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Title Page

Influence of Clinical, Psychological and Psychophysical Variables on Long-term Treatment Outcomes in Carpal Tunnel Syndrome: Evidence from a Randomized Clinical Trial

Running Head: Prognostic factors in carpal tunnel syndrome

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Abstract

Objective: To assess the influence of clinical, psychological and psychophysical variables on long-term clinical outcomes after the application of either physical therapy or surgery in women presenting with carpal tunnel syndrome (CTS).

Methods: A secondary analysis of a randomized trial investigating the efficacy of manual therapy including desensitization maneuvers of the central nervous system against surgery in 120 women with CTS was performed. Clinical outcomes including pain intensity, function or symptoms severity were assessed at 6- and 12-months post-intervention. Participants completed at baseline several clinical (pain intensity, function, and symptoms severity), psychological (depression), and psychophysical (pressure pain thresholds and pain extent) variables which were included as predictors. Multiple regression analyses were conducted to assess the relationship between baseline variables and clinical outcomes at 6- and 12-months post-intervention.

Results: The regression models indicated that higher scores of each clinical outcome, i.e., intensity of pain or symptom severity, at baseline predicted better outcomes 6- and 12-months post-intervention (from 15% to 65% of variance) in both groups. Lower pressure pain thresholds over the carpal tunnel at baseline predicted poorer clinical outcomes 6- and 12-months post -intervention (from 5% to 20% of variance) in the physical therapy group, whereas higher depressive symptoms at baseline contributed to poorer outcomes at 6- and 12-months post-intervention (from 5% to 15% of the variance) within the surgery group. **Conclusion:** This study found that baseline localized pressure pain sensitivity and depression were predictive of long-term clinical outcomes in women with CTS following physical therapy or surgery, respectively.

Key Words: Carpal tunnel syndrome; Outcome; Depression; Pressure Pain; Physical Therapy, Surgery

Influence of Clinical, Psychological and Psychophysical Variables on Long-term Treatment Outcomes in Carpal Tunnel Syndrome: Evidence from a Randomized Clinical Trial

Introduction

Carpal tunnel syndrome (CTS) is a painful condition usually attributed to compression of the median nerve with an incidence rate of 1.8/1000[1] and a prevalence rate ranging from 6.3% to 11.7%.[2] Since CTS usually affects middle-age active workers,[3] it is associated with substantial health care costs and, therefore, presents a large economic burden. For instance, the overall cost associated with CTS in the United States of America (USA) exceeds $2 billion annually.[4]

The management of CTS includes conservative or surgical approaches; however, no consensus exists on which is the best therapeutic strategy.[5] Although clinical differences between surgery and conservative treatment are smaller than expected,[6,7] surgery continues to be common for these patients.[8] In fact, carpal tunnel surgery forms the highest utilization rate of surgical procedures performed in USA for the upper extremity.[9] Nevertheless, most patients with CTS attempt to avoid surgery in favor of conservative management.[10]

Most trials comparing conservative interventions to surgery have included localized therapeutic strategies targeting the carpal tunnel as the conservative approach, i.e., splints or steroid injections. Yet, recent studies support the presence of sensitization mechanisms in CTS indicating that this condition should not only be considered as a local entrapment neuropathy and, therefore, therapeutic strategies should consider nociceptive changes in the central nervous system.[11] A recent clinical trial investigating the effects of physical therapy including desensitization maneuver of the central nervous system against surgery in women with CTS found that physical therapy exhibited better short-term and similar long-term effects on pain and function than surgery, providing promising results for the management of CTS.[12] However, depending on the patient's presentation and pain mechanisms driving the painful condition, different results could be expected.

Previous studies have identified predictive factors that indicate likely responses to treatment; but these have mainly focused on surgical, and not conservative, interventions.[13] For example, a recent study reported that localized pressure pain sensitivity, centrally mediated symptoms (assessed by the central sensitivity inventory) and female gender were associated with poorer functional outcomes 3, but not 12 months, after surgery in CTS.[14]Most trials investigating prognostic factors of outcomes following conservative treatments have focused on local treatments such as corticosteroid injections.[13] A recent review found preliminary evidence suggesting that central sensitization in musculoskeletal pain conditions is associated with poorer outcomes in response to either surgical or conservative treatment.[15] Although there is evidence supporting the presence of central sensitization in CTS, studies addressing the relationship between sensitization and treatment outcomes are lacking. Indeed, no previous trial has investigated if pain sensitivity can influence treatment outcomes in response to conservative treatment in this population.

