International Journal of Stroke
0(0) 1–10

DOI: 10.1177/1747493020937192
journals.sagepub.com/home/wso

Poststroke shoulder pain in subacute patients and its correlation with upper limb recovery after robotic or conventional treatment: A secondary analysis of a multicenter randomized controlled trial

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Abstract

Background and aims: Poststroke shoulder pain is a common complication. We aimed to investigate the prevalence of poststroke shoulder pain, with attention to the neuropathic component, and the relationship between poststroke shoulder pain and upper limb improvement in motor function, strength, disability, and quality of life after upper limb rehabilitation.

Methods: This is a secondary analysis of a multicenter randomized controlled trial to compare upper limb conventional or robotic rehabilitation on 224 patients enrolled in eight rehabilitation centers. We assessed poststroke shoulder pain (using the Numerical Rating Scale and the Douleur Neuropathique 4), and upper limb motor function, strength, disability, and quality of life at baseline (T0), after 30 rehabilitation sessions (T1), and three months after the end of rehabilitation (T2).

Results: A moderate/severe poststroke shoulder pain was reported by 28.9% of patients, while 19.6% of them showed a neuropathic component. At T0, the intensity of pain was higher in women and in patients with neglect syndrome, positively correlated with the time since stroke and disability and negatively correlated with motor function, strength, and the physical aspects of the quality of life.

Moderate/severe pain and neuropathic component significantly reduced after both treatments and this reduction was maintained at T2. Finally, the intensity of pain at baseline was negatively correlated with the improvement of upper limb motor function.

Conclusions: Poststroke shoulder pain negatively impact on motor performance, strength, disability, and physical aspects of the quality of life as well as on upper limb motor recovery; however, it can be reduced after a robotic or a conventional rehabilitation. Therefore, we suggest considering poststroke shoulder pain when planning the rehabilitation intervention.

Keywords

Pain, stroke, shoulder, rehabilitation, robotics, randomized controlled trial

Received: 29 January 2020; accepted: 27 April 2020

Introduction

Poststroke shoulder pain (PSSP) is a common complication.[1] Data reported on PSSP prevalence are heterogeneous due to different methodologies (recruitment criteria, latency from stroke, severity of paresis and

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assessment tools). A review reported an average rate of 22–23% in global stroke survivors, but also of 54–55% in selected stroke populations undergoing rehabilitation treatment.[2] The exact PSSP pathophysiology is largely unclear.[3,4] Generally, the frequency of PSSP increases with time,[5] being 17, 20, and 27% at one week, one month, and six months, respectively.

PSSP can have negative impacts on rehabilitation outcomes and health-related quality of life (QoL).[6–8] Chae et al.[9] showed that the PSSP is a negative prognostic factor on functional recovery, being associated with increased length of hospital stay and reduction in patients' QoL; Aprile et al.[10] reported a negative influence of the poststroke pain on the rehabilitation program. However, to date, there are few data about the influence of PSSP on upper limb recovery after rehabilitation. A recent study showed that a shoulder rehabilitation robot as an adjuvant therapy can improve hemiplegic shoulder pain[11] but, to the best of our knowledge, other data on the effect of the robotic upper limb rehabilitation on PSSP are not available.

Aims

This study aims to: (a) evaluate the prevalence and the characteristics of PSSP (including the neuropathic component) in a wide sample of subacute stroke patients undergoing upper limb conventional or robotic rehabilitation and (b) analyze the correlations between PSSP and the outcomes of the rehabilitation, in terms of motor function, strength, and QoL.

Methods

Study design and setting

This is a retrospective analysis focused on pain prevalence; characteristics; and the associations between PSSP and upper limb motor function, strength, and QoL improvement, in a cohort of patients undergoing a rehabilitation intervention. This is a secondary analysis of a multicenter randomized controlled trial,[12] approved by our institutional ethics committee (FDG_6.4.2016) and registered at clinicaltrials.gov (NCT02879279). All participants gave informed consent according to the Declaration of Helsinki.

