Comprehensive measurement of long-term outcomes and costs of rehabilitation in patients with stroke

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Chapter 2

The trajectory of pain and pain intensity in the upper extremity after stroke over time: a prospective study in a rehabilitation population

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Abstract

Purpose

To assess the presence of upper extremity pain after stroke over time and the course of its intensity in patients with persistent pain.

Materials and methods

Patients with stroke completed a question on the presence of upper extremity pain (yes/no) and rated its intensity with a visual analogue scale (0-10) at 3, 18 and 30 months after starting multidisciplinary rehabilitation. The presence of upper extremity pain and its intensity over time were analysed with Generalized Estimating Equations models and Linear Mixed Models, respectively.

Results

678 patients were included. The proportions of patients reporting upper extremity pain were 41.8%, 36.0% and 32.7% at 3, 18 and 30 months, respectively, with the decline in proportions reaching statistical significance (odds ratio 0.82, confidence interval 0.74-0.92, $p < 0.001$). At all time points, in those reporting pain the median intensity was 5. (interquartile ranges (IQR) 4.0-7.0 at 3 and 3.0-6.0 at 18 and 30 months). In the 73 patients with persistent pain, there was no significant change in intensity over time.

Conclusions

The proportion of patients reporting upper extremity pain after stroke was considerable, despite a significant decrease in 2.5 years. In patients reporting persistent pain, the intensity did not change over time.

Introduction

Pain is a common symptom after stroke, with a prevalence of up to 50%[1,2]. The presence of pain in patients with stroke was associated with more fatigue and lower quality of life[1]. Pain after stroke was also related to anxiety, depression and even a predictor of suicidality[1-3]. However, pain after stroke remains an underrecognized medical problem[4,5]. More than one-third of patients with post-stroke pain were not treated for this pain at all[6].

The most common location of pain after stroke is the upper extremity: in 60% of patients reporting pain after stroke the upper extremity is involved, either or not in combination with pain elsewhere in their body[7,8]. Pain in the upper extremity was found to be associated with prolonged hospitalization, less functional improvement and more cognitive decline[9,10]. Risk factors associated with the development of upper extremity pain included muscle weakness, stroke severity, sensory abnormalities, spasticity and a low Barthel Index Score[10].

Knowledge on the course of upper extremity pain over time is fragmented and to some extent contradictory. Upper extremity pain is described to typically develop around three weeks after stroke[11]. Nevertheless, this pain can also develop later on as described by Hansen et al.[8] in a study with 299 patients from a hospital-based population. This study demonstrated an increase in the frequency of upper extremity pain (defined as Numeric Rating Scale ≥ 4) from 13.1% at three months to 16.4% at six months after stroke[8]. In contrast, in a population-based study with 416 patients, a much higher prevalence of upper extremity pain (defined as Visual Analogue Scale ≥ 40 mm) was reported and this prevalence decreased from 60% at four months to 45% at 16 months after stroke[7]. Besides these contradictory results, there seems to be a knowledge gap on the long-term course of pain beyond 16 months after stroke.

Therefore, the aims of the present prospective cohort study were: 1) to assess the presence of upper-extremity pain in patients with stroke until 30 months after starting rehabilitation; 2) to compare characteristics of patients with and without upper extremity pain at three months after starting rehabilitation; and, 3) to assess changes in pain intensity in patients with persistent upper extremity pain.

Materials and methods

Study design

The Stroke Cohort Outcomes of REhablitation (SCORE) study is an observational, prospective study, describing the outcomes of consecutive patients with stroke who receive multidisciplinary rehabilitation in a rehabilitation center in the Netherlands[12]. For the present study we used the collected data on pain from this sample. Rehabilitation treatment was provided by a multidisciplinary team, consisting of a rehabilitation physician, physical therapist, occupational therapist, speech therapist, social worker, psychologist and other professionals if needed. The care was delivered in either an inpatient or an outpatient setting. The intensity and duration of the multidisciplinary care depended on the capacity of the patient. Delivery of care was in accordance with the Dutch national guideline on the management of stroke[13].