There is also increasing evidence supporting a role of psychological factors in CTS.[16,17] In fact, psychological factors, particularly depression, are strongly correlated with symptoms than electrophysiological findings in CTS patients.[18,19] Nevertheless, the role of depression on treatment outcomes is controversial. Most studies found that preoperative depressive levels were not a predictive factor of functional outcomes after surgery;[20-22] although one study observed that preoperative depressive levels were predictors influencing satisfaction after CTS surgery.[23] No study has investigated the role of depression as a prognostic factor after conservative treatment.

The objective of this study was to determine the influence of clinical, psychological and psychophysical variables on treatment outcomes after the application of physical therapy or surgery in women with CTS. We hypothesized that physical therapy including desensitization maneuvers of the central nervous system will produce better outcomes in those women with CTS showing greater sensitization.

Methods

Design

A secondary analysis was conducted alongside a randomized clinical trial,[12] performed in a General Hospital in Madrid (Spain), to determine the predictive influence of clinical, psychological and psychophysical variables on long-term treatment outcomes after the application of physical therapy including desensitization maneuvers of the central nervous system or surgery in women with CTS. Full details of the trial, participants, interventions, and results of the clinical outcomes are reported elsewhere.[12] The design was approved by the Hospital Universitario Fundación Alcorcón (HUFA) Institutional Review Board (PI01223-HUFA12/14) and the clinical trial was prospectively registered (ClinicalTrials.gov: NCT01789645).

Participants

Consecutive women diagnosed with CTS according to clinical (i.e., pain and paresthesia in the median nerve distribution, increasing symptoms during the night, positive Tinel sign, and positive Phalen sign) and electrophysiological findings (according to the guidelines of the American Association of Electrodiagnosis, the American Academy of Neurology, and American Physical Medicine and Rehabilitation Academy)[24] from a local regional Hospital (Madrid-Spain) were screened for eligibility criteria. Symptoms had to have persisted for at least 12 months. Patients were excluded if they exhibited: 1, sensory/motor deficits in the ulnar or radial nerves; 2, aged greater than 65 years; 3, previous hand surgery; 4, previous corticosteroid injections; 5, multiple diagnoses of the upper extremity; 6, cervical, shoulder, and/or upper extremity trauma; 7, systemic underlying medical diseases causing CTS, e.g., diabetes mellitus, thyroid disease; 8, co-morbid musculoskeletal medical conditions, e.g., rheumatoid arthritis, fibromyalgia; 9, presence of depressive symptoms (Beck Depression Inventory, BDI-II>8 points); or 10, pregnancy. All subjects signed an informed consent prior to their inclusion in the study.

Randomization and interventions

Participants were randomly assigned to receive either physical therapy or surgery. Details on the randomization procedure have been previously published.[12] Participants allocated to the physical therapy group received 3 treatment sessions of physical therapy of 30-min duration, which included desensitization maneuvers of the central nervous system, once per week. Briefly, the desensitization maneuvers consisted of soft tissue mobilization including manual techniques targeting those anatomical sites of potential entrapment of the median nerve such as the scalene, pectoralis minor, biceps brachii, bicipital aponeurosis, pronator teres, wrist flexors, transverse carpal ligament, palmar aponeurosis, or lumbricals muscles.[25] Further, lateral glides applied to the cervical spine, and tendon and nerve gliding exercises targeting the median nerve[26] were also applied.

Finally, all participants received an educational session on performing the tendon/nerve gliding exercises as home exercises. A complete description of the intervention can be found elsewhere.[12]

Patients randomly allocated to the surgery group underwent open or endoscopic release of the carpal tunnel. Since no evidence supports one particular surgical procedure, surgery was pragmatically applied based on the surgeon and patient preferences.[27] Patients allocated to this group also received the same educational session for performing the tendon and nerve gliding exercises as the physical therapy group.[12]

Clinical Outcomes

Outcomes on the original clinical trial were assessed at baseline, and 1, 3, 6, and 12 months after the intervention. [12] The primary outcome was the intensity of hand pain. An 11-point Numerical Pain Rating Scale (NPRS, 0: no pain; 10: maximum pain) was used to determine the patient's mean intensity of hand pain and the worst level of pain experienced in the preceding week.[28] Secondary outcomes included two subscales (functional status and severity) of the Boston Carpal Tunnel Questionnaire (BCTQ).[29] This questionnaire is valid, reliable, and responsive for individuals with CTS.[30]

In the current predictive analysis, changes on each clinical outcome, either primary or secondary, measured as the difference between scores at 6 and 12 months after intervention and scores at baseline, were analysed.