Participants

Inclusion criteria were: (1) a first-ever stroke (cerebral infarction or hemorrhage), confirmed by CT or MRI; (2) a time since stroke ranging from 14 to 180 days; (3) age between 40 and 85 years; (4) cognitive and language abilities sufficient to follow instructions. Exclusion criteria were: (1) upper extremity Fugl–Meyer score >58; (2) behavioral and cognitive disorders and/or reduced compliance that would interfere with active therapy; (3) fixed contraction deformity in the affected limb that would interfere with active therapy (ankylosis, Modified Ashworth Scale = 4); (4) inability to discriminate distinctly the images shown on a 22 monitor placed at the eye level of each subject at a distance of about 50 cm, even with corrective glasses.

Treatment

Patients were randomized to the robotic group (RG) or the conventional group (CG).

In the RG, patients were treated with a set of robotic and sensor-based devices (Motore, Humanware; and Amadeo, Diego, and Pablo, from Tyromotion (Figure 1))[13]; while in the CG, the treatment focused on sensory stimulation, stretching, passive mobilizations, functional training, and task practice. In both groups, the treatment was performed daily for 45 min, five days a week, for 30 sessions. Patients underwent a comprehensive rehabilitation program including individual conventional physiotherapy (six times/week), lasting 45 min, focused on lower limbs, sitting and standing training, balance, and walking. During this additional comprehensive treatment, therapists were instructed not to give additional upper limb therapy. More details on the treatments were previously reported.[12]

Assessment

Patients were assessed with the following clinical scales: the Fugl–Meyer Assessment for Upper Extremity, to evaluate motor function[14]; the Motricity Index, to evaluate muscle strength[15]; the Modified Barthel Index, to evaluate activities of daily living and mobility[16]; and the 36-Item Short Form Health Survey (SF-36), to assess QoL, using the two sub-scores, i.e. the Physical Composite Score and the Mental Composite Score.[17]

To evaluate PSSP, we used the Numerical Rating Scale (NRS), a unidimensional measure of pain intensity to diagnose and quantify pain in adults, in which a respondent selects a number from 0 (no pain) to 10 (extreme pain) that best reflects the intensity of his/her pain.[18] A score between 1 and 4 was categorized as "mild pain/influence", from 5 to 6 as "moderate pain/influence" and a score equal to or higher than 7 as "severe pain/influence" (Figure 2). This cutoff point (CP) scheme, i.e. the $CP_{4,6}$ scheme (where 4 and 6 are the upper limits of moderate and mild categories, respectively) was suggested by several authors.[19–23] Finally, we used the Douleur Neuropathique 4 (DN4)[4,24] to diagnose neuropathic pain. It ranges from 0 to 10, and a

Figure 1. Set of robotic and sensor-based devices. (a) Amadeo (Tyromotion); (b) Diego (Tyromotion); (c) Motore (Humanware); and (d) Pablo (Tyromotion).

score equal or higher than 4 means a neuropathic origin of pain. According to the DN4 scores, patients were categorized as DN4 + (≥4) or DN4− (<4).

To verify that shoulder pain was caused by the stroke, patients were asked if it had occurred after the stroke. In the case of a positive answer, pain was categorized as "PSSP."

Regarding the pharmacological treatment when the NRS score was between 1 and 4, pain was first treated with paracetamol (acetaminophen), in case of no recent use with an adequate dose. In case of treatment failure, patients switched to a nonsteroidal anti-inflammatory drug (NSAID) and eventually to a second NSAID when the NRS score was from 5 to 6; when the score was higher than 7 pain was treated with opioids[25,26] for a short time (<15 days). For patients who complained of neuropathic pain, antiepileptics or SNRI antidepressants were used as suggested by the literature data.[27–29]