The SCORE study started in March 2014 and inclusion of patients ended in December 2019. The study protocol was approved by the Medical Ethical Committee of the Leiden University Medical Center (protocol number NL465321.058.13) and is registered in the Netherlands Trial Register (number NL4293). The results are reported according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines[14].

Study sample

Consecutive patients with stroke who received inpatient or outpatient multidisciplinary rehabilitation were invited by their treating rehabilitation physician to participate in the SCORE study when they were 18 years or older and when they had a first or recurrent stroke less than six months ago. Patients with dementia or a psychiatric disorder (as reported in the referral letter from the rehabilitation physician in the referring hospital) and patients who were not able to complete questionnaires in Dutch were excluded. For inclusion in the current analyses, patients also had to have completed at least one questionnaire concerning upper extremity pain.

Procedure

In the first week of rehabilitation patients were invited by their treating physician. All patients provided written informed consent before participation.

The assessments consisted mainly of questionnaires, with the exception of clinical characteristics. Patients completed questionnaires on paper or online, depending on their preference, either or not with the help of a proxy. When there was no response within 10 days, patients were contacted by telephone or email by the study coordinator or research nurse, with a maximum of two reminders. When patients did not complete two consecutive

questionnaires they were considered lost-to-follow-up and received no further invitations to complete assessments.

The study protocol and all questionnaires were critically appraised by a panel of 8 stroke patients, the patient research partners connected to the study. Their appraisal included a review of the self-developed questions that were not part of validated questionnaires.

Measures

Sociodemographic and clinical characteristics

Age, sex and stroke type (ischemic or hemorrhagic stroke) were extracted from the patients' medical file. Alcohol usage prior to stroke, education level and living situation were collected through a questionnaire at the start of the rehabilitation (baseline). Comorbidities were assessed at baseline by the Dutch Life Situation Cohort Questionnaire, comprising 16 chronic diseases including diabetes[15].

In patients who received inpatient rehabilitation, a nurse completed the Barthel Index (BI) at baseline in the rehabilitation center and reported this in the patients' medical file. The BI measures functional dependence and ranges from 0 (i.e. totally dependent) to 20 (i.e. totally independent)[16].

Pain

At 3, 18 and 30 months after baseline patients completed questions on upper extremity pain. They were asked whether they experienced pain in their shoulder, arm, wrist or hand in the past week (hereafter called upper extremity pain). If yes, they were asked to rate the worst pain in the past week on a Visual Analogue Scale (VAS) ranging from 0 (i.e. no pain at all) to 10 (i.e. the worst imaginable pain). A VAS was previously found to be a valid and reliable method to measure pain[17]. The VAS was presented in a vertical way, to decrease the probability of bias because of visuo-spatial neglect.

Other Patient Reported Outcome Measures (PROMs)

At three months after baseline, patients completed three domains of the Stroke Impact Scale (SIS) version 3.0, the Hospital Anxiety and Depression Scale (HADS) and the EuroQol-5Dimensions-3Levels (EQ-5D-3L).

The SIS is a stroke-specific health status measure, that assesses several domains[18]. Items were rated on a five-point Likert scale and transformed to a score ranging from 0 to 100, with higher scores indicating better functioning on that specific domain. The domains Communication and Memory and thinking were administered in all patients. In April 2015, the domain Mobility was added.

The HADS consists of two subscales, measuring depressive and anxiety symptoms[19]. Each subscale comprises seven items that are rated on a four-point Likert scale, with higher scores indicating more depressive or anxiety symptoms.

The EQ-5D-3L was used to measure health-related quality of life (HR-QoL)[20]. The EQ-5D-3L consists of five dimensions (i.e. mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension has three levels of severity. The score index ranges from -0.33 (serious problems on all five dimensions) to 1 (perfect health). In addition, the EQ-5D-3L comprises a vertical VAS, ranging from 0 to 100, that is used as a quantitative measure of overall health status.