Predictor variables

Several clinical, psychological, and psychophysical outcomes were included as predictor variables. Clinical variables included mean pain intensity, worst pain intensity, functional status and symptoms severity at baseline.[28-30] Depressive symptoms, as assessed by the Beck Depression Inventory (BDI-II), were included as a measure of psychological health.[31] The BDI-II is easily adapted in most pain conditions for detecting depressive symptoms.[32]

Psychophysical outcomes included the analysis of pain extent and pressure pain sensitivity. Participants were asked to draw their perceived pain area on four different paper body charts: palmar/dorsal view of the hand and frontal/dorsal view of the upper extremity. Pain drawings were digitized and imported into custom made image analysis software as previously described.[33] The reliability of this process has been established.[34] The automatic computation of pain extent was performed with custom software developed with Matlab® as described previously.[33] The software generates the number of shaded pixels from the pain drawing and exports this data as total pain extent. The total number of pixels (frontal and dorsal) was reported as the pain extent for each patient and expressed as a percentage of total body chart area. Additionally, widespread pressure pain sensitivity was assessed by determining pressure pain thresholds (PPTs) bilaterally over C5-C6 joint, carpal tunnel, and tibialis anterior following previous guidelines[35,36] with an electronic algometer (Somedic AB©, Farsta, Sweden). The pressure was increased approximately at a rate of 30 kPa/sec. The mean of three trials was calculated for each site. Since no side-to-side differences were found in PPT, data of both sides were pooled for each location for the predictive analysis. A 30-second resting period was allowed between each measure. The reliability of the pressure algometry is high.[37]

Sample Size Calculation

Sample size calculation for the clinical trial was based on changes in the intensity of pain at 12-months follow-up as previously described. [12] A range from 10 to 15 subjects per potential predictor, with no more than 5 predictor variables, are usually recommended to develop an adequate sample size for prediction models and avoiding overestimation of the results.[38] Therefore, a sample size of at least 50 subjects per group was required given the maximum cut-off of five predictors included in the final model.

Statistical analysis

Descriptive statistics were used to describe participant characteristics in both groups and can be found in the original report of the trial.[12] Multiple linear regression analysis was used, aimed at determining if any predictor variable was associated with the clinical outcomes (changes in pain, function, symptoms severity). The following baseline variables were considered for inclusion within the model: baseline mean pain, worst pain, function, symptoms severity, depressive symptoms, pain extent, PPT neck, PPT carpal tunnel, PPT tibialis anterior. Further, age, severity of CTS (assessed by electrodiagnostic findings), and years with pain were also included as predictor variables.

First, correlations between the predictor variables and the clinical outcomes (changes on pain, function and severity) were investigated using Pearson correlation coefficients to ensure a linear relationship was present between each predictor and the clinical outcomes. Correlations among the predictors were also used to check for multicollinearity and shared variance between the variables. All analyses were conducted in both groups separately at both 6- and 12-month follow-up periods.

Subsequently, all candidate predictors were included in a multiple linear regression model to estimate whether baseline variables predicted outcomes at 6 and 12 months after the intervention. To examine the proportions of explained variance of each clinical outcome a hierarchical regression analysis was conducted by group. The significance criterion of the critical F value for entry into the regression equation was set at $P<0.05$. Changes in R^2 were reported after each step of the regression model to assess the association of the additional variables. Lastly, those variables that significantly contributed any clinical outcome at each follow-up period were selected for inclusion into parsimonious final regression model.

Results

From a total of 120 patients that were initially included and randomly allocated into physical therapy (n=60) or surgery (n=60) group; 111 (92.5%) were included in the final analysis[12] and the current predictive analysis. Two patients from the physical therapy group dropped out at the 6-month follow up and another three dropped out at 12 months. Similarly, four patients allocated to the surgical group dropped out at the 12-month follow-up. The flow diagram of patient recruitment and retention is illustrated within **Figure 1**.[12] Baseline variables were not significantly different between groups as previously described[12] (**Suppl. Table 1**).

Both groups experienced similar improvements in all clinical outcomes at 6 and 12 months after treatment as previously reported[12] and showed in **Supplementary Table 2**.

Prediction of outcomes following physical therapy

Significant correlations existed between the predictor variables, but none were considered to be multicollinear (defined as r>0.80); therefore, each significant predictor variable was included in the regression analyses.

Significant correlations between the clinical outcomes and some predictor variables were found at 6 and 12 months within the physical therapy group (**Supplementary tables 3-4**). In particular, PPT over the carpal tunnel was significantly negatively correlated with all clinical outcomes at both 6 and 12 months after the treatment (all, P<.001).