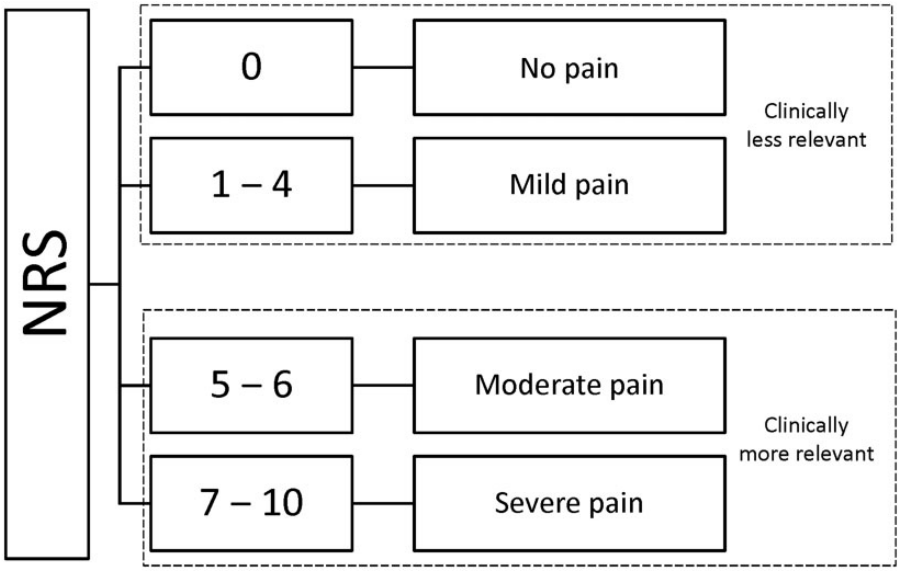
Timing of the evaluations

Patients were evaluated at baseline (T0), after the conventional or robotic rehabilitation treatment (T1) and three months after the end of the treatment (T2).

Statistical analysis

Descriptive statistics were used to report the prevalence and the distribution of PSSP. To evaluate the relationships between pain at baseline and demographic and clinical characteristics, we used the Mann–Whitney U test, or the Spearman's rank correlation coefficient, as appropriate.

Figure 2. Classification of pain severity, according to the Numerical Rating Scale (NRS).



To compare the evolution of pain in the robotic and the conventional rehabilitation group, we used a mixed Anova test, with *group* as between-subject factor and *time* (three levels: T0, T1, and T2) as within-subject factor. When appropriate, we performed pairwise comparisons, with a Bonferroni correction for multiple testing. The same analysis was conducted also considering patients with a clinically more relevant (NRS ≥ 5) or less relevant (NRS < 5) pain, separately.

Finally, to study the relationships between PSSP and the effects of the rehabilitation intervention, we analyzed the correlation between the changes from baseline of all the investigated outcome measures and the NRS at baseline.

All the above-mentioned analyses were conducted on both the whole sample of patients and in patients with a DN4 score equal or higher than 4 (DN4+), to evaluate the impact of the neuropathic component on rehabilitation. A p value lower than 0.05 was considered significant. Statistical analysis was performed using SPSS (version 25) and GraphPad Prism (version 8).

Results

A sample of 224 consecutive patients with subacute stroke was enrolled in eight different rehabilitation centers of our Institution; 84.8% of these patients (190 patients) were evaluated after a rehabilitation treatment and 54.5% (122 patients) three months after the end of the treatment. The low rate of subjects at T2 was due to the fact they lived too far away from the rehabilitation department, or did not have anyone who could assist them in getting to the department, and was unrelated to adverse events or dissatisfaction with the type of treatment received. Comparing the baseline characteristics of patients with a T2 evaluation, with those who did not return to the rehabilitation center, we found that the only significant difference was a higher mean age of patients who dropped the follow-up evaluation, compared with the ones who did not (mean difference: 3.5 ± 1.5 years, $p = 0.007$).

Baseline assessment

Demographic, clinical characteristics, and baseline outcome assessment of the sample are shown in Table 1.

The prevalence of pain is reported in Figure 3. PSSP (NRS > 0) was present in 141 cases (62.9%). In particular, the intensity of PSSP was mild (NRS between 1 and 4) in 76 cases (33.9%), moderate (NRS between 5 and 6) in 38 cases (17.0%), and severe (NRS ≥ 7) in 27 cases (12.1%). A DN4 score equal to or higher than 4 was detected in 44 cases (19.6% of the whole sample).

Pain severity was higher in women ($p < 0.001$), and in patients with unilateral spatial neglect ($p = 0.014$), while no relationships between pain and stroke etiology (hemorrhagic vs. ischemic) or language impairment were found (Table 2). Pain was higher in women also when considering only patients with a neuropathic component ($p = 0.008$).