Statistical analyses

All data were anonymized when entered in a database and were analyzed with SPSS for Windows, version 25.0 (IBM Corp, Armonk, New York, USA). A two-sided *p* value of 0.05 was considered statistically significant.

Data are described as numbers (N) with percentages (%), as means with standard deviations (SD) or as medians with interquartile ranges (IQR) depending on their nature and their distribution. The Kolmogorov-Smirnov test was used to assess whether or not continuous variables were normally distributed.

Age and sex were compared between patients who did and did not complete the questions concerning pain using the Fisher's exact test or the Mann-Whitney U test. These tests were also used to compare the sociodemographic and clinical characteristics and other PROMs between patients who did and did not have upper extremity pain at three months. Patients were classified in the pain group if they had answered yes to the question whether they experienced pain in their shoulder, arm, wrist or hand in the past week and no pain if they had answered no to this question.

To assess whether the proportions of patients reporting upper extremity pain changes over time, a Generalized Estimating Equations (GEE) model with an exchangeable correlation structure was estimated with upper extremity pain (yes/no) as a dependent variable, time as independent variable, and patient as repeated subject. A GEE model was used due to the presence of repeated measurements. In order to adjust for potential confounders and interaction effects, first each characteristic or PROM was added as variable individually to the model with an interaction term with time. For each characteristic and PROM the influence on the odds ratio (OR) of having upper extremity pain over time was assessed and whether or not the interaction term was statistically significant. Secondly, each influencing variable and each significant interaction term were included in a multivariable GEE model.

To study whether or not the pain intensity measured with the VAS changed over time, a Linear Mixed Model was estimated. Time was included as independent variable and patient as random intercept in the model. This analysis was performed by using data of patients that had upper extremity pain at all time points. This was done to avoid spurious results: for patients reporting no pain at one specific time point with pain at all other time points, a VAS would be imputed as this VAS was not known leading to a relatively high estimation, while the real VAS would be low at that time point.

Results

Patients

Between March 2014 and December 2019, 836 patients with stroke were included in the SCORE study. Of these patients, 158 (18.9%) were excluded from the current analyses, because they did not complete any questionnaires on upper extremity pain. Age and sex of these excluded patients did not statistically significantly differ from those of the 678 included patients (62.0 (IQR 52.6-69.8) years versus 63.5 (IQR 55.2-70.0), p = 0.237, and 40.5% females versus 38.1% females, *p* = 0.587).

Upper extremity pain at three months

At three months after baseline, 622/678 patients completed the upper extremity pain question, with 260 (41.8%) reporting the presence of upper extremity pain.

Table 1 shows the sociodemographic and clinical characteristics and other outcome measures of patients with and without upper extremity pain at three months. Patients reporting upper extremity pain were statistically significantly more often female, more often lived alone, had more comorbidities, and had worse scores on the BI, the SIS Memory and thinking, the SIS Mobility, the HADS depression score and anxiety score and the EQ-5D-3L index and the EQ-5D-3L VAS than patients without upper extremity pain.

Table 1. Sociodemographic and clinical characteristics of patients with stroke and a comparison of those with and without upper extremity pain three months after start of rehabilitation

