysis in this meta-analysis. Evidence with a high risk of bias showed a significant improvement in generally perceived pain in chronic SCI patients following exercise, but no such effect was observed in the amelioration of chronic shoulder pain (Supplementary Material 5).

We considered the level of evidence for our included preclinical articles to be moderate, due to serious risks of bias. Conversely, it is recently argued that the current guidelines for the evaluation of the risk of bias in preclinical studies are not in compliance with the guidelines on how to conduct them; therefore, the risk of bias could be overestimated due to the lack of reporting in some domains of risk of bias assessment, simply because the authors did not document them in their manuscripts.[72] Since our results demonstrated an acceptable efficacy for exercise in the management of neuropathic pain, we prominently recommend further clinical research with robust methodologies in this field. In order to have more reliable findings, it should be emphasized that the blinding of participants and caregivers in studies that involve active physical activity is an important cause for bias; active exercise requires the patient's cooperation with the assessor, and the lack of blinding is inevitable. Therefore, we recommend more attention to proper blinding in future studies.

In addition, our analyses for the detection of publication bias demonstrated no bias. However, in order to address the asymmetry in our funnel plots, it is noteworthy that according to the study by Egger et al.,[73] asymmetry in funnel plots could be due to different reasons: publication bias, selective outcome reporting, poor methodological quality, the presence of substantial heterogeneity, sampling variations, and by chance. Therefore, the observed asymmetry could be due to the aforementioned reasons.

As an inevitable limitation of review articles, it is important to draw attention to the low number of included experiments for some subgroups, and the importance of cautious interpretation of findings. For instance, even though we found a significantly more effect size in compression models of SCIs and in mild SCIs, only 1 article with 4 experiments was included in mild SCI, and 4 articles out of the included 15 executed a compression model of SCI. Notably, all compression SCIs were mild to moderate in severity, and contusion SCIs were all moderate to severe. Nevertheless, sensitivity analyses demonstrated a similar level of difference in the effect sizes of different subgroups, omitting the possible role of the observed heterogeneity in our findings.

At last, we would like to acknowledge that the protocol of this systematic review was not registered on an open-access database. The design and methodology of the present study validate the robustness of our results, but it is important to mention that protocol registration contributes to a better evaluation of outcomes and prevents duplicate efforts.

CONCLUSION

Continuous voluntary exercise initiated in the subacute phase of moderate to severe SCI is strongly associated with the amelioration of neuropathic pain in rodents. Although physical activity improves the general perception of pain in chronic SCI patients, its efficacy in the amelioration of shoulder pain should be further evaluated in further studies.

NOTES

Supplementary Materials: Supplementary Materials 1-6 can be found via https://doi.org/10.14245/ns.2346588.294.

Conflict of Interest: The authors have nothing to disclose.

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Supplementary Material 1. Search strategies

MEDLINE (PubMed)