The correlation analysis between baseline demographic/clinical variables and pain is shown in Table 3. In the whole group of patients, PSSP was

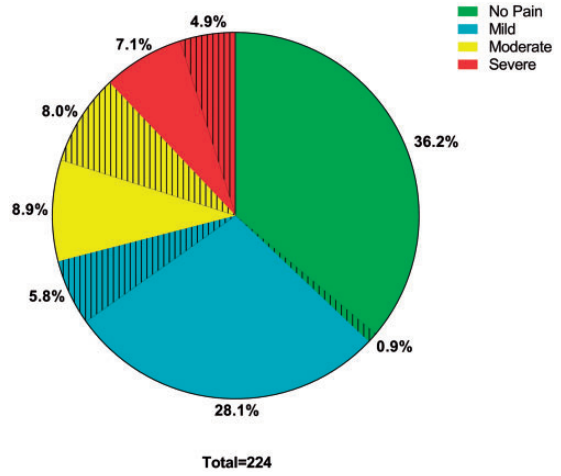
Table 1. Baseline characteristics of the sample ($N = 224$)

Age (years)	69.0 (11.2)
Sex	
Men	127 (56.7%)
Woman	97 (43.3%)
Index stroke type	
Ischemic	165 (73.7%)
Hemorrhagic	59 (26.3%)
Index stroke location (ischemic stroke)	
Lacunar stroke	24 (14.5%)
Partial anterior circulation stroke	99 (60.0%)
Total anterior circulation stroke	17 (10.3%)
Posterior circulation stroke	25 (15.2%)
Affected side	
Right	106 (47.3%)
Left	118 (52.7%)
Language impairment	45 (20.1%)
Neglect syndrome	46 (20.5%)
Time since stroke (days)	46.6 (40.8)
NRS	2.7 (2.8)
DN4	1.7 (1.8)
DN4 $\geq$ 4	44 (19.6%)
Upper extremity Fugl–Meyer assessment	23.4 (16.4)
Upper extremity Motricity Index	35.4 (28.2)
Modified Barthel Index	33.6 (26.6)
SF36—Physical Composite Score	28.3 (7.0)
SF36—Mental Composite Score	40.9 (12.1)

DN4: Douleur Neuropathique 4; NRS: Numerical Rating Scale. Non-categorical values are expressed as mean (SD). Categorical values are expressed as *n* (%).

significantly associated with the elapsed period since the stroke, with an increase of pain intensity as the time since stroke increases ($r = 0.173$, $p = 0.010$), but not with age. Moreover, higher pain intensity was related to worse upper limb motor functions and strength, higher disability, and a lower QoL (physical aspects).

Figure 3. Prevalence of pain in the investigated sample of subacute stroke patients, according to the Numerical Rating Scale (NRS). A score between 1 and 4 on NRS was categorized as "mild," a score from 5 to 6 was categorized as "moderate" and a score equal to or higher than 7 as "severe pain." For each pain category, the areas with black lines represent the percentage of patients with a neuropathic component (DN4 score equal to or higher than 4).



Considering only DN4 + patients, no significant correlations were found.

Concerning the rehabilitation treatment, pain at baseline in the two groups was similar (conventional: 2.6 ± 2.7; robotic: 2.8 ± 2.9; $p = 0.653$).

The evolution of pain intensity in the two groups is depicted in Figure 4. The interaction factor *time* × *group* was never significant, neither considering the whole sample ($N = 121$, $p = 0.961$), nor in the subgroup analysis (NRS < 5: $N = 88$, $p = 0.987$; NRS $\geq$ 5: $N = 33$, $p = 0.746$; DN4+: $N = 27$, $p = 0.977$). Concerning the main effect of time, no differences were detected for NRS average scores ($p = 0.816$). However, considering patients with or without a clinically significant pain separately (i.e., with NRS $\geq$ 5 and NRS < 5, respectively), we obtained different results. Specifically, patients with mild or lower pain intensity at baseline increased their pain intensity ($p = 0.004$), but this increase was lower than the minimal clinically important difference (MCID) of the scale (2 points[30]), while patients with higher pain at baseline (NRS $\geq$ 5) showed a clinically relevant reduction of pain over time ($p < 0.001$). Post hoc analysis showed that, in both subgroups, pain significantly changed at the end of the treatment and follow-up, when compared with the baseline value; on the contrary, no differences were detected between T1 and T2. Similarly, considering only DN4 + patients, we observed a similar trend