	All patients n = 678		**Patients *with* upper extremity pain** n = 260[2]		**Patients *without* upper extremity pain** n = 362[2]		***p* value**[3]
	n		n		n		
Age in years	617	63.7 (55.2-70.0)	258	62.9 (53.4-69.3)	359	64.3 (56.5-70.5)	0.064
Female sex	622	235 (27.8%)	260	111 (42.7%)	362	124 (34.3%)	**0.036**
Inpatient rehabilitation	622	491 (78.9%)	260	214 (82.3%)	362	277 (76.5%)	0.090
Low education level	598	221 (37.0%)	246	81 (32.9%)	352	140 (39.8%)	0.102
Living alone	599	152 (25.4%)	247	74 (30.0%)	352	78 (22.2%)	**0.036**
Alcohol use >2 a day	590	58 (9.8%)	242	22 (9.1%)	348	36 (10.3%)	0.674
Comorbidities	474	1.0 (1.0-2.0)	198	2.0 (1.0-3.0)	276	1.0 (1.0-2.0)	**0.049**
Diabetes Mellitus	599	103 (17.2%)	247	49 (19.8%)	352	54 (15.3%)	0.155
Ischemic stroke	617	499 (80.9%)	257	204 (79.4%)	360	295 (81.9%)	0.468
Barthel Index[1]	378	17.0 (11.0-19.0)	171	15.0 (10.0-19.0)	207	18.0 (13.0-19.0)	**<0.001**
SIS Communication	610	92.9 (82.1-100.0)	255	92.9 (78.6-100.0)	355	92.9 (82.1-100.0)	0.137
SIS Memory and thinking	613	89.3 (75.0-96.4)	256	85.7 (71.4-96.4)	357	89.3 (75.0-96.4)	**0.019**
SIS Mobility	376	91.7 (77.8-100.0)	157	86.1 (63.9-97.2)	219	94.4 (86.1-100.0)	**<0.001**
HADS depression score	605	4.0 (2.0-8.0)	254	5.0 (2.8-9.0)	351	4.0 (2.0-7.0)	**<0.001**
HADS anxiety score	605	4.0 (2.0-7.0)	254	5.0 (3.0-8.0)	351	4.0 (2.0-6.0)	**<0.001**
EQ-5D-3L index	604	0.81 (0.69-0.90)	249	0.73 (0.56-0.81)	355	0.86 (0.77-1.0)	**<0.001**
EQ-5D-3L VAS	607	70.0 (60.0-80.0)	251	65.0 (50.0-75.0)	356	74.0 (65.0-83.8)	**<0.001**

[1]for inpatients only [2]622/678 patients completed the pain questions at three months of whom 260 reporting and 362 not reporting upper extremity pain [3]*p* values are shown based on the Fisher exact or Mann Whitney U Test.
Abbreviations: EQ-5D-3L EuroQol-5Dimension-3Level; HADS Hospital Anxiety and Depression Scale; PROM Patient Reported Outcome Measure; SIS Stroke Impact Scale; VAS Visual Analogue Scale.
Data are described as numbers (n) with percentages (%) or as medians with interquartile ranges.

The prevalence of upper extremity pain over time

At 18 months after baseline, 519 patients completed the questions about upper extremity pain and 187 of them (36.0%) reported that they experienced upper extremity pain. At 30 months, 446 patients completed the questions and 146 (32.7%) reported that they experienced upper extremity pain. The decrease in proportions of patients reporting upper extremity pain was statistically significant (OR 0.82, confidence interval (CI) 0.74-0.92, $p < 0.001$) (Table 2).

The GEE analysis showed that sex, education level, living situation, number of comorbidities, type of stroke, BI, SIS Communication, SIS Memory and thinking, SIS Mobility, HADS depression

score and anxiety score, and EQ-5D-3L index and EQ-5D-3L VAS was associated with the outcome, and therefore these variables and PROMs were included in the multivariable model. There were no significant modifiers, therefore none of the interactions terms were added to the multivariable model. After adjusting for these characteristics and PROMs, the decrease in proportions of patients reporting upper extremity pain over time remained statistically significant (adjusted OR 0.62, CI 0.49-0.79, $p < 0.001$).

