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SYSTEMATIC REVIEW

Arthralgia: a map of Cochrane evidence relevant to rehabilitation for people with post COVID-19 condition

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ABSTRACT

INTRODUCTION: Rehabilitation focuses on impairments, activity limitations and participation restrictions being informed by the underlying health condition. In the current absence of direct "evidence on" rehabilitation interventions for people with post COVID-19 condition (PCC), we can search and synthesize the indirect "evidence relevant to" coming from interventions effective on the symptoms of PCC in other health conditions. The World Health Organization (WHO) required this information to inform expert teams and provide specific recommendations in its Guidelines. With this overview of reviews with mapping we aimed to synthesize the Cochrane evidence relevant to rehabilitation for arthralgia due to PCC in a map.

EVIDENCE ACQUISITION: We searched the last five years' Cochrane Systematic Review (CSRs) using the terms "arthralgia," "joint pain," and "rehabilitation" and their synonyms in the Cochrane Library. We extracted and summarized all the available evidence using a map. We grouped the included CSRs for health conditions and interventions, indicating the effect and the quality of evidence.

EVIDENCE SYNTHESIS: We found 200 CSRs published between 2016 and 2021, and included 11 in this overview. They provided data from 7 health conditions, with osteoarthritis (5 studies) being the most studied. Effective rehabilitation interventions included exercise training, transcranial magnetic stimulation, different types of electrical stimulation and Tai chi. The overall quality of evidence was mainly low to very low, and moderate in a few cases.

CONCLUSIONS: These results provided the requested information to the WHO and served as the basis for one recommendation on treatments for arthralgia due to PCC in the current Guidelines for clinical practice. These results should be interpreted as a first step of indirect evidence able to generate helpful hypotheses for future research.

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KEY WORDS: COVID-19; post-acute COVID-19 syndrome; Physical and rehabilitation medicine; Arthralgia; Pain.

Introduction

This short paper is part of the series developed by Cochrane Rehabilitation in collaboration with the World Health Organization (WHO) to identify the Cochrane evidence relevant to post COVID-19 condition (PCC) symptoms management.[1, 2] The focus of this study is arthralgia due to PCC.

In recent years, respiratory viral infections (parainfluenza, coronaviruses and metapneumoviruses) have been considered potential causes of rheumatoid arthritis onset or flare-ups.[3] Similarly to other coronaviruses, also COVID-19

has been found to cause a wide variety of rheumatic symptoms.[4-6] In line with these observations, some authors reported the presence of arthralgia among the most common PCC symptoms.[7, 8] In particular, Lopez-Leon *et al.* estimated that arthralgia could be present in PCC patients with a 1:5 ratio.[8] Cui *et al.* found mild to moderate joint pain in a cohort of 160 COVID-19 patients suffering rheumatic symptoms 12 months after the infection. Additionally, quality of life assessment demonstrated physical and mental impairments with the EuroQol-5 dimensions-5 levels questionnaire.[9]

Some hypotheses have been suggested to explain COVID-related rheumatic symptoms, even if the underlying specific mechanisms are not well understood. In the first place, excessive or uncontrolled cytokine responses seem to play an important role in COVID-19 progression, similar to spondylarthritis and psoriatic arthritis.[10] Interestingly, some anti-rheumatic drugs, like hydroxychloroquine, colchicine, baricitinib, and tocilizumab, have been shown to affect COVID-19[11] positively. Moreover, SARS-CoV-2 antigens activate cross-reactive T cells through molecular mimicry or host self-antigens released from damaged tissue, allowing autoreactive T cells to activate, which induces pathological processes.[9, 12]

From a rehabilitative point of view, no specific treatments for arthralgia in PCC are suggested, but several interventions are already applied for similar symptoms in the field. With the present review, we aimed to map the current Cochrane evidence on the efficacy of rehabilitation treatments proposed for arthralgia in other health conditions. The subsequent findings could partially fill the knowledge gap in PCC-related arthralgia management and help clinicians select appropriate treatments for their patients. Results from the present study can also stimulate new research hypotheses and facilitate the identification of research priorities for future studies.

