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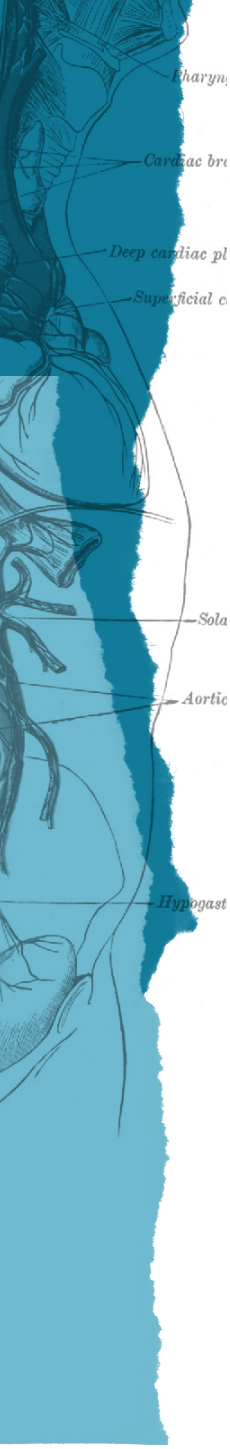

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Relationship between Hemineglect and Pain: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Relación entre heminegligencia y dolor: Una revisión sistemática y metanálisis de ensayos controlados aleatorizados

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ABSTRACT

Objective: To identify the relationship between hemineglect and pain.

Methods: We conducted a systematic review with meta-analysis, examining the relationship between hemineglect and pain. The PRISMA criteria and the Covidence platform were used to select articles and extract data. Methodological quality was evaluated, a comparison was made using pain as an outcome measure, assessed with the visual analog scale (VAS).

Results: Out of a total of 340 studies, 4 were selected, 2 of which made it possible to unify pain measured through VAS; the effects were summarized using standardized mean differences (SMD), yielding -0.65, with values of [-1.02, -0.29], with statistical significance.

Conclusions: There is moderate evidence of the relationship between negligence and pain. Despite the fact that from the clinical care processes it is presented regularly, and even the little scientific information available, it was established that there are specific pathologies that carry negligence and pain.

Keywords: Negligence; Hemineglect; Pain; Randomized clinical study; Systematic review.

RESUMEN

Objetivo: Identificar la relación entre hemineglegencia y dolor.

Métodos: Realizamos una revisión sistemática con metanálisis que examina la relación entre hemineglegencia y dolor. Se utilizaron los criterios PRISMA y la plataforma Covidence para seleccionar artículos y extraer datos. Se evaluó la calidad metodológica, se realizó una comparación utilizando el dolor como medida de resultado, evaluado con la escala visual analógica (EVA).

Resultados: De un total de 340 estudios, se seleccionaron 4, de los cuales 2 permitieron unificar el dolor medido mediante EVA; los efectos se resumieron utilizando diferencias de

medias estandarizadas (DME), obteniendo -0,65 con valores de [-1,02, -0,29] con significancia estadística.

Conclusiones: Existe evidencia moderada de la relación entre negligencia y dolor. A pesar de que a partir de los procesos de atención clínica se presenta con regularidad y aún con la poca información científica disponible, se estableció que existen patologías específicas que conllevan negligencia y dolor.

Palabras claves: Negligencia; Hemineglígencia; Dolor; Estudio clínico aleatorizado; Revisión sistemática.

INTRODUCTION

Hemineglect (also called neglect syndrome or unilateral negligence) was defined by Allegri (2000) as the difficulty of the patient in orienting himself, acting or responding to stimuli or actions that occur on the contralateral side to hemispheric injury, that is to say, the visual hemifield (half the visual field) opposite next to the injury (1).

In clinical neurology, the term "negligence" denotes the lack of attention to sensory contralateral stimuli to an injury of the temporoparietal junction, the lower parietal cortex or upper temporal cortex of the right hemisphere (2) (3).

The concept of negligence in neuropsychology describes a flaw in referring, responding to, or targeting a stimulus that is present contralaterally in a brain injury, as long as the disorder is not due to an elementary motor or sensory disturbance (4) (5) (6).