Tables 1-8 summarize the hierarchical regression analysis in the physical therapy group for each clinical outcome at 6 and 12 months. The regression coefficients indicated that higher scores of each clinical outcome, i.e., mean pain intensity or symptom severity, at baseline predicted better outcomes at 6 and 12-months post-intervention, i.e., higher change scores on mean pain intensity or symptoms severity (explaining from 17% to 65% of the variance in the respective outcome). The regression model also revealed that lower PPTs over the carpal tunnel at baseline predicted poorer outcomes at 6 and 12 months following the intervention, i.e., smaller change scores, in all the clinical outcomes investigated in this trial (contributing from 5% to 20% of the variance in the respective outcome). Pain extent at baseline was not predictive of outcome.

Prediction of outcomes following surgery

Significant correlations between clinical outcomes and some predictor variables in the surgery group were also observed (Supplementary Tables 3-4). In particular, depressive symptoms were significantly and negatively correlated with all clinical outcomes at 6 and 12 months (all, P<.001).

Tables 1-8 summarize the hierarchical regression analysis in the surgery group for each clinical outcome at 6 and 12 months. In general, the regression coefficients obtained indicate that higher scores of each clinical outcome, i.e., mean pain intensity or symptoms severity, at baseline predicted better outcome at 6- and 12-months following surgery, i.e., higher change scores on mean pain intensity or symptoms severity (explaining from 15% to 55% of the variance in the respective outcome). The regression model also revealed that another predictor in the surgery group was depression, where higher depressive symptoms at baseline contributed to poorer outcomes at both 6- and 12-months following treatment, i.e., smaller change scores (contributing from 5% to 15% of the variance in the respective outcome). The size of the patient's pain extent at baseline was not predictive of outcome.

Discussion

This study found different predictor variables of long-term outcomes in women with CTS depending on whether they received physical therapy or surgery. The multiple regression analysis revealed different models for each group explaining between 30% to and 70% of the variance in the clinical outcomes (changes in pain intensity, function or symptom severity) at 6- and 12-months post-intervention. In particular, pressure pain hypersensitivity over the carpal tunnel and higher depressive symptoms at baseline were associated with poorer clinical outcomes at 6 and 12 months following physical therapy or surgery, respectively.

All regression models revealed that higher baseline scores on a particular variable, i.e., pain intensity or symptoms severity, predicted better outcomes 6- and 12-months post-intervention (from 15% to 65% of the variance) in both groups. These results seem to be expected since it would be easier to elicit higher changes in a clinical outcome with higher baseline scores. Similarly, it is also possible that individuals who had lower pain and less disability had less room to demonstrate improvement. Our results agree with the results reported by Burke et al supporting that greater pre-operative symptoms resulted in higher post-operative improvements.[39] Similar results have been also observed in other pain conditions. For instance, some studies have reported that higher disability scores at baseline were associated with greater reduction in the same clinical outcome in subjects with whiplash-associated neck pain after receiving an exercise intervention.[40,41] However, it is important to consider that cohort studies have shown that higher levels of pain intensity at baseline are a consistent factor for predicting poor outcomes in the same population.[42,43] It is possible that the prognostic role of higher levels of pain and related-disability would be different if patients receive treatment versus just following the natural history of the condition.

We also observed that baseline pressure pain hypersensitivity over the carpal tunnel was consistently associated with poorer clinical outcomes at 6 and 12 months (explaining between 5% to 20% of the variance) when women with CTS received physical therapy, but not surgery. Higher localized pressure hyperalgesia at the carpal tunnel suggests that peripheral sensitization, but not central sensitization, was associated with worse response to physical therapy, probably related to the presence of peripheral neurogenic inflammation of the median nerve and higher nerve damage. This would be a relevant finding for clinicians, since early identification of peripheral sensitization (decreased PPTs) over the carpal tunnel (and potentially more median nerve damage) could lead to prompt derivation to surgery or other therapeutic approaches, e.g., corticoid steroid injections, instead manual therapy. There is no previous study investigating the prognostic role of sensitivity to pressure pain in patients with CTS receiving physical therapy. Our results are similar to those previously reported by Roh et al. who also showed that localized pressure pain sensitivity was not a predictor of 12-months outcomes after CTS surgery.[14] However, current results are also contrary to those previously observed in subjects with whiplash-associated disorders where patients exhibiting augmented central pain processing obtained worse clinical outcomes than those subjects exhibiting localized mechanical hyperalgesia after receiving an exercise treatment program.[44] In addition, the lack of a prognostic role of central sensitization is also contrary to what is seen in musculoskeletal pain conditions.[15] It is possible that the role of central sensitization in neuropathic conditions would be different than in musculoskeletal pain conditions. It is also plausible that the physical therapy treatment applied in this trial, based on nociceptive pain mechanisms and targeting the central nervous system, would lead to best management of the sensitization process.