Table 2. Comparison of the Numerical Rating Scale (NRS) values between clinical and demographic groups, in the whole sample, and in patients with neuropathic components (DN4+)

	Whole sample ($N = 224$)		DN4+ ($N = 44$)	
	M (SD)	P	M (SD)	P
Sex				
Man	2.1 (2.5)	**<0.001**	4.1 (2.0)	**0.008**
Woman	3.5 (3.0)		6.1 (2.6)	
Index stroke type				
Ischemic	2.8 (2.7)	0.534	5.3 (2.5)	0.538
Hemorrhagic	2.7 (3.1)		4.8 (2.5)	
Affected side				
Right	2.3 (2.4)	0.096	4.4 (2.0)	0.185
Left	3.1 (3.1)		5.4 (2.7)	
Language impairment				
Yes	2.8 (2.2)	0.369	4.1 (1.6)	0.179
No	2.7 (3.0)		5.3 (2.6)	
Neglect syndrome				
Yes	3.9 (3.3)	**0.014**	5.7 (2.9)	0.237
No	2.4 (2.6)		4.7 (2.2)	

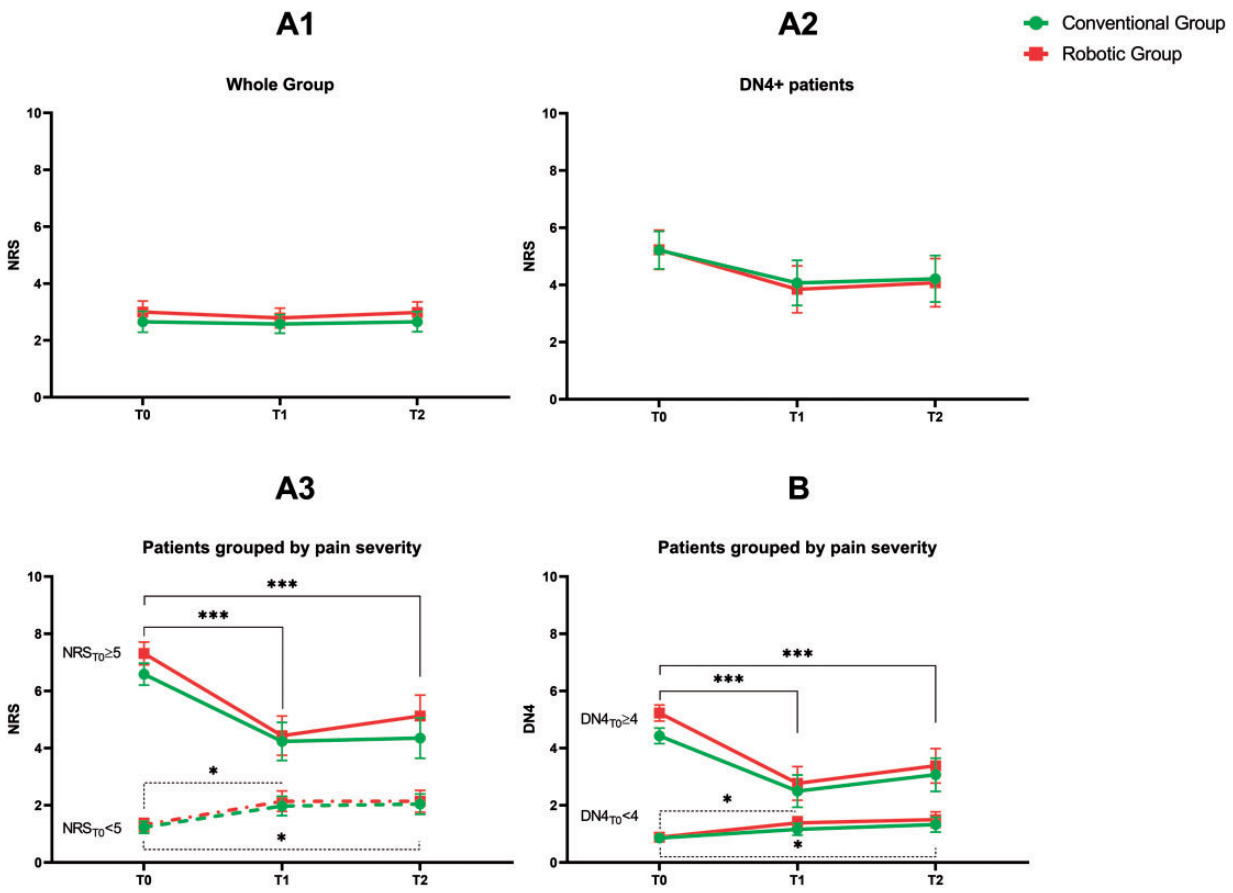
Boldface values indicate a statistically significant difference ($p < 0.05$).