The first study reported on negligence and pain was the one described by Galer in 1995, it was based on clinical experience and, then, it was summarized in a questionnaire that addresses the cognitive elements and drivers of negligence, indicating that reflex sympathetic dystrophy was a chronic pain disorder associated with autonomic deregulation that most commonly involves a limb (7) (8). In addition, it is important to consider all components of chronic pain, because pain should be considered as a major public health problem, accounting for 70% of emergency care and a third of medical visits (9) (10).

The main findings that have emerged from neuroimaging studies is that "chronic pain is considered a brain disease"(11) (12) (13). There are currently a variety of critical studies on the poor integration

of the social and psychological factors of western biomedicine into pain assessment and treatment (14) (15). Studies show that malpractice symptoms occur in patients with complex regional pain syndrome (CRPS), and in patients with other chronic pain disorders (16) (5). In addition, there are pathologies in which Neglect-Like symptoms are observed. However, the clinical significance of Neglect-Like symptoms and their relationship to pain symptoms is largely unknown.

In some chronic diseases such as CRPS, more severe self-reported "neglect-like" symptoms and spatial attention and motor biases have been related to greater pain intensity and worse long-term pain outcomes (37) (38) (39) (40).

The study of nociceptive processing and pain perception in relation to spatial perception is very relevant, not only to understand the role of pain in the cortical processes that underlie coordination between threat detection and defensive action, but also to develop new neuropsychological and rehabilitating techniques that make the response mechanisms from the associations possible, since there is a reduction in the response capacity to treat chronic pain. It was, therefore, the aim of our study to systematically review and meta-analyze the relationship between hemineglect and pain.

METHODS

Protocol

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement checklist (17).

Literature search

Queries of the literature were performed using the electronic databases Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, and MEDLINE (all: until 27 October 2019). The search strategy included a combination of the following Medical Subject Headings (MeSH) terms: pain AND acute pain AND chronic pain AND perceptual disorders AND neglect-like. Keyword iterations related to these terms were also used (Table 1).

Table 1. Search strategy.

MEDLINE
1. randomized controlled trial[Publication Type] 2. controlled clinical trial[Publication Type] 3. randomi*ed[Title/Abstract] 4. trial [Title] 5. "clinical trials as topic"[MeSH Major Topic] 6. #1 OR #2 OR #3 OR #4 OR #5 7. pain[Title/Abstract] 8. pain*[Title/Abstract] 9. neglect-like[Title/Abstract] 10. neglect*[Title/Abstract] 11. chronic pain*[Title/Abstract] 13. #7 OR #8 OR #9 OR #10 OR #11
CENTRAL (Cochrane Central Register of Controlled Trials)
(((((((randomized controlled trial) OR controlled clinical trial) OR randomied) OR trial) OR "clinical trials as topic") AND pain) AND chronic pain) OR acute pain) OR neglect-like) AND neglect
EMBASE
((((((randomized AND controlled AND trial) OR controlled) AND clinical AND trial) OR randomied OR trial OR 'clinical trials as topic'/exp OR 'clinical trials as topic') AND (pain/exp OR pain) OR (overweight/exp)) AND chronic pain) OR Acute pain/exp OR acute pain OR chronic pain/exp OR chronic pain) AND (neglect-like/exp OR neglect)

Source: Own elaboration.

In addition, the reference list of each of the included studies was reviewed to find potential studies that could be used in this review. Details and selection of articles were carried out using the algorithm recommended by Cochrane Collaboration (18) (19).

Eligibility criteria

The selected articles were given a second filter by making a critical reading to the full text, where they were evaluated according to the following criteria:

The criteria for a study to be included in the systematic review were the following: (i) Human studies; (ii) a randomized controlled trial (RCT) design; (iii) Clinical studies evaluating as a clinical outcome measure: pain.

We excluded those studies with the following characteristics: (i) Clinical studies involving patients with multiple musculoskeletal or neurological pathologies. Titles, abstracts, and full texts were assessed for eligibility independently by two authors (JMM and MMO) for potential inclusion. If necessary, a third researcher (SGP) was consulted. Finally, only those papers written in the English language were included.

Data extraction

The Covidence platform was used to identify and select the studies (https://www.covidence.org/home). Initially, duplicates were removed from the total of identified articles. Two authors reviewed the remaining article titles and abstracts to determine whether they met the inclusion criteria. Next, an independent reviewer screened the articles that had not been selected to ensure they should be excluded. Any article eliciting doubts or disagreement was fully reviewed by the independent reviewers until a decision was finally reached on its inclusion or exclusion.