Evidence acquisition

The design of this study is an overview of reviews with mapping. We reported the methods used in a previous publication.[2] In this short paper, we included Cochrane Systematic Reviews (CSRs) relevant to PCC that considered arthralgia. We summarize the search string in Table I.

TABLE I.—*Impairment, related symptoms and outcomes relevant to post COVID-19 condition included in the study, as identified by WHO Rehabilitation Program.*

Impairment	Synonyms/variations	Outcomes
Arthralgia	Arthralgia, joint pain	Subjective assessment of pain

Evidence synthesis

We screened 200 CSRs, excluding 170 at the title and abstract stage. We screened 30 full texts, with 11 CSRs that met the inclusion criteria (Supplementary Digital Material 1: Supplementary Table I). We included 5 CSRs on adults with osteoarthritis, and one each on adults with ankylosing spondylitis, aromatase inhibitor-induced musculoskeletal symptoms, chronic pain, hemophilia, neuropathic pain, patellofemoral pain syndrome and rheumatoid arthritis. The "A MeaSurement Tool to Assess systematic Reviews" (AMSTAR) 2 assessment indicated high methodological quality for all CSRs included (Supplementary Digital Material 2: Supplementary Table II). All the reviews evaluated the quality of evidence using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach.[13-23]

Compared to no intervention in patients with ankylosing spondylitis, exercise programs seem to have a relevant effect on short-term pain and spinal mobility (very low to low-quality evidence). Compared to no intervention, exercise (also in aquatic settings) proved effective on pain and self-efficacy (low- to moderate-quality evidence) in patients with hemophilia and osteoarthritis. Repetitive transcranial magnetic stimulation (rTMS) and transcutaneous electrical neurostimulation (TENS) showed beneficial effects in patients with chronic pain, neuropathic pain and osteoarthritis (very low-quality evidence). Neuromuscular electrical stimulation (NMES) showed positive results in patients with patellofemoral pain syndrome (very low-quality evidence). Finally, tai chi contributed to pain reduction in patients with rheumatoid arthritis, compared to no tai chi or other exercises (very low- quality evidence).

Discussion

This paper mapped the Cochrane evidence relevant to managing arthralgia due to PCC in different health conditions. Considering CSRs that included people with osteoarthritis, ankylosing spondylitis, aromatase inhibitor-induced musculoskeletal symptoms, chronic pain, neuropathic pain, hemophilia, patellofemoral pain syndrome and rheumatoid arthritis, we found that exercise training performed with various modalities, TMS, different types of electrical stimulation and tai chi effectively manage arthralgia.

When implementing the "evidence relevant to," we need to check 1) if there are specific pathophysiological mechanisms of PCC suggesting avoiding any of the identified treatments; 2) if there are treatments specific for the reported health conditions that would not be appropriate

for PCC. Obviously, in the implementation phase, the need to check individual contraindications in single patients remains. The WHO identified one red flag for PCC rehabilitation: post-exertional symptom exacerbation.[24] This can represent an individual contra-indication for all the treatments considered below.

Current evidence strongly supports the use of physical activity and exercise programs for improving disease remission, activities and participation in people with rheumatic and musculoskeletal diseases.[25] In 2018, the European League Against Rheumatism released a paper reporting that general exercise recommendations,[26] including four domains (cardiorespiratory fitness, muscle strength, flexibility and neuromotor performance), are applicable, feasible and safe for people with rheumatoid arthritis, spondylarthritis and osteoarthritis.[27] Similar positive effects could be obtained in patients with PCC using the same recommendations, adjusting the training prescription to the presence of other limiting symptoms like dyspnea and fatigue. Interestingly, as observed in other short papers of this series,[28, 29] dyspnea and fatigue could also benefit from exercise interventions.