Another important result of the current study was that higher depressive symptoms were associated with poorer clinical outcomes at 6 and 12 months (explaining between 5% to 15% of the variance) when women with CTS received surgery, but not physical therapy. Although Rosenberger et al suggested that success of surgical treatment can be complicated by the presence of depressive symptoms;[45] most studies did not find pre-operative levels of depression as a predictive factor of outcomes after surgery in CTS.[20-22] Discrepancies between studies could be related to differences in depression levels between samples. We should consider that depressive levels in our sample were small since we excluded patients with depression (BDI-II>8 points); however, they were similar to previous scores provided in a population-based study.[19] Nevertheless, we should remark that in our study, individuals with depression were excluded; therefore, current results should be considered with caution at this stage. We do not currently know if similar results would be observed in women with CTS with depression.

The fact that higher depressive symptoms were associated with poorer outcomes in the surgery, but not physical therapy, group may be intrinsically related to a higher patient-therapist interaction during the physical therapy intervention or personal expectations. For instance, the personal interaction between the patient and the physical therapist during the treatment sessions could provoke some particular expectative in the patient. This could be related to the intrinsic placebo effect of manual therapies.[46] This patient-therapist personal interaction is not present during the surgical process. Perhaps those patients who had higher expectations for benefit from the surgical intervention expected more than they received and were disappointed. Similarly, surgery usually need one month for proper tissue healing recovery after the procedure; therefore, patients receiving this procedure could also expect a quicker recovery. Therefore, clinicians should evaluate the presence of depressive levels in patients with CTS who will receive surgery for avoiding unexpected outcomes after the procedure and, for instance, for including cognitive or psychological strategies coadjutant to the surgical procedure. Future clinical trials should analyze the prognostic role of patient expectations after physical therapy or surgery in CTS.

Our results should be considered according to the strengths and limitations of the trial as previously described.[12] Potential strengths include its prospective design, the inclusion of patients with clinical and electrophysiological findings, a systematic application of baseline and clinical outcomes, the follow-up period, and the high retention rate. Further, at least 5 individuals were used for each predictor variable when developing the current prediction model, which minimizes the risk of overestimating the results.[47] Among the limitations, multi-center trials including patients from the general population and the inclusion of men would help to better extrapolate the results. Second, patients in the physical therapy group received just three sessions based on the authors' clinical experience; therefore, we do not know if a greater number of sessions would affect the results. In fact, patients and clinicians were not blinded to the treatment group due to the nature of the interventions.[12] Third, we should also recognize that patients in both groups received education about use of tendon and nerve gliding exercises. Therefore, future trials could include a comparison treatment-as-usual group as a control. Fourth, we assessed the clinical outcomes at 6 and 12 months, so we do not know if the identified prognostic variables would change with longer periods of time. Fifth, other potential psychological variables such as anxiety level or sleep quality, or patient's expectative were not included in this study. Finally, these results should not be extrapolated to men with CTS since only women with CTS were included.[12]

Conclusions

This study found different predictors of long-term outcomes in women with CTS depending on whether they received physical therapy or surgery. Localized pressure pain sensitivity over the carpal tunnel at baseline was associated with poorer outcomes at 6 and 12 months following physical therapy, whereas higher depressive symptoms at baseline were associated with poorer clinical outcomes 6- and 12-months following surgery. These results should be considered when conservative or surgical approaches are applied to patients with CTS.

Author contributions

All authors contributed to the study concept and design. CFdlP, AIdlLR and CC contributed to analysis and interpretation of data. CFdlP, MB and DF contributed to drafting the paper. MB and DF provided administrative, technical and material support. JLAB and DB supervised the study. All authors revised the text for intellectual content and have read and approved the final version of the manuscript.

Conflict of Interest Statement

The Author(s) declare(s) that there is no conflict of interest.

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Legend of Figure

Figure 1: Flow diagram of patients throughout the course of the study.

Table 1: Summary of the Stepwise Regression Analyses to determine Predictors of Changes in Mean Pain Intensity at 6 Months

	Predictor Outcome	***B***	**SE B**	**95% CI**	**β**	**t**	**P**
Physical Therapy	Step 1						
	Mean Pain Intensity	.798	.154	.489, 1.107	.591	5.18	<.001
	Step 2						
	Mean Pain Intensity	.853	.146	.560, 1.145	.632	5.68	<.001
	Symptoms Severity	-.900	.322	-1.548, -.252	-.301	-2.80	.007
	Step 3						
	Mean Pain Intensity	.852	.141	.569, 1.135	.631	6.06	<.001
	Symptoms Severity	-.747	.320	-1.390, -.104	-.250	-2.33	.024
	PPT over carpal tunnel	.004	.002	.000, .008	.225	2.11	.040
Surgery	Step 1						
	Mean Pain Intensity	.791	.145	.502, 1.081	.577	5.47	<.001
	Step 2						
	Mean Pain Intensity	1.047	.166	.715, 1.378	.763	6.32	<.001
	Depression (BDI-II)	-1.523	.553	-2.630, - .416	-.332	-2.75	.008