Table 3. Correlations between numerical demographic/clinical variables and pain at baseline

	Whole sample ($N = 224$) NRS_{T0}	DN4 + patients ($N = 44$) NRS_{T0}
Age	0.083 (0.215)	0.236 (0.123)
Time since stroke	**0.173 (0.010)**	0.133 (0.388)
Fugl–Meyer assessment	**−0.206 (0.002)**	−0.063 (0.686)
Motricity Index UL	**−0.215 (0.001)**	−0.037 (0.810)
Modified Barthel Index	**−0.242 (<0.001)**	−0.113 (0.465)
Physical Composite Score	**−0.399 (<0.001)**	−0.19 (0.234)
Mental Composite Score	−0.047 (0.487)	−0.044 (0.785)

DN4: Douleur Neuropathique 4; NRS: Numerical Rating Scale.
The Spearman rank correlation coefficients (p values) are reported. Boldface values indicate statistically significant correlations ($p < 0.05$).

Figure 4. (a1, a2, and a3) Evolution of pain in the two rehabilitation groups, according to the Numerical Rating Scale (NRS). (b) Evolution of the Douleur Neuropathique 4 (DN4) scores in patients with (DN4 $\geq$ 4) or without (DN4 < 4) a neuropathic component at baseline. The time points are the baseline (T0), after 30 conventional or robotic rehabilitation sessions (T1), and three months after the end of rehabilitation (T2). Statistical analysis showed that both pain scores evolved similarly in the two groups. The asterisks indicate a significant difference between time points, as shown by the post hoc tests (*$p < 0.05$; ***$p < 0.001$).



($p = 0.064$). Note that patients with neuropathic component ($N = 27$) showed a resolution of component after treatment passing from the DN4 + to the DN4− group (Figure 4).

Finally, as reported in Table 4, we found that pain intensity at baseline was inversely correlated with the improvement in the upper limb motor function, as measured by the change from baseline of the FMA ($r = -0.172$, $p = 0.018$); on the contrary, when considering only patients with a DN4 score ≥ 4, pain at baseline was uncorrelated with the improvements obtained after the treatment.

Discussion

The current study shows that PSSP impacts upper limb motor functions, disability, and QoL, as well as on functional recovery, but it can be reduced after a rehabilitation intervention.

In the current study, we focused on PSSP in a cohort of subacute poststroke patients undergoing upper limb rehabilitation, and we found that about 30% of them complained of PSSP from moderate to severe and about 20% presented symptoms of neuropathic pain. Other authors reporting on PSSP found higher percentages of PSSP among stroke patients in rehabilitation settings. In a review, Kalichman and Ratmansky[2] observed PSSP in about 55% of patients, but the authors stressed the strong association between the elapsed period since the stroke and the PSSP. Therefore, the difference with these data can be explained since we have focused on a homogeneous population with a specific time since stroke. Our data confirmed previous data showing that about 30% of

Table 4. Correlations between clinical improvement after the treatment and pain at baseline