((“Spinal Cord Injuries”[mesh] or “Spinal Cord Injuries”[tiab] or “Cord Contusions, Spinal”[tiab] or “Spinal Cord Trauma”[tiab] or “Cord Trauma, Spinal”[tiab] or “Cord Traumas, Spinal”[tiab] or “Spinal Cord Traumas”[tiab] or “Trauma, Spinal Cord”[tiab] or “Traumas, Spinal Cord”[tiab] or “Traumas, Spinal Cord”[tiab] or “Injuries, Spinal Cord”[tiab] or “Cord Injuries, Spinal”[tiab] or “Cord Injury, Spinal”[tiab] or “Injury, Spinal Cord”[tiab] or “Spinal Cord Injury”[tiab] or “Spinal Cord Transection”[tiab] or “Cord Transection, Spinal”[tiab] or “Cord Transections, Spinal”[tiab] or “Spinal Cord Transections”[tiab] or “Transection, Spinal Cord”[tiab] or “Transections, Spinal Cord”[tiab] or “Spinal Cord Laceration”[tiab] or “Cord Laceration, Spinal”[tiab] or “Cord Lacerations, Spinal”[tiab] or “Laceration, Spinal Cord”[tiab] or “Lacerations, Spinal Cord”[tiab] or “Spinal Cord Lacerations”[tiab] or “Spinal Cord Contusion”[tiab] or “Contusion, Spinal Cord”[tiab] or “Contusions, Spinal Cord”[tiab] or “Cord Contusion, Spinal”[tiab] or “Spinal Cord Contusions”[tiab] or “Spinal Cord Compromised”[tiab] or “spinal cord lesion”[tiab] or “Quadriplegia”[tiab] or “paraplegia”[tiab] or “tetraplegia”[tiab] or “spinal cord rupture”[tiab] or “cervical spinal cord injury”[tiab])) AND (((“Neuralgia”[Mesh] OR “Pain”[Mesh] OR “Chronic Pain”[Mesh] OR “Chronic Pains”[tiab] OR “Neuropathic pain”[tiab] OR “Neuropathic Pains”[tiab] OR “allodynia”[tiab] OR “hyperalgesia”[tiab] OR “Atypical Neuralgia”[tiab] OR “Atypical Neuralgias”[tiab] OR “hypoalgesia”[tiab] OR “Paroxysmal Nerve Pain”[tiab] OR “Paroxysmal Nerve Pains”[tiab] OR “Nerve Pain”[tiab] OR “Nerve Pains”[tiab])) AND (“Exercise”[mesh] or “Exercise”[tiab] or “Aerobic Exercise”[tiab] or “Exercises”[tiab] or “Exercise, Physical”[tiab] or “Exercises, Physical”[tiab] or “Physical Exercise”[tiab] or “Physical Exercises”[tiab] or “Exercise, Isometric”[tiab] or “Exercises, Isometric”[tiab] or “Isometric Exercises”[tiab] or “Isometric Exercise”[tiab] or “Exercise, Aerobic”[tiab] or “Aerobic Exercises”[tiab] or “Exercises, Aerobic”[tiab] or “Physical”[tiab] or “Circuit Training”[tiab] or “Training, Circuit”[tiab] or “Cool-Down”[tiab] or “Warming-Down”[tiab] or “Warm-Down”[tiab] or “Cooldown”[tiab] or “Warm-Up”[tiab] or “Cooling-Down”[tiab] or “Warmup”[tiab] or “Therapy, Exercise”[tiab] or “Exercise Therapies”[tiab] or “Therapies, Exercise”[tiab] or “Exercise Tests”[tiab] or “Test, Exercise”[tiab] or “Tests, Exercise”[tiab] or “Treadmill Test”[tiab] or “Test, Treadmill”[tiab] or “Tests, Treadmill”[tiab] or “Treadmill Tests”[tiab] or “Exercise Therapies”[tiab] or “Therapies, Exercise”[tiab] or “Sports”[tiab] or “Physiotherapy exercises”[tiab] or “Flexibility Exercises”[tiab] or “Motion Exercises”[tiab] or “Adaptive Aerobics”[tiab] or “Aerobic training”[tiab] or “Voluntary wheel running”[tiab] or “Gait training”[tiab] or “Locomotor training”[tiab] or “Upper extremity training”[tiab] or “Motor Activity”[tiab] or “activity”[tiab])))

Embase

#1 ‘spinal cord injury’/exp OR ‘spinal cord injury’ OR ‘spinal cord contusion’/exp OR ‘spinal cord contusion’ OR ‘spinal cord hemisection’/exp OR ‘spinal cord hemisection’ OR ‘spinal cord transsection’/exp OR ‘spinal cord transsection’ OR ‘cervical spine injury’/exp OR ‘cervical spine injury’ OR ‘spinal compression’:ab,ti OR ‘spinal cord trauma’:ab,ti OR ‘trauma, spinal cord’:ab,ti OR ‘injured spinal cord’:ab,ti OR ‘spinal cord injured’:ab,ti OR ‘spinal cord injuries’:ab,ti OR ‘nerve transection’/exp OR ‘nerve transection’