Also, water-based exercise therapy in swimming pools heated between 32 °C and 36 °C could be considered to diminish arthralgia.[19] Hall *et al.* hypothesized that the pain-relieving effect might be due to the combined action of warm water and buoyancy on joint receptors or to the effect of warm water to increase blood flow and thereby reduce nociception.[30] Aquatic exercise may be considered in the first part of an exercise training program to introduce patients with PCC to a subsequent land-based intervention.

Among non-invasive stimulations, we found rTMS, TENS and NMES. The rTMS could be a useful approach for managing chronic pain symptoms since motor cortex stimulation seems to modulate activity in brain networks involved in pain processing and to promote descending pain inhibitory mechanisms.[31, 32] TENS induces analgesia acting on peripheral, spinal and supra-spinal mechanisms.[17] NEMS, usually proposed to increase muscle force and promote muscle contraction,[33] could serve as a complementary treatment in patients where exercise interventions exacerbate pain and inflammation, reducing voluntary muscle activation.[34]

Finally, we identified tai chi as an intervention potentially relevant for PCC rehabilitation. This approach combines diaphragmatic breathing and relaxation techniques with slow isometric and isotonic movements, paying attention to body postures.[23] Isometric exercises allow exercising specific muscle groups while avoiding joint motion, while isotonic exercises contract muscles inducing joint movement.[23] Similarly to other exercise interventions, tai chi could promote mobility and break the vicious cycle due to existing/worsening symptoms and a sedentary lifestyle.

Looking at the indirect evidence provided with this research and at the current direct evidence coming from the rapid living systematic review produced by Cochrane Rehabilitation,[35-37] the experts conveyed by the WHO provided the following conditional recommendation for the clinical rehabilitation management of adults with PCC:[24]

• Arthralgia: a combination of pain education, skills training on self-management strategies, prescription of short-term anti-inflammatory drugs, and in the absence of post-exertional symptom exacerbation, physical exercise training.[24]

Our map of CSRs focuses on the best current evidence relevant to rehabilitation for people with arthralgia due to PCC. However, other high-quality systematic reviews

Intervention	Osteoarthritis (hand/hip/knee/knee+hip)				Ankylosing spondylitis					Aromatase inhibitor-induced musculoskeletal symptoms		Hemophilia	Chronic pain		Neuropathic pain	Patellofemoral pain syndrome		Rheumatoid arthritis	
Acupuncture	M**																		
Aquatic exercise	M*																		
Exercise	M*	L*	L*	VL*	M§	L§	VL§	L§	VL*	L*	VL*	L*						VL*	VL*
NMES																VL*	VL*		
rTMS													L**	VL**					
TENS	VL**			VL**											VL**				

Figure 1.—Evidence map of interventions for arthralgia symptoms compared to control, sham intervention, no therapy.
Lines represent the interventions. Columns represent the health conditions where the searched outcome has been considered. Colors in each cell reported the type of effect (effect against the intervention – black; effect in favor of the intervention – white; no definite results – grey). Quality of evidence was reported into each cell the with the following acronyms: VL: very low-quality; L: low-quality; M: moderate-quality; H: high-quality; na: not available.
Comparisons: *Control group or other intervention; **sham group; §no intervention.
rTMS: repetitive transcranial magnetic stimulation; TENS: transcutaneous electrical nerve stimulation; NMES: neuromuscular electrical stimulation.

could not be considered in the selection process because they were not included in the Cochrane Library (Figure 1).

We must interpret the findings carefully because most included CSRs provided very low-quality evidence. This aspect has to be improved in future studies dedicated to different health conditions, including PCC. Moreover, our study did not provide direct evidence on rehabilitation for people with arthralgia due to PCC. Still, it can provide useful information to help filling the knowledge gap that currently characterizes the field. These findings can be helpful for clinicians in delivering more specific treatments and promote the development of new studies with more focused research questions.

Conclusions

Specific rehabilitation interventions that have been successfully used in different health conditions may improve arthralgia symptoms due to PCC. Future research priorities are improving the methodological quality of the primary studies in people with chronic diseases and producing new and specific evidence on PCC.

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