	Whole sample ($N = 190$) NRS_{T0}	DN4 + patients ($N = 38$) NRS_{T0}
ΔFMA	**−0.172 (0.018)**	−0.060 (0.720)
ΔMI	−0.117 (0.109)	0.075 (0.656)
ΔmBI	−0.08 (0.270)	0.086 (0.607)
ΔPCS	0.004 (0.961)	−0.273 (0.112)
ΔMCS	−0.005 (0.951)	−0.032 (0.855)

DN4: Douleur Neuropathique 4; FMA: Fugl–Meyer assessment; mBI: modified Barthel Index; MCS: Mental Composite Score; MI: Motricity Index; NRS: Numerical Rating Scale; PCS: Physical Composite Score. The Spearman rank correlation coefficients (p values) are reported. Boldface values indicate statistically significant correlations ($p < 0.05$).

patients complained of PSSP within six months from stroke.[5] Neuropathic pain is defined by the International Association for the Study of Pain (IASP) as "pain caused by a lesion or disease of the somatosensory nervous system."[31] It can be a consequence of either a peripheral lesion or disease, as in diabetes, or a central lesion or disease (as in stroke).[32] Some pathophysiological mechanisms have been hypothesized for central pain; among those, a central sensitization, alterations in spinothalamic tract function, disinhibition theories, or thalamic changes can be listed.[33]

To the best of our knowledge, few studies reported that pain can be different between women and men after stroke and it should be considered in the management of the PSSP, nevertheless it is well known that sex differences in pain exist. According to the review of Bartley and Fillingim,[34] an interaction of biological (influence of sex hormones, sex-related cortical differences during the processing of pain-related stimuli, differences in the endogenous opioid system, and interaction between genotype and sex), as well as psychological and sociocultural factors, likely contribute to these differences.

Interesting is the result of the higher prevalence of PSSP in patients with neglect syndrome. Neglect syndrome is characterized by reduced awareness of stimuli on one side of space and the body (left side).[35] The relationship between neglect syndrome and pain is controversial. Our results are in agreement with those of Sobrinho et al.[36] Conversely, Ratmansky et al.[37] found that neglect can attenuate pain perception. Finally, Blennerhassett et al.[38] or Poulin de Courval et al.[39] did not find a relationship between neglect syndrome and pain. A potential explanation for these conflicting findings is the mean time poststroke of our sample, in fact in our study it was about one month longer than that of the sample analyzed by Blennerhassett et al. Indeed, it is known that the prevalence of pain increases with time post stroke. Analyzing the PSSP, Niessen et al.[40] found a relationship between shoulder proprioception, kinematics, and pain. In our previous study, we showed the strong relationship between neuropathic pain and sensory impairment: patients with hypoesthesia showed a significantly higher NPSI and DN4 score than patients with normal sensory function.[10] Unfortunately, in the current study, we did not assess the sensory impairment because the study aimed to evaluate the effect of rehabilitation on pain, motor, and functional upper limb recovery as well as on pain, disability, and QoL. It is also known that pain intensity is mainly encoded in the primary somatosensory cortex.[41] Moreover, according to Kenntner-Mabiala and Pauli,[42] the primary somatosensory cortex is involved in attention-related pain modulations. Patients with neglect show a left primary somatosensory cortex damage with reduced attention for the paretic side that, according to the above-mentioned findings, could explain for the relationship between neglect and pain, but further studies on the topic are needed. Summing up these results, we believe that the relationship between hemispatial neglect and PSSP deserves further investigations.

As expected, pain intensity at baseline was associated with lower upper limb motor function, higher disability, and lower QOL.[10] No similar relationship was observed between neuropathic pain component and function, disability, and QoL at baseline.

It is interesting to observe as PSSP (when moderate or severe) and neuropathic pain improved after a rehabilitation program (either robotic or conventional) and this improvement was maintained in the short-term follow-up.