#2 ‘neuropathic pain’/exp OR ‘chronic pain’/exp OR ‘pain’/exp OR ‘hyperalgesia’/exp OR ‘allodynia’/exp

#3 ‘exercise’/exp OR ‘aerobic exercise’/exp OR ‘isometric exercise’/exp OR ‘cool down’/exp OR ‘warm up’/exp OR ‘kinesiotherapy’/exp OR ‘gait’/exp

#1 AND #2 AND #3

Scopus

#1 (“spinal cord injury”) OR (“Spinal cord injuries”) OR (“spinal cord contusion”) OR (“spinal cord hemisection”) OR (“spinal cord transsection”) OR (“cervical spine injury”) OR (“Spinal compression”) OR (“spinal cord trauma”) OR (“injured spinal cord”) OR (“spinal cord injured”) OR (“nerve transection”)

#2 (“Pain”) OR (“Chronic Pain”) OR (“Chronic Pains”) OR (“Neuropathic pain”) OR (“Neuropathic Pains”) OR (“allodynia”) OR (“hyperalgesia”) OR (“Nerve Pain”) OR (“Nerve Pains”)

#3 (“Exercise”) OR (“Aerobic Exercise”) OR (“Exercises”) OR (“Exercise, Isometric”) OR (“Exercises, Isometric”) OR (“Isometric Exercises”) OR (“Isometric Exercise”) OR (“Exercise, Aerobic”) OR (“Aerobic Exercises”) OR (“Exercises, Aerobic”) OR (“Circuit Training”) OR (“Training, Circuit”) OR (“Cool-Down”) OR (“Warming-Down”) OR (“Warm-Down”) OR (“Cooldown”) OR (“Warm-

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Up") OR ("Cooling-Down") OR ("Warmup") OR ("Therapy, Exercise") OR ("Exercise Therapies") OR ("Therapies, Exercise") OR ("Exercise Therapies") OR ("Therapies, Exercise") OR ("Sports") OR ("Physiotherapy exercises") OR ("Flexibility Exercises") OR ("Motion Exercises") OR ("Adaptive Aerobics") OR ("Aerobic training") OR ("Voluntary wheel running") OR ("Gait training") OR ("Locomotor training") OR ("Upper extremity training") OR ("Motor Activity")

#1 AND #2 AND #3

Web of Science

#1 TS = ("spinal cord injury" OR "Spinal cord injuries" OR "spinal cord contusion" OR "spinal cord hemisection" OR "spinal cord transsection" OR "cervical spine injury" OR "Spinal compression" OR "spinal cord trauma" OR "injured spinal cord" OR "spinal cord injured" OR "nerve transection")