Table 2. The prevalence of pain in the upper extremity and its intensity over time in patients with stroke

	3 months		18 months		30 months		OR (CI)	*p* value
	n		n		n			
Patients reporting upper extremity pain	622	260 (41.8%)	519	187 (36.0%)	446	146 (32.7%)	0.82 (0.74-0.92)[2]	**<0.001**[2]
							0.62 (0.49-0.79)[3]	**<0.001**[3]
							β (CI)	***p* value**
Intensity of pain in all patients reporting pain at a time point[1]	259	5.0 (4.0-7.0)	187	5.0 (3.0-6.0)	146	5.0 (3.0-6.0)	*	*
Intensity of pain in 73 patients with upper extremity pain at all time points[1]	72	6.0 (5.0-7.0)	70	5.0 (4.0-7.0)	73	5.0 (4.0-7.0)	-0.22 (-0.46-0.01)	0.06[4]

[1]measured with a visual analogue scale (range 0-10) [2]OR and *p* value shown of GEE model [3]OR and *p* value shown of GEE model adjusted for confounders [4]*p* value shown of Linear Mixed model
Abbreviations: CI confidence interval; OR Odds Ratio.
Data are described as numbers (n) with percentages (%) or as medians with interquartile ranges.
*No p value calculated to avoid spurious results: for patients reporting no pain at one specific time point with pain at all other time points, a VAS would be imputed as this VAS was not known leading to a relatively high estimation, while the real VAS would be low at that time point.

Pain intensity in patients with upper extremity pain

In patients reporting upper extremity pain, the median pain intensity was 5.0 (IQR 4.0-7.0) at 3 months, 5.0 (IQR 3.0-6.0) at 18 months and 5.0 (IQR 3.0-6.0) at 30 months. There were 73 patients who reported upper extremity pain at all time points. Of these 73 patients, 69 (95%) scored the intensity of this pain on a VAS: at three months after baseline the median VAS score was 6.0 (IQR 5.0-7.0), at 18 and 30 months 5.0 (IQR 4.0-7.0). Linear Mixed Model showed that there was no significant change in pain intensity over time: β -0.22, 95% CI -0.46 – 0.01, $p = 0.06$.

Discussion

This study showed that in this sample from a rehabilitation-based stroke population taking part in an observational cohort study, the frequency of upper extremity pain statistically significantly decreased between 3 and 30 months after starting rehabilitation. Nevertheless, still 32.7% of patients reported upper extremity pain at 30 months. Patients who reported upper extremity pain at 3 months were more often female, lived alone more often, reported more comorbidities, worse functional independence, memory and thinking, mobility and

health related quality of life and a higher score for depression and anxiety than patients without upper extremity pain. In patients with persistent upper extremity pain at all time points, the intensity of pain did not diminish significantly. These results confirmed that upper extremity pain is a common problem after stroke[8] and showed that this is also the case long-term after stroke in one-third of the patients.

Characteristics of patients with stroke with upper extremity pain

In the present study, having upper extremity pain at three months after starting rehabilitation was associated with more functional dependency measured with the BI and more depressive symptoms. These associations were also found in previous studies[2,9,10]. In addition, our results showed that patients with upper extremity pain experienced more restrictions on the SIS domains Memory and thinking and Mobility. A recent study found that worse arm function measured with the Fugl–Meyer Assessment (FMA), Action Research Arm Test (ARAT), and Motor Activity Log (MAL) was associated with post-stroke complex regional pain syndrome (CRPS)[21]. Previous studies showed that pain in general after stroke was associated with female sex and with quality of life[1,4,8,9]. This study showed that these associations are also found for upper extremity pain after stroke. These results confirm that the more severely affected patients have a higher chance of experiencing upper extremity pain and that this pain seems to negatively influence quality of life.

The prevalence of upper extremity pain over time

Regarding the course of upper extremity pain in patients with stroke over time, the present study found a decrease in the presence of upper extremity pain over time. This is in accordance with results from a hospital based study on the prevalence and intensity of pain after stroke where 32% of the patients reported moderate to severe pain 4 months after stroke and 21% at 16 months[7]. The present study also found a decrease 18 months after starting rehabilitation. However, before the first measurement moment 3 months after starting rehabilitation in the present study, the frequency of pain might have increased as suggested by previous literature. Dromerick et al.[11] described that 37% of stroke patients reported hemiplegic shoulder pain on average 19 days after stroke during inpatient stroke rehabilitation. Furthermore, a more recent study in acute and follow-up stroke services also described that within 72 hours after stroke 35% of patients reported hemiplegic shoulder pain and this increased to 44% at 8-10 week follow-up[22]. These results suggest that pain arises in the subacute phase after stroke and can decrease in the chronic phase.