Risk of Bias of Individual Studies

The methodological quality of the included studies was also assessed by 2 independent reviewers (JMM, MMO), for which the PEDro scale was used. This scale has validated some of its psychometric properties (20), reporting in some RS in the field of Physiotherapy an inter-evaluator reliability in a range between regular and good (20–22). Although there is no absolute consensus, a study is considered to be of high methodological quality if it has a score of ≥ 7 points (23).

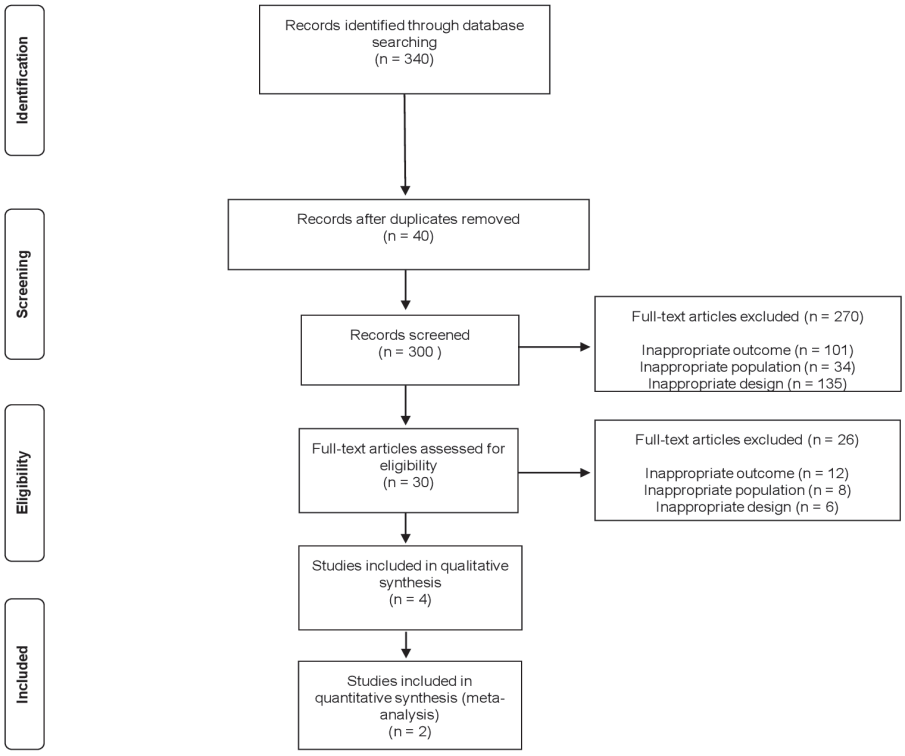
Statistical Analyses

All analyses were carried out using the Software (Review Manager 5.3), using standardized mean differences (SMD) that allowed calculating the effect estimates. The percentage of total variation across studies due to heterogeneity (Cochran's Q test) was used to calculate the I2 statistic, attributing it to values above 40% and using the fixed effects method for estimation. Clinical heterogeneity was made from analysis of the results (19).

RESULTS

Study Selection

The electronic search strategy retrieved 340 records. After removal of duplicate references, and screening of titles and abstracts, we excluded 40 articles. Of the remaining 300 articles, and after full-text screening and checking the reference lists of included studies and previous reviews for additional relevant articles, a total of 30 studies were read in full. The reasons for exclusion based on full text were (1) inappropriate study design (6 articles); (2) inappropriate study population (8 articles); and (3) inappropriate outcome measurement (12 articles). 4 Studies were included in qualitative synthesis. Finally, 2 were included in the final meta-analysis (24, 26). The PRISMA flow diagram is shown in Fig. 1.



Source: Own elaboration.

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart

Methodological quality of the ACEs included according to the PEDro SCALE

Of the 4 ECAs included in our RS, the average score on the PEDro scale was 6.5 points with a standard deviation (SD) of 0.96 (Table 2). The percentage of agreement in the methodological quality assessment between the two reviewers was high (kappa index of 0.91). The average total bias score was 6.5 with a range from 6 to 7. Only two studies obtained a high-quality score (i.e., ≥ 7) (24,5).

Table 1.