The results on the effects of robotic therapy on pain in subacute stroke are controversial. Abdullah et al. did not observe changes in pain in subacute stroke patients who underwent robotic therapy,[43] while other authors found a significant reduction of pain in a sample of acute stroke recruited within one month from stroke and underwent upper limb robotic device.[44,45] Only a recent study compared robotic with conventional therapy to treat pain after stroke[11] but, in contrast to what was found by Kim et al., we did not evidence better results, in terms of pain reduction, in the RG, when compared to the CG. However, it is worthy to note that in the work of Kim et al., the robotic intervention was expressly aimed at reducing pain, using a prototype robot performing joint mobilization and stretching exercises (i.e., only passive mobilisation) in a single degree of freedom of the shoulder (abduction

movement). Finally, an important finding of our study is that the recovery during rehabilitation is negatively influenced by PSSP at baseline. In particular, when we analyzed the impact of pain on recovery, we found that pain intensity at baseline was inversely correlated with the improvement of upper limb motor function, as measured by the Fugl–Meyer assessment. These results support the hypothesis that PSSP has an impact on the rehabilitation outcomes in patients with stroke and, therefore, should be considered when planning the rehabilitation intervention.

This study has potential limitations. First, the use of a self-report measurement scale to assess pain that could lead to a bias, because of the unblinding of patients to their treatment allocation (as usual in rehabilitation clinical trial), and the possible variation in when pain was assessed. Moreover, the use of the DN4 scale that does not allow to discriminate central and peripheral sources of neuropathic pain as well as the lack of information about the number of patients with potential central sources of pain (as internal capsule stroke, thalamic stroke, or medullary stroke). In addition, the lack of information about fluctuations in patients' compliance with pain medication or doses given. Finally, the high number of dropouts at follow up (three months after the end of the treatment).

Nevertheless, our study confirms the hypothesis that pain in patients with stroke negatively influences the rehabilitation program, suggesting that pain can reduce the ability of patients to reach their maximum functional potential after stroke.

Acknowledgments

The authors would like to acknowledge the contribution of the members of Fondazione Don Gnocchi Robotic Rehabilitation Group: Stefania Lattanzi, Laura Cortellini, Giuliana Liberti, Francesca Panzera, Piera Mitrione, Dario Ruzzi, Giuliana Rinaldi, Camilla Galli, Sabina Insalaco, Luca Padua, Fabio De Santis, Pietro Spinelli, Serena Marsan, Ilaria Bastoni, Annarita Pellegrino, Tommasangelo Petitti, Costanza Pazzaglia, Chiara Di Blasi (Roma); Anna Castagna, Cristina Grosso, Paola Ammenti, Davide Cattaneo, Luca Azzinnaro, Daniela Barbieri, Silvia Cassani, Chiara Corrini, Matteo Meotti, Riccardo Parelli, Albino Spedicato, Marta Zocchi, Marcella Loffi, Domitilla Manenti, Laura Negri, Furio Gramatica, Valerio Gower (Milano); Fulvia Noro, Luca Medici, Romina Garattini, Federica Bariselli, Marin Luli, Mauro Ricca, Stefano Negrini (Rovato); Elena Giannini, Assunta Gabrielli, Benedetta Gnetti, Barbara Deidda, Paola Beatini, Stefania Callegari, Beatrice Cabano (La Spezia); Francesco Converti, Assunta Pizzi, Antonella Romanelli, Gabriella De Luca, Federica Vannetti, Elisabetta Simoncini, Monica Martini, Elisa Peccini (Firenze); Lucia Avila, Maria Assunta Gabrielli, Manuele Barilli, Elisabetta Bertocchi, Giorgia Giannarelli, Elisabetta Lerda, Miriam Vasoli, Paolo Rossi, Valter Marsili, Brunella Tognoli, Andrea Bertolini (Massa and Fivizzano); Giovanni Vastola, Massimo Colella, Rita Mosca, Gaetanina Competiello, Antonietta Chiusano, Antonella Della Vecchia, Soriano Pasqualina, Michela Pagliarulo (Sant'Angelo dei Lombardi); Vito Remollino, Marcello Magliulo, Giuseppe Araneo, Lucia Galantucci, Nicola Lioi, Federico Marrazzo, Stefano Larocca, Roberta Calia, Sara Benevento, Olga Toscano, Michele Lategana (Acerenza and Tricarico).

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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