Prognostic factors for response to treatment by corticosteroid injection or surgery in carpal tunnel syndrome (PaLMS study): a prospective multi-centre cohort study

Running title: prognostic factors for CTS treatment

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/mus.26459

Tel: 01603 593316

Acknowledgements: We thank the patients who participated in this study; the local Principal Investigators at the following collaborating NHS sites: Julian Blake and Adrian Tearle (Norfolk and Norwich University Hospitals NHS Trust), Ann Harvey (Ipswich Hospital), Stephen Scott (James Paget Hospital, Gt Yarmouth), Jeremy Bland (Kings College Hospital), Lionel Christopher Bainbridge (Royal Derby Hospital); lay members from the local Patient and Public Involvement in Research Panel: Jenny Griffiths and Sue Spooner; Tony Dyer and Antony Colles for database support (Norwich Clinical Trials Unit); and Research Associates Leanne Miller and Kate Humble for assistance with data collection and data entry.

Abstract: 147 words

Manuscript (excluding abstract, references, tables and figure legends): 3782

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflicts of Interests: Author CJH was funded by the National Institute for Health Research (NIHR Senior Research Fellowship). Author ECFW was funded by the NIHR Cambridge Biomedical Research Centre. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, NHS or the Department of Health.

The remaining authors have no conflicts of interest to disclose.

Abstract

Introduction: Studies of prognosis for surgery and corticosteroid injection for carpal tunnel syndrome have considered only a limited range of explanatory variables for outcome.

Methods: Data were prospectively collected on patient-reported symptoms, physical and psychological functioning, comorbidity and quality of life at baseline and 6 monthly for up to 2 years. Outcomes were patient-rated change over a 6-month period and symptom-severity score at 18 months.

Results: 754 patients with CTS completed baseline questionnaires and 626 (83%) completed follow-up to 18 months. Multivariable modelling identified, independent of symptom severity at outset, higher health utility, fewer comorbidities and lower anxiety as significant predictors of better outcome from surgery. In patients treated by steroid injection, independent of symptom severity at outset, shorter duration of symptoms and having no prior injection were significant predictors of better outcome.

Discussion: These multivariable models of outcome may inform shared decision-making about treatment for CTS.

Keywords: carpal tunnel syndrome, corticosteroid injection, surgical decompression, prognostic factors, outcome

Introduction

Carpal tunnel syndrome (CTS) is the most common upper limb entrapment neuropathy, caused by compression of the median nerve at the wrist[1]. CTS can cause significant physical disability[2] and is associated with anxiety, depression and reduced quality of life [3 4]. Non-operative treatments such as immobilisation with a wrist brace and steroid injections, sometimes repeated [5], can provide effective short-term relief of symptoms[6]. Surgical release, however, is most effective for long-term symptom resolution [7], though it carries a greater risk of complications [8 9] and is possibly unnecessary for some [10 11]. Further surgery is more costly than conservative measures. In the UK a total of 52,806 carpal tunnel releases or revisions were undertaken in 2011 costing £42 million[12] whilst in the USA 500,000 operations are performed annually for CTS at a cost of $2 Billion per year[13].

Some healthcare systems use restrictive policies where surgery is only offered in cases, where symptoms persist for more than three months after initial conservative therapy, or where the patient suffers from significant functional impairment or has neurological deficit [14]. Several studies have explored a range of prognostic factors for outcome from surgical and conservative treatments[15-18]. However, these studies were either limited by small sample sizes, a poor ratio of events to number of factors being studied resulting in overfitting, a restricted range of variables, the use of univariable analysis rather than multivariable models or were retrospective. There is a need for prospective studies to identify useful prognostic information in CTS which could be used to develop stratified care pathways, better inform shared decision-making about individual treatment choices and guide treatment policies[19].

Prognostic research can be categorised into four types described by the PROGnosis RESearch Strategy (PROGRESS) partnership[20 21], namely: i) fundamental prognosis research (studies of the course of a condition in the context of current care) ii) prognostic factor research (studies to identify specific factors associated with prognosis); iii) prognostic model research (development and validation of a statistical model that can predict individual risk of a future outcome) and iv) stratified medicine (using prognostic information to tailor treatment to patients with particular characteristics and evaluation of its impact).