	Items											
Authors	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**Total Score***
Hanger et al. (24) 2014	+	+	+	+	-	-	+	-	+	+	+	7
Moseley et al. (25) 2013	+	-	-	+	+	-	-	+	+	+	+	6
Ratmansky et al. (26) 2012	+	+	-	+	-	-	+	+	-	+	+	6
Kolb et al. (5) 2012	+	+	-	+	-	+	+	+	-	+	+	7

Table 2. Quality of the studies included in the systematic review

Column numbers correspond to the following criteria on the PEDro scale:
1 eligibility criteria were specified
2 subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)
3 allocation was concealed
4 the groups were similar at baseline regarding the most important prognostic indicators
5 all subjects were blinded
6 all the therapists who administered the therapy were blinded
7 all the assessors who measured at least one key outcome were blinded
8 measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups
9 all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"
10 the results of between-group statistical comparisons are reported for at least one key outcome
11 the study provides both point measures and measures of variability for at least one key outcome
+ Indicates the criterion was clearly satisfied; - indicates that it was not;? indicates that it is not clear if the criterion was satisfied.

Source: Own elaboration.

Characteristics of the population and intervention of the studies

In the 4 selected ECAs (n=192 patients), sample sizes ranged from 10 to 98 patients. Table 3 shows the general characteristics of the included studies (5)(24)(25)(26). Hanger et al. (24) evaluated whether strapping the shoulder in hemiplegic stroke patients prevents the development, or reduces the severity, of shoulder pain, preserves range of movement in the shoulder, and improves the functional outcomes for the arm and patient overall. Considering whether the presence of hemineglect could independently predict the poor outcome in the final evaluation. The results indicated that the presence of hemineglect in patients with post-shoulder pain was associated with lower scores in the Functional Independence Measure (FIM), the Motor Assessment Scale, and the disability index.

Table 3. Characteristics of the included studies

Study	Participants	Intervention	Endpoints	Main results
Hanger et al. (24) 2014	n=98 patients 49 strapped, 49 controls. 59 (women) 39 (men) Acute hemiplegic stroke, who had pain and persisting weakness of shoulder	Shoulder strapping versus no strapping Duration: 6 weeks	VAS SROMP FIM MAS RDI	↓Pain Shoulder strapping group (VAS mean (median, SD) 1.8 (0, 3.1) versus 2.5 (2, 2.7) respectively, p= 0.09)

Study	Participants	Intervention	Endpoints	Main results
Moseley et al. (25) 2013	n=10 patients 6 (women) 4 (men) Unilateral Complex regional pain syndrome	Use of prism lenses that laterally displaced the visual field by 20 ° Duration: 9 minutes	Temperature: infrared thermal imaging FLIR SC620: field of view = 24; accuracy 2% of reading; sensitivity to change < 40 mK	↑ (Δ°C=+0.47 ± 0.14°C) Placing the affected hand on the healthy side of the body midline increased its temperature ↑ (Δ°C=+0.28 ± 0.14°C) Prism glasses made the affected hand appear to be on the healthy side of the body midline, even though it was not, the affected hand warmed up ↓ (Δ°C=-0.30 ± 0.15°C) Prism glasses made the healthy hand appear to be on the affected side of the body midline, even though it was not, the healthy hand cooled down
Ratmansky et al. (26) 2012	n= 24 patients 9 (women) 15 (men) Hemiplegic patients with shoulder pain	Group 1: SNMT combined with standard hospital SNMT Group 2: standard therapy (Control)	VAS Fugl-Meyer arm score for upper-limb function Ashworth scale for spasticity Hand behind neck test	SNMT: ↑ T4 (p = 0.014) and T5 (p = 0.0078) Fugl-Meyer arm score for upper-limb function ↓Pain Neer test advantage (p = 0.014) (p = 0.068)

Study	Participants	Intervention	Endpoints	Main results
Kolb et al. (5) 2012	n= 60 patients CP 15 (women) 5 (mem) NC 15 (women) 5 (men)	CP, NC, PC Aplication quantitative sensory testing and motor. Neuropsychological test battery assessing different parietal lobe functions, including visual neglect	Numerical scoring scale Skin temperature Infrarot-Thermometer IR-364 DASH score for Disability	PC (20) CP (19) reported pain on movement (PC = 56.65 ± 5.42, CP = 56.00 ± 6.69)

Source: Own elaboration.