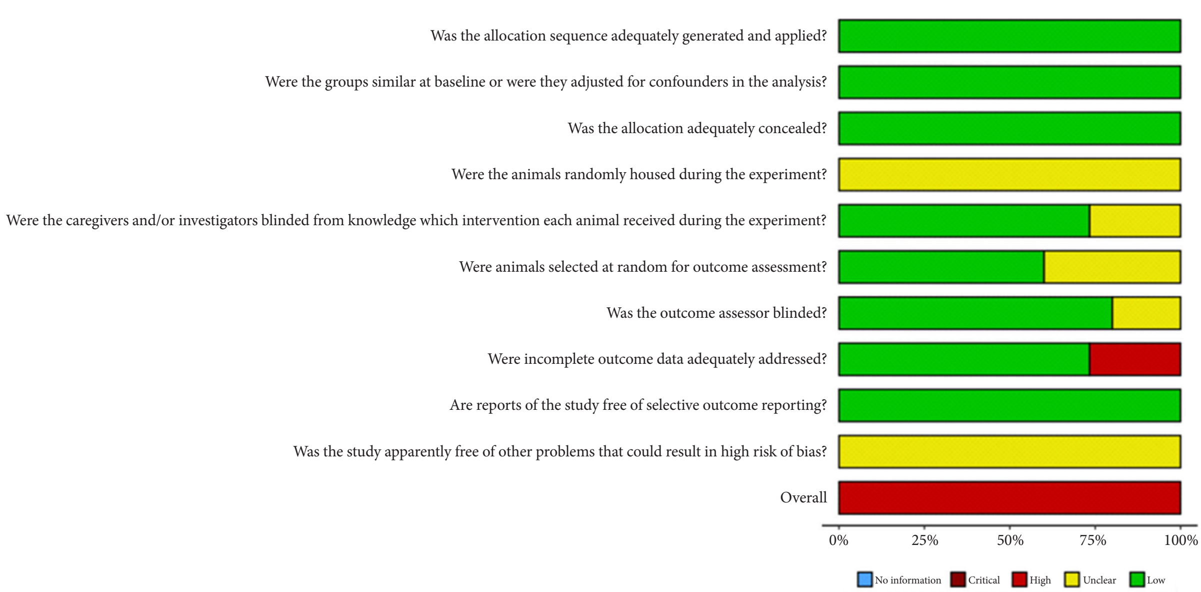
#2 TS = ("Pain" OR "Chronic Pain" OR "Chronic Pains" OR "Neuropathic pain" OR "Neuropathic Pains" OR "allodynia" OR "hyperalgesia" OR "Nerve Pain" OR "Nerve Pains")

#3 TS = ("Exercise" OR "Aerobic Exercise" OR "Exercises" OR "Exercise, Isometric" OR "Exercises, Isometric" OR "Isometric Exercises" OR "Isometric Exercise" OR "Exercise, Aerobic" OR "Aerobic Exercises" OR "Exercises, Aerobic" OR "Circuit Training" OR "Training, Circuit" OR "Cool-Down" OR "Warming-Down" OR "Warm-Down" OR "Cooldown" OR "Warm-Up" OR "Cooling-Down" OR "Warmup" OR "Therapy, Exercise" OR "Exercise Therapies" OR "Therapies, Exercise" OR "Exercise Therapies" OR "Therapies, Exercise" OR "Sports" OR "Physiotherapy exercises"OR "Flexibility Exercises" OR "Motion Exercises" OR "Adaptive Aerobics" OR "Aerobic training" OR "Voluntary wheel running" OR "Gait training" OR "Locomotor training" OR "Upper extremity training" OR "Motor Activity")

#1 AND #2 AND #3

D1: Item 1: Was the allocation sequence adequately generated and applied?
D2: Item 2: Were the groups similar at baseline or were they adjusted for confounders in the analysis?
D3: Item 3: Was the allocation adequately concealed?
D4: Item 4: Were the animals randomly housed during the experiment?
D5: Item 5: Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?
D6: Item 6: Were animals selected at random for outcome assessment?
D7: Item 7: Was the outcome assessor blinded?
D8: Item 8: Were incomplete outcome data adequately addressed?
D9: Item 9: Are reports of the study free of selective outcome reporting?
D10: Item 10: Was the study apparently free of other problems that could result in high risk of bias?

Judgement
High
Unclear
Low



Supplementary Material 2. Risk of bias assessment of the included preclinical studies according to the SYRCLE's risk of bias assessment tool.

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Supplementary Material 3. The certainty of evidence

Outcome	No. of experiments	Risk of bias	Imprecision	Inconsistency (I2 range)	Indirectness	Publication bias	Judgment	Level of evidence
Mechanical allodynia	31	Serious	No serious imprecision	No serious inconsistency*	No serious indirectness	No publication bias	Level of evidence was down rated one grade due to possible risk of bias	Moderate
Thermal hyperalgesia	17	Serious	No serious imprecision	No serious inconsistency*	No serious indirectness	No publication bias	Level of evidence was down rated one grade due to possible risk of bias	Moderate
Cold allodynia	6	Serious	No serious imprecision	No serious inconsistency*	No serious indirectness	No publication bias	Level of evidence was down rated one grade due to possible risk of bias	Moderate

*There is no serious inconsistency since the sources of heterogeneity were identified.