Physical Therapy: R^2 adj. = .350 for step 1, R^2 adj. = .439 for step 2, R^2 adj. = .487 for step 3;

Surgery: R^2 adj. = .322 for step 1, R^2 adj. = .389 for step 2

Table 2: Summary of the Stepwise Regression Analyses to determine Predictors of Changes in Worst Pain Intensity at 6 Months

	Predictor Outcome	***B***	**SE B**	**95% CI**	**B**	**t**	**P**
Physical Therapy	Step 1						
	PPT over carpal tunnel	.011	.003	.005, .016	.457	3.64	<.001
	Step 2						
	PPT over carpal tunnel	.010	.003	.004, .016	.408	3.50	<.001
	Worst Pain Intensity	.588	.184	.219, .957	.373	3.20	.002
	Step 3						
	PPT over carpal tunnel	.011	.003	.005, .017	.441	3.93	<.001
	Worst Pain Intensity	.591	.175	.239, .943	.375	3.37	.001
	Years with Pain	-.356	.148	-.654, -.058	-.267	-2.40	.020
Surgery	Step 1						
	Worst Pain Intensity	.683	.211	.261, 1.104	.386	3.24	.002
	Step 2						
	Worst Pain Intensity	1.128	.227	.674, 1.583	.638	4.97	<.001
	Symptoms Severity	-2.465	.672	-3.810, - 1.119	-.470	-3.66	.001
	Step 3						
	Worst Pain Intensity	1.620	.271	1.078, 2.161	.916	5.98	<.001
	Symptoms Severity	-1.652	.676	-3.006, -.299	-.315	-2.44	.018
	Depression (BDI-II)	-.421	.164	-.750, -.0092	-.301	-2.56	.013

Physical Therapy: R^2 adj. = .193 for step 1, R^2 adj. = .319 for step 2, R^2 adj. = .380 for step 3;

Surgery: R^2 adj. = .135 for step 1, R^2 adj. = .283 for step 2, R^2 adj. = .377 for step 3

Table 3: Summary of the Stepwise Regression Analyses to determine Predictors of Changes in Symptoms Severity at 6 Months

	Predictor Outcome	***B***	**SE B**	**95% CI**	**Β**	**t**	**P**
Physical Therapy	Step 1						
	Symptoms Severity	.770	.119	.530, 1.009	.674	6.46	<.001
	Step 2						
	Symptoms Severity	.773	.114	.543, 1.002	.677	6.75	<.001
	PPT over carpal tunnel	.002	.001	.000, .004	.230	2.30	.025
Surgery	Step 1						
	Symptoms Severity	.656	.089	.478, .835	.688	7.35	<.001
	Step 2						
	Symptoms Severity	.735	.091	.552, .918	.770	8.03	<.001
	Depression (BDI-II)	-.103	.010	-.206, -.001	-.236	-2.45	.017

Physical Therapy: R^2 adj. = .444 for step 1, R^2 adj. = .488 for step 2;

Surgery: R^2 adj. = .465 for step 1, R^2 adj. = .507 for step 2

Table 4: Summary of the Stepwise Regression Analyses to determine Predictors of Changes in Function at 6 Months

	Predictor Outcome	***B***	**SE B**	**95% CI**	**Β**	**t**	**P**
Physical Therapy	Step 1						
	Function	.843	.141	.559, 1.127	.645	5.97	<.001
	Step 2						
	Function	.862	.133	.595, 1.130	.660	6.48	<.001
	PPT over carpal tunnel	.002	.001	.001, .003	.278	2.73	.009
Surgery	Step 1						
	Function	.576	.092	.403, .771	.636	6.37	<.001
	Step 2						
	Function	.0681	.0.098	.485, .878	.738	6.93	<.001
	Depression (BDI-II)	-.103	.010	-.206, -.001	-.416	-3.64	.027

Physical Therapy: R^2 adj. = .405 for step 1, R^2 adj. = .473 for step 2;

Surgery: R^2 adj. = .394 for step 1, R^2 adj. = .433 for step 2

Table 5: Summary of the Stepwise Regression Analyses to determine Predictors of Changes in Mean Pain Intensity at 12 Months

	Predictor Outcome	***B***	**SE B**	**95% CI**	**Β**	**t**	**P**
Physical Therapy	Step 1						
	Mean Pain Intensity	.739	.163	.411, 1.067	.539	4.52	<.001
	Step 2						
	Mean Pain Intensity	.862	.133	.595, 1.130	.660	6.48	<.001
	PPT over carpal tunnel	.003	.002	.001, .005	.265	2.74	.020
Surgery	Step 1						
	Mean Pain Intensity	.925	.106	.712, 1.138	.746	8.68	<.001
	Step 2						
	Mean Pain Intensity	1.07	.104	.864, 1.279	.865	10.32	<.001
	Depression (BDI-II)	-.351	.093	-.536, -.166	-.318	-3.79	<.001

Physical Therapy: R^2 adj. = .276 for step 1, R^2 adj. = .312 for step 2;

Surgery: R^2 adj. = .557 for step 1, R^2 adj. = .644 for step 2

Table 6: Summary of the Stepwise Regression Analyses to determine Predictors of Changes in Worst Pain Intensity at 12 Months

	Predictor Outcome	***B***	**SE B**	**95% CI**	**B**	**t**	**P**
Physical Therapy	Step 1						
	PPT over carpal tunnel	.010	.003	.004, .016	.426	3.32	.002
	Step 2						
	PPT over carpal tunnel	.008	.003	.003, .014	.362	2.88	.006
	Worst Pain Intensity	.476	.203	.068, .884	.294	2.34	.023
	Step 3						
	PPT over carpal tunnel	.009	.003	.004, .0014	.406	3.29	.002
	Worst Pain Intensity	.470	.196	.076, .865	.291	2.39	.021
	Years with Pain	-.347	.165	-.678, -.016	-.253	-2.10	.040
Surgery	Step 1						
	Worst Pain Intensity	.859	.189	.481, 1.237	.506	4.54	<.001
	Step 2						
	Worst Pain Intensity	1.18	.194	.796, 1.572	.697	6.10	<.001
	Depression (BDI-II)	-.559	.153	-.867, - .252	-.416	-3.64	.001
	Step 3						
	Worst Pain Intensity	1.392	.206	.981, 1.804	.820	6.76	<.001
	Depression (BDI-II)	-.480	.152	-.775, -.165	-.350	-3.09	.003
	Symptoms Severity	-1.439	.600	-2.639, -.0239	-.286	-2.40	.020

Physical therapy: R^2 adj. = .165 for step 1, R^2 adj. = .234 for step 2, R^2 adj. = .284 for step 3;

Surgery: R^2 adj. = .244 for step 1, R^2 adj. = .372 for step 2, R^2 adj. = .448 for step 3

Table 7: Summary of the Stepwise Regression Analyses to determine Predictors of Changes in Symptoms Severity at 12 Months

	Predictor Outcome	***B***	**SE B**	**95% CI**	**B**	**t**	**P**
Physical Therapy	Step 1						
	Symptoms Severity	.967	.097	.773, 1.162	.816	9.69	<.001
	Step 2						
	Symptoms Severity	.970	.092	.786, 1.155	.818	10.58	<.001
	PPT over carpal tunnel	.001	.001	.000, .002	.205	2.65	.011
Surgery	Step 1						
	Symptoms Severity	.688	.092	.503, .872	.693	7.45	<.001
	Step 2						
	Symptoms Severity	.803	.097	.608, .997	.809	8.27	<.001
	Depression (BDI-II)	-.071	.026	-.123, -.020	-.269	-2.75	.008