Abbreviations: Δ°C = temperature change; CP = CRPS-patients; DASH = disability of shoulder and hand; FIM = functional Independence Measure; FLIR = infrared termal imaging; MAS = motor assessment scale; mK = Millikelvin; NC = normal control group; PC = pain control group; RDI = rankin disability index; SD = standard deviation; SNMT = segmental neuromyotherapy; SROMP = shoulder range of movement to the point of pain; VAS = visual analogue scale for pain Moseley et al. (25) proposed that, in the case of patients with CRPS, the temperature of the hands is modulated according to the location of the arms in relation to the midline of the body, is dependent on the perceived location of the hands, but not so their actual location or its anatomical alignment.

They measured skin temperature before and after the 9-minute periods in which the position of a hand was changed in patients with binocular lenses. The placement of the affected hand on the healthy side of the body in the midline increased its temperature (Δ°C= 0.47 ± 0.14 °C), but not if the binocular lenses made the hand appear to be in the midline of the body (Δ°C= 0.07 ± 0.06 °C).

Similarly, when the binocular lenses made the affected hand appear to be on the healthy side of the midline of the body, even if it was not, the affected hand was heated.

When the binocular lenses made the healthy hand appear to be on the affected side of the midline of the body, even if it wasn't, the healthy hand cooled down (Δ°C= 0.30 ± 0.15 °C) (Δ°C= 0.28 ± 0.14 °C).

Ratmansky et al. (26) evaluated the effectiveness of segmental neuromyotherapy combined with standard hospital therapy compared to standard therapy alone in patients with hemiplegic shoulder pain. Patients in the group receiving segmental neuromyotherapy had a higher prevalence of harm in the right hemisphere and unilateral spatial neglect, which was the only factor showing significant difference (p. 0.004) between groups. Decrease in pain scores reported by the VAS was described in one of the treatment groups (p 0.068).

Kolb et al. (5) indicated that patients with CRPS showed some signs of neglect and extrapersonal visuospatial problems beyond those seen in patients simply suffering from limb pain.

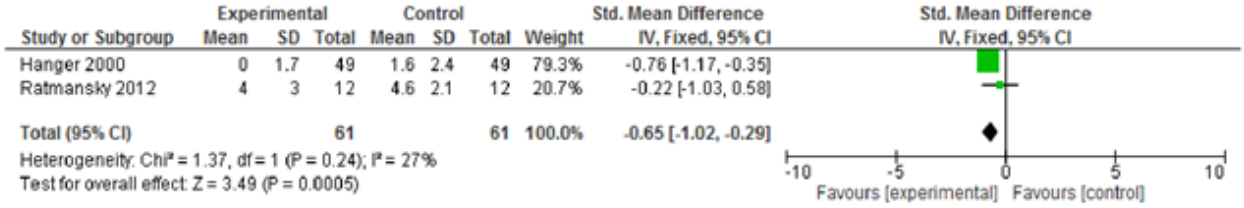
They used quantitative sensory tests and motor assessments aimed at detecting motor and sensory loss, a standardized questionnaire calculating a negligence score, and a detailed questionnaire of neuropsychological tests evaluating different functions of the parietal lobe, including visual negligence. 20 patients with CRPS and 2 control groups were examined, one consisting of healthy subjects and the other from patients with limb pain other than CRPS. Results showed significantly higher neglect scores for CRPS patients and the pain control group, but curiously, CRPS patients and pain patients were indistinguishable. The results of neuropsychological test questionnaires did not demonstrate systematic variations, which would be indicative of classical neurological negligence in CRPS patients. In their conclusions, they indicated that "negligence-type syndrome" in most CRPS patients is different from typical negligence.

Data synthesis and analysis

Taking into account the analysis of data from studies that met the eligibility criteria in relation to negligence and pain, a meta-analysis could not be performed because not all authors reported their results as continuous measures to be able to take them to a one-off estimator. Therefore, it was not possible to evaluate or consider for the final analysis of the review the statistical heterogeneity of the results. A qualitative method for the synthesis of evidence will be used, based on the criteria recommended by Van Tulder et al., Cochrane Back Group (27) with the use of evidence levels for data synthesis.