Supplementary Material 4. Sensitivity analyses on mechanical allodynia and thermal hyperalgesia

Variable	No. of experiments	Sensitivity analyses		
		SMD (95% CI)	p-value	I^2 (p-value)
Mechanical allodynia				
Studies conducted on rats only				
Both sides	14	-1.35 (-2.2 to -0.49)	0.002	90.16 (< 0.001)
Contralateral	6	-1.9 (-3.41 to -0.38)	0.014	92.53 (< 0.001)
Ipsilateral	7	-1.75 (-3.02 to -0.48)	0.007	91.39 (< 0.001)
Thoracic/thoracolumbar injuries*				
Both sides	18	-1.43 (-2.16 to -0.7)	< 0.001	89.86 (< 0.001)
Moderate to severe injuries				
Both sides	18	-1.43 (-2.16 to -0.7)	< 0.001	89.86 (< 0.001)
Contralateral	4	-0.74 (-1.3 to -0.18)	0.009	34.09 (0.2)
Ipsilateral	5	-0.76 (-1.16 to -0.36)	< 0.001	0.00 (0.728)
No stratifications were made for the development of allodynia prior to exercise				
Both sides	18	-1.43 (-2.16 to -0.7)	< 0.001	89.86 (< 0.001)
Ipsilateral	3	-3.03 (-5.6 to -0.44)	< 0.001	94.54 (< 0.001)
Only limbs were evaluated				
Both sides	16	-1.63 (-2.41 to -0.86)	< 0.001	89.21 (< 0.001)
Contralateral	6	-1.9 (-3.41 to -0.38)	0.014	92.53 (< 0.001)
Ipsilateral	7	-1.75 (-3.02 to -0.48)	0.007	91.39 (< 0.001)
Bipedal/quadrupedal gait training				
Both sides	16	-1.58 (-2.39 to -0.77)	< 0.001	90.59 (< 0.001)
Contralateral	6	-1.9 (-3.41 to -0.38)	0.014	92.53 (< 0.001)
Ipsilateral	7	-1.75 (-3.02 to -0.48)	0.007	91.39 (< 0.001)
Thermal hyperalgesia				
Rats				
Both sides	10	2.35 (1.14–3.56)	< 0.001	91.37 (< 0.001)
Thoracic/thoracolumbar injuries				
Both sides	13	1.94 (0.95–2.93)	< 0.001	91.37 (< 0.001)
Moderate to severe injuries				
Both sides	13	1.94 (0.95–2.93)	< 0.001	91.37 (< 0.001)
No stratifications were made for the development of allodynia prior to exercise				
Both sides	13	1.94 (0.95–2.93)	< 0.001	91.37 (< 0.001)
Only limbs were evaluated				
Both sides	13	1.94 (0.95–2.93)	< 0.001	91.37 (< 0.001)
Bipedal/quadrupedal gait training				
Both sides	11	2.02 (0.82–3.23)	0.001	93.24 (< 0.001)

SMD, standardized mean difference; CI, confidence interval.
*Sensitivity analyses were performed only if a with sufficient number of experiments were included.