Despite the diminishing frequency over time, the proportion of patients experiencing upper extremity pain at all time points is still considerably higher compared to the general population. The frequency of upper extremity pain in the general population was estimated at 20.8% in a

Swedish study[23]. This higher frequency can be explained by pathophysiological mechanisms specific for stroke, such as spasticity, thalamic pain and glenohumeral joint subluxation[24].

Pain intensity in patients with upper extremity pain

Next to the relatively high frequency of upper extremity pain on the long-term after stroke, our results showed that the intensity of pain did diminish over time, but this was not statistically significant in a small subgroup of patients who reported persistent upper extremity pain. The p-value was 0.06 which might suggest that in a larger number of patients a significant decrease in pain intensity would be seen. The median VAS level of 5.0 found in these patients is in line with previous literature: Hansen et al.[8] also reported a median pain intensity level of 5 three months after stroke and Paoluccci et al.[5] reported median pain intensity levels between 5 and 6 at a follow-up duration of six months after stroke. This indicates that when pain is present the intensity is moderate to severe[7,25].

Clinical implications

These results seems to indicate that that upper extremity pain is treated suboptimal in line with the findings of Widar et al.[6]. Therefore, these results highlight the importance for clinicians to recognize upper extremity pain as a complication after stroke on the long-term, and initiate adequate treatment accordingly. Prediction models for hemiplegic shoulder pain during inpatient stroke rehabilitation as for example by Feng et al.[26] might help clinicians to identify those at risk and monitor these patients more carefully. A recent review of Dyer at al.[27] reported significant pain reduction by a wide range of treatments including orthoses, botulinum toxin injection and electrical stimulation that appear promising, however many of the included studies showed methodological limitations. This review concluded that due to the complex etiology, clinicians should consider a range of potential treatments for upper extremity pain and tailor their approach to individual presentation[22]. Furthermore, two recent reviews showed that adding botulinum toxin type A injection, pulsed radiofrequency treatment, suprascapular nerve block, intraarticular injections of novel anti-inflammatory agents, robotics, electric stimulation and trigger-point dry needling to conventional rehabilitation was significantly more effective than conventional rehabilitation alone in the treatment of patients with hemiplegic shoulder pain[28,29].

Strengths and limitations

A strength of this study is that in a large number of patients upper extremity pain was prospectively mapped with a long-term follow-up after starting stroke rehabilitation. This allowed to gain insight in the course of the frequency of upper extremity pain. In addition, we corrected for a large number of factors of influence. Another strength was that we also had data on the intensity of pain.

A limitation of this study was that the pain questionnaire did not specifically ask whether pain in the upper extremity was located on the affected side and whether this pain started after stroke. Therefore, the reported pain could be present on the affected side due to stroke, present on the unaffected side due to overuse since their stroke, or pre-existing or non-stroke related pain. Another limitation of this study is that there were no data available on whether the pain reported by the patients of our population was recognized or not, whether spasticity was involved or not, whether treatment for pain was initiated, what this treatment consisted of and whether treatment was successful or not. Thus, future research should include the nature and effect of treatment of upper extremity pain during and after rehabilitation. Finally, although patients who were considered unable to complete questionnaires in Dutch were not eligible for the present study, it can indeed not be totally ruled out that the presence of mild cognitive impairments, aphasia and/or neglect could have influenced the answers on the pain questions.

Conclusion

It can be concluded that, although the percentage of patients with upper extremity pain in a rehabilitation-based stroke sample diminished over time, about a third of patients still reported upper extremity pain up to 30 months after starting rehabilitation. If upper extremity pain persisted, its intensity did not decrease over time, with a median VAS (0-10) of 5.0. The results of the present study suggest that there is room for improvement of diagnosis and treatment of upper extremity pain in stroke patients.

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