Physical Therapy; R^2 adj. = .659 for step 1; R^2 adj. = .695 for step 2

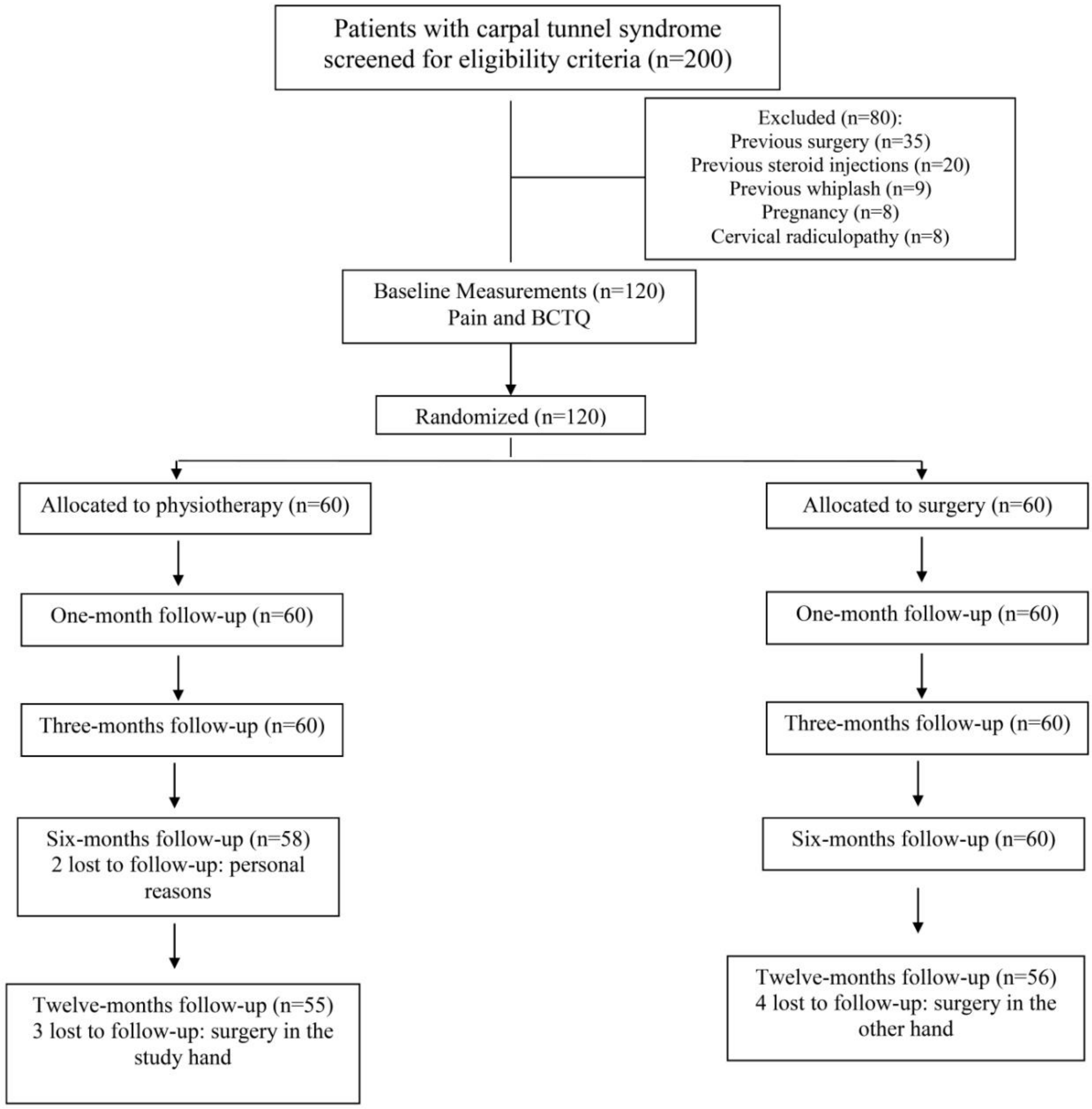
Surgery: R^2 adj. = .472 for step 1; R^2 adj. = .524 for step 2.

Table 8: Summary of the Stepwise Regression Analyses to determine Predictors of Changes in Function at 12 Months

	Predictor Outcome	*B*	SE B	95% CI	Β	t	P
Physical Therapy	Step 1						
	Function	.881	.139	.601, 1.160	.667	6.32	<.001
	Step 2						
	Function	.901	.130	.640, 1.162	.682	6.93	<.001
	PPT over carpal tunnel	.002	.001	.000, .004	.297	2.98	.005
Surgery	Step 1						
	Function	.555	.093	.369, .742	.611	5.97	<.001
	Step 2						
	Function	.691	.102	.486, .896	.759	6.73	.001
	Depression (BDI-II)	-.072	.027	-.127, -.017	-.297	-2.63	.011

Physical Therapy: R^2 adj. = .433 for step 1, R^2 adj. = .509 for step 2;

Surgery: R^2 adj. = .362 for step 1, R^2 adj. = .420 for step 2


Patients with carpal tunnel syndrome screened for eligibility criteria (n=200)
Excluded (n=80):
Previous surgery (n=35)
Previous steroid injections (n=20)
Previous whiplash (n=9)
Pregnancy (n=8)
Cervical radiculopathy (n=8)
Baseline Measurements (n=120)
Pain and BCTQ
Randomized (n=120)
Allocated to physiotherapy (n=60)
Allocated to surgery (n=60)
One-month follow-up (n=60)
One-month follow-up (n=60)
Three-months follow-up (n=60)
Three-months follow-up (n=60)
Six-months follow-up (n=58)
2 lost to follow-up: personal reasons
Six-months follow-up (n=60)
Twelve-months follow-up (n=55)
3 lost to follow-up: surgery in the study hand
Twelve-months follow-up (n=56)
4 lost to follow-up: surgery in the other hand