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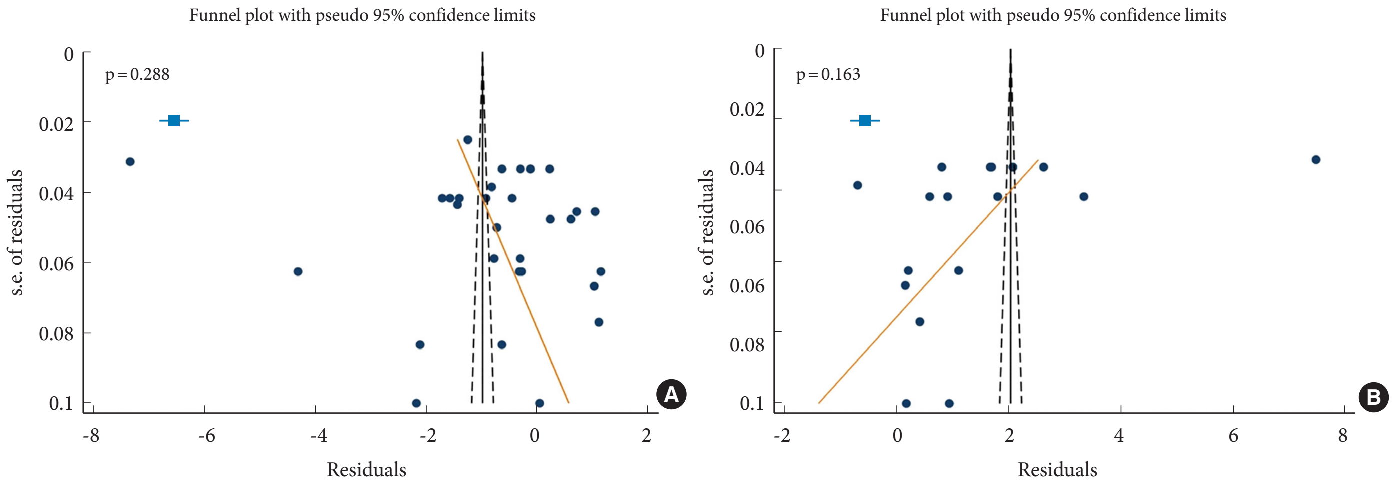
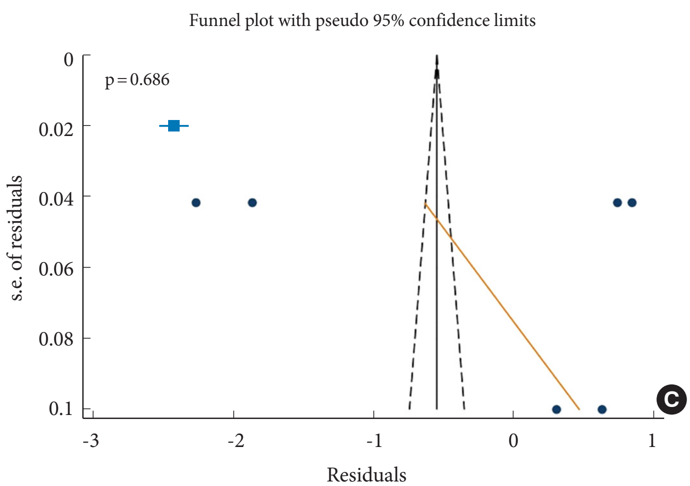
Supplementary Material 5. Risk of bias assessment for the randomized clinical trials

Study	Year	Selection bias		Performance bias		Detection bias		Attrition bias	Reporting bias	Other bias	Overall
		Random sequence	Allocation concealment	Blinding of participants	Blinding of study team	Random outcome assessment	Blinding of outcome assessor	Incomplete outcome data	Selective outcome data	Yes	
Cardenas et al.[46]	2020	Low	High	High	Low	Low	Low	Low	Low	Low	High
Ginis et al.[47]	2003	Low	High	High	High	Low	High	Low	Low	Low	High
Hicks et al.[48]	2003	Low	High	High	High	Low	High	High	Low	Low	High
Nightingale et al.[49]	2018	Low	High	High	High	Low	High	Low	Low	Low	High
Mulroy et al.[21]	2011	Low	High	High	Low	Low	Low	Low	Low	Low	High





Supplementary Material 6. Publication bias for mechanical allodynia (A), thermal hyperalgesia (B), and cold allodynia (C). s.e., standard error.

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