For the quantitative synthesis, a comparison is made using the pain valued with the VAS as an outcome measure, an estimate is made finding a trend towards improvement with the use of a clamping technique and a localized technique (neuromyotherapy); described in the studies by

Hanger (2000) and Ratmansky (2012), respectively. Although there is no heterogeneity and a significance towards improvement is seen, these results should be used with caution since an exact intervention was not generated, that would allow an adequate comparative process to be carried out, see figure 2.



Source: Own elaboration.

Figure 2. Forest plot showing pain outcomes with the interventions used, it was performed with fixed effects. p value represents significance for the heterogeneity test. 95%CI = 95% confidence interval

DISCUSSION

Despite the clinical heterogeneity, the present meta-analysis found a combination between the intervention based on restraint and another based on myotherapy, with the intensity of pain established as a common characteristic as an outcome measure. Although this is not conclusive, it leaves the possibility for the development of future investigations that use any of these strategies unifying the evaluative processes. It should be noted that although the 4 selected articles were reported as "randomized" clinical studies, in 3 of them (25) (26) (5), the text stated how the randomization had been performed and in only 1 article (24) the randomization was hidden, although it is true, most studies present patient losses during treatment and/or follow-up time, none considered in their design a statistical analysis of intent to treat, nor do they describe the use of some method to perform the calculation of the sample size, and have not registered their protocol in any of the registration systems currently in existence, so that they can cross-check the methodological planning data of the pre-implementation study.

The pathology in which hemineglect has been studied the most were CRPS and cerebrovascular accident (CVA), but in our search, we were able to find other pathologies such as lower back pain and some types of osteoarthritis (28)(29). Despite the fact that the reports in the clinical processes of care of patients with hemineglect usually show some process of pain related to this, the studies have little evidence in this regard; however, some authors (30) (31) indicate that hemineglígence added to other factors (subluxation, flaccidity such as hypertonicity, scapular retraction, sensory loss, effects of immobilization, and poor management) may be causes of shoulder pain after the CVA, while other authors have not been able to replicate these findings (32).

Ratmansky et al. (26) indicated that negligence is likely to attenuate and distort pain perception (as well as perception of other forms of somatic feeling), which originates from nociceptive stimulation on the body side contralateral to the injured hemisphere. They also emphasized that future research in patients with hemiplegic shoulder pain should consider the analysis of unilateral negligence as a variant, likely to affect the outcome independently.

The CRPS is characterized by severe pain, with autonomic, sensory, and endocrine dysfunction (33) and is associated with altered spatial perception (34). For example, hand-delivered stimuli placed on the affected side of the space (i.e., the side of the space where the painful hand is usually found) are given a lower weight than the identical stimuli delivered to the hand placed on the non-side, regardless of which hand is where (35). This phenomenon is similar to that seen in patients who develop hemineglect after a stroke (36), and a similar spatially defined deficit has recently been observed in people with chronic unilateral back pain (28).

Moseley et al. (25) indicated that the cortical mechanisms responsible for encoding the perceived location of the limbs in space modulate the temperature of the hands. This might suggest that modifying the central mechanisms that modulate central nervous system could modulate signs and symptoms of CRPS patients, such as temperature and pain.

Hanger et al. (24) considered in their research whether the presence of sensory loss, negligence, or subluxation at the start of the study could independently predict a poor outcome in the final evaluation. Neglect was associated with lower scores in their functional independence and degree of disability or dependence on daily activities.

Despite the extensive search strategy, it is always possible that a study has not been identified, the main methodological limitations of our review are the inclusion of unpublished material and the realization of some strategy to detect possible publication bias. All these considerations should be evaluated when interpreting the results of the different studies and trying to draw conclusions about the relationship between hemineglect and pain.

CONCLUSIONS

Based on the results found in the studies included in our review, there is moderate evidence of the relationship between neglect and pain. Despite the little scientific information available, it was established that there are specific pathologies that carry negligence and pain. Most of the research studied in this systematic review relates to pain as a part of the context of the patient's pathology, as well as its hemineglect, but neither explains its possible subordination or dependence between the two.

It is suggested that studies be carried out that unify the interventions with the use of scales that are widely disseminated in such a way that it is possible to estimate the effect and generate a recommendation regarding interventional processes in patients with hemineglect.

Data availability statement

The data that support the findings of this review are available on request from the corresponding author (Marco Morales-Osorio).

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