The objective of our research was to identify which factors are associated with outcome from surgical release or steroid injection and therefore inform development of a prognostic model for further validation and testing.

Methods

We conducted a multi-centre, prospective observational cohort study of patients diagnosed with CTS and managed according to best evidence (the 'PalmS' study). The study protocol has been published[22].

The study was approved by National Research Ethics Service Committee East of England – Norfolk (reference 13/EE/0106) and local Research Governance approval at each participating trust was obtained prior to recruitment. All participants gave written informed consent prior to enrolment into the study.

Derivation cohort

Eligible patients were identified by a clinical neurophysiologist or hand surgeon whilst attending as out-patients at 5 secondary care sites in England between July 2013 and December 2015. Patients were invited to participate if they fulfilled the following criteria: aged ≥18 years with newly diagnosed CTS in at least one hand confirmed by nerve conduction studies (NCS). Exclusion criteria were: carpal tunnel decompression in the affected (worst) hand in the last 12 months, pregnancy or up to 12 months post-partum, serious co-morbidities, other limb mono-neuropathies, sensory or motor disturbances secondary to stroke, multiple sclerosis or nerve injury, and inability to read and write English.

Candidate prognostic factors

Putative prognostic factors of outcome from conservative or surgical treatment were identified through a literature search with consideration of what could be practically collected using patient report. Data were collected using a patient-completed report-form combining standardised validated and bespoke questionnaires. They included: patient reported symptom severity using the shortened Boston Carpal Tunnel Questionnaire (CTS-6)[23], patient-reported hand function using the 3 subscales of the Michigan Hand Questionnaire[24], psychological status using the Hospital Anxiety and Depression Scale[25], health-related quality of life (EQ5D-3L)[26] reported as utilities using UK-specific preference weights[27], comorbidities using the Self-Assessed Comorbidity Questionnaire[28]. Baseline, 6, 12, 18 and 24 months follow-up questionnaires were completed by participants either online or by mail. The following clinical and sociodemographic information was collected at baseline only: age, gender, ethnicity, duration of symptoms, height and weight, smoking status, weekly alcohol consumption in units (1 unit equivalent to 10ml pure alcohol), work status and type, and household income. Nerve conduction studies conducted at enrolment were obtained from participating centres and graded for electro-diagnostic severity according to Bland's criteria[29] to derive a baseline disease severity grade (grade 1 to 6).

Patients recruited between July 2015 and December 2015 completed follow-up to 18 months only. All data collection was finalised by July 2017.

Outcome measures

The primary outcome of interest was treatment success or failure defined with respect to the patient-reported global rating of change (GROC) for their worst hand only. This was collected at 6 monthly intervals by using a 5-point GROC for each hand (worse=1, unchanged=2, slightly better=3, much better=4, cured=5) compared to six months previously. This scale was then dichotomised into a 'success' (a GROC of 3, 4 or 5) or a 'failure' (a GROC of 1 or 2). Surgical outcome by GROC was also modelled using a more stringent dichotomisation by 'much improved' or 'cured' (GROC 4 and 5 only). When considering corticosteroid injections, an outcome was further considered a 'failure' if an individual later had surgery within the same 6 month period.

A secondary outcome was symptom severity captured using the CTS-6 score[23] at 18 months.

With the exception of nerve conduction studies all other putative prognostic factors were patient-reported as were the outcomes. Treatments by injection or surgical release were also patient reported. For a randomly sampled subset of participants (10%) the General Practitioners were asked to complete a brief questionnaire about any steroid injection or surgery received for CTS and dates as captured in the patients' primary care record. These were compared to the patients' self-report to estimate the level of misreporting of treatments received.

Statistical analysis

All analyses were based on the hand with CTS. In those who had bilateral CTS the worst hand was selected and the corresponding subscales of the CTS-6, MHQ and GROC for that side. The principal analysis was of treatment success or failure, i.e. the dichotomised GROC variable at the

follow-up time point immediately after treatment. A binary logistic regression model was used. As data were collected in repeated 6-month time periods, each individual participant could have an intervention more than once during the total follow-up period. Therefore, Generalised Estimating Equations (GEEs) were used to account for the correlation between observations from different time periods within individuals. It was intended to use an auto-regressive error structure, i.e. assuming the correlation to be weaker between ti me periods further apart than those closer together. However, due to the paucity of events this estimation was not possible and an independent error structure was used in the GEEs (which nonetheless would account for correlation between repeated observations within individuals when providing standard errors). Explanatory variables were the putative prognostic variables at baseline (when measured only once) or at the beginning of the 6 month period (where repeated measurements were made). The association between explanatory and outcome (treatment success or failure) was expressed as an odds ratio (OR) with 95% confidence intervals.

A second analysis was also made with the 18 month CTS-6 score as outcome, assessing the relationship with putative prognostic factors at baseline. In this case, a general linear model with a Normal error term was used.

For both analyses, initially univariable models were used, containing one putative prognostic variable alone. Then, a 'full model' was constructed containing all putative prognostic variables. A backwards deletion approach was then applied to reduce the model to include statistically significant explanatory variables only. This involved removing one variable at a time, the least statistically significant, until only statistically significant (set at the 5% level) variables remained in

the model. This was termed the 'final model'. The univariate, full and final models are all reported. Complete-case analysis was used and no imputation for missing data was applied.

Sample size

There is no consensus on the approach to compute power and sample size for logistic regression. However, to provide a target sample size we followed the approach of Demidenko[30]. Assuming a binary explanatory variable with equal subjects in each category, and a 33 % probability of successful outcome, 535 observations within the model would provide 90% Power to detect a significant association at the 5% level with an odds ratio of 1.79; assuming a probability of success of 80%, the same statistical power would be conferred with around the same number for an odds ratio of 2.3. Not all individuals would have an intervention during the follow-up period (and therefore not be included in the modelling), though it was assumed the majority would. Allowing for up to 20% loss to follow-up a minimum target sample of 642 recruited was aimed for.

Data management and data quality

A bespoke database was built using MS SQL Server and a bespoke website and associated software was built using MS ASP.NET. Both were hosted by the Norwich Clinical Trials Unit secure server at the University of East Anglia. Patients who opted to complete their questionnaires online were sent a password protected email link inviting them to complete their next questionnaire. For those patients who chose to complete paper copies returned via business reply mail all data were entered by research associates. Online submission of a questionnaire was only possible once all

mandatory fields were completed. Those returning incomplete paper questionnaires were contacted by the researchers to obtain any missing data where possible.

For data entered into the database from paper copies a random sample of 100 completed baseline questionnaires were checked. The error rate was less than 0.3% (29 errors in 11000 fields) and therefore data quality was considered to be high.

Results

A total of 1918 patients were invited to participate in the study, of whom 754 gave consent, met all eligibility criteria and returned full baseline questionnaires (see STROBE diagram Figure 1). A total of 626 patients completed follow-up to 18 months (83%) and were included in the primary analysis. Their mean age was 61.5 (SD=12.4) years and 404 (65%) were women. The right hand was the worst hand in 409 (65%) cases and 422 (67%) reported bilateral CTS. The median duration of symptoms was 12 to 18 months and mean symptom severity was 3.0 (SD=0.8) points on CTS-6. The median disease severity by NCS grade for the worst hand was 3 (range 1 to 6).

Of those participating, 318 (51%) underwent surgery for CTS in their worst hand within the first 6 months post study entry, whilst 56 (9%) had a steroid injection only and 252 (40%) underwent no treatment. By 18 months, 403 (64%) had their worst hand treated surgically. Repeated surgery was reported by 3 cases (<1%). A second injection in their worst hand was reported by 21 patients with 3 cases also receiving a third injection. By 18 months 165 patients (26%) remained untreated for their worst hand.

Verification against the patients' primary care records in a random sample of 84 participants (13%) showed that patient-report and primary care records for treatments by steroid and/or surgery concurred in 92% of cases (77 of the 84 surveyed). Steroid injections prior to surgical release and repeated injections were the most common discrepancies between the primary care record and the patient's report, however only in 2 cases would this have led to a misclassification of treatment group.

Analyses of surgery outcome

A global rating of change (GROC) at the first follow-up post-surgery was available for 455 surgical procedures over the full 18 months follow-up. These 455 were included in the GEE analysis. Of these, a successful outcome (using GROC≥3) was reported in 412 (91%) and 43 (9%) had a negative outcome (unchanged or worse). A comparison between those reporting a positive or negative outcome is presented in Table 1. Higher health utility derived from EQ5D-3L was the only consistent statistically significant prognostic factor for a positive outcome from surgery in the univariable, full and final model (Table 2). Lower anxiety and depression scores (HADS) were significantly associated with GROC but only in the univariable analysis and did not remain in the full or final model. A sensitivity analysis based on a more stringent cut-off for success (GROC 4 & 5 only) identified 353 procedures (78%) as having a positive outcome from surgery. Lower comorbidity score and lower anxiety were the only consistently significant predictors for outcome in the univariable and final model (comorbidity OR=0.93. 95% CI: 0.89 to 0.98, p= 0.011; HADS Anxiety OR=0.94, 95%CI: 0.89 to 0.99). p=0.11) (Supplementary Table 1).

The second analysis was based upon 406 surgically treated patients with symptom severity (CTS-6) available at 18 months. The explanatory variables were all recorded at baseline. These general linear models identified 3 baseline variables associated with lower symptom severity at 18

months which were statistically significant in both the full and final models: lower comorbidity score (β=0.03, 95%CI: 0.02 to 0.04, p<0.001), lower CTS-6 score at baseline (β= 0.11, 95%CI: 0.03 to 0.18, p=0.007), and lower anxiety (β= -0.02, 95%CI: 0.01 to 0.04, p<0.001) (Supplementary Table 2). For the final model, the R^2 was 12.0% and the adjusted R^2 was 11.3%.

Analyses of steroid injection outcome

The dichotomised outcome from 150 GROCs post-steroid injections were available for analyses. Table 3 gives the clinical and demographic details by outcome, either positive or negative. A shorter duration of symptoms and not having had a previous steroid injection were consistent statistically significant predictors of a positive outcome (Table 4).

Using CTS-6 at 18 months as outcome, a general linear model was constructed with the same baseline explanatory variables, as in the surgical model. Lower baseline CTS-6 score (β=0.55, 95%CI: 0.33 to 0.77, p<0.001) was the only consistent statistically significant predictor of better symptom score in the full and final models (Supplementary Table III). For the final model R^2 was 22.9% and adjusted R^2 was 21.3%.

A summary of predictive factors by outcome model and intervention is given in table 5.

Discussion

Our multivariable models included a total of 18 variables. Of these 4 were found to be consistently associated with patient perceived improvement or lower symptom scores (CTS-6) after surgery: a higher health-related quality of life index (EQ-5D utility), a lower comorbidity score, lower symptom-severity score and lower anxiety score. In patients treated by steroid injections, 3 prognostic variables were consistently associated with a positive outcome or lower symptom score at 18 months: shorter duration of symptoms, not having had a prior steroid injection and lower symptom score at baseline. It is likely that some of the predictor variables are related and hence there is potential for collinearity, for example the EQ-5D and comorbidity score, as observed in the models of surgery outcome when using two different cut-offs for GROC . This may also explain why some variables were statistically significant in the univariable model but not in the full or final model.

The two different outcome measures, the dichotomised GROC and CTS-6, gave rise to differing sets of models and identified associations. This is perhaps not surprising. The GROC models were based upon data over a relatively short time period, 6 months, whilst the CTS-6 models covered an 18 month period and there is no reason why prognostic factors would be the same over differing time spans. Further, the GROC outcome required a comparative reporting by the patients; in contrast the CTS-6 modelling was based upon symptoms reported at 18 months without reference to any previous time point.

Our findings concur in part with previous studies, however direct comparison is not possible due to the wide variation in explanatory variables included and the way outcome was modelled.

Two very recently published studies have examined predictors of outcome from surgery for CTS [31] [32]. Jansen et al[31] modelled outcome using the Boston Carpal Tunnel Questionnaire (BCTQ) at 6 months post-surgical decompression in 1,049 patients and found pre-surgical BCTQ score and presence of other hand comorbidities to be the strongest predictors of outcome. In contrast to our findings, it was a lower BCTQ score which predicted poorer outcome and those with more severe symptoms at intake showed the greatest change in BCTQ score. Measures of psychological status, health-related quality of life and comorbid health conditions were not included. Moreover, they modelled outcome using change in BCTQ score over 6 months only which may explain why their findings differ from ours.

A study by Bowman et al[32] based on 3332 surgically treated patients applied both logistic regression and artificial neural network analysis on a total of 87 candidate variables, although several pertained to individual questions within the same questionnaire, increasing the risk of overfitting from collinearity in the regression model [32]. Both the derivation cohort and subsequent validation cohort identified that those with moderately severe nerve conduction abnormalities, female gender, nocturnal waking, family history of CTS and a good response to corticosteroid injection were predictors for surgical success. Outcome was modelled using the same global rating of change as our study, although Bowman et al used 'much better' or 'cured' as criteria for success. Conversely, greater functional impairment, presence of diabetes and hypertension and having surgery on the dominant hand were associated with poorer outcome. We did not find diabetes was an independent predictor however, overall lower comorbidity score was when using the same GROC cut-off for classifying success as Bowman et al[32].

Fewer studies have examined prognostic factors for steroid injection. Evers et al[17] considered only a limited range of prognostic factors for treatment failure after initial steroid injection and also did not include psychological status, health-related quality of life or comorbidity. Patients were followed up over a median of 7.4 years. Re-intervention (i.e. treatment failure) was reported in 67% of 595 patients. Lower disease severity (from nerve electrodiagnostic tests) and higher injectate volume were associated with lower likelihood of failure. The authors acknowledge the limitations of using re-intervention as an outcome.

Our finding that higher baseline health utility predicts a successful outcome after surgery concurs with Rege et al [33] who report poorer pre-operative health status, assessed by the Nottingham Health Profile, was associated with lower satisfaction after surgery at 4 months. Similarly, we found comorbidity score to be an independent predictor for surgical outcome when assessed by symptom score at 18 months. Our study included a comprehensive measure of comorbidity, the SACQ[28], which not only encompasses the number of self-reported comorbidities but also weights each according to whether it requires treatment and limits activities.

The finding that lower anxiety was an independent predictor for better surgical outcome in CTS is consistent with existing low quality evidence from the CTS literature[15].

The generalisability of our findings is high. The sociodemographic and clinical characteristics of the study sample were representative of the population and compares well with regards to age, male to female ratio with that of Bowman et al's large sample drawn from the Canterbury carpal tunnel clinic[32].

There are some limitations. Except for NCS, all data were patient-reported, which made it easy to collect by mail or online, but is subject to bias from misreporting. A disadvantage of using global rating of change is the potential for recall bias [34]. On the other hand they are quick, easy to complete and have been shown to have high test-retest reliability (ICC=0.9) and strong correlations with other measures of health status indicating construct validity [35]. In this study patients had to estimate relative change over a 6 months period and for each hand separately. Therefore outcome models were also constructed using a symptom status measure (CTS-6) as an additional patient-reported outcome, which captures symptoms at the actual point of follow-up, without any risk of recall bias. Patients were obviously not blind to the treatments received. This may have influenced their scoring of symptoms, function and overall outcome. Patients' beliefs, expectations from different treatments may have heightened their vigilance to symptoms and affected treatment seeking behaviours, though the fact that data were not collected by the treating clinicians may have mitigated against any social desirability effects in their responses. The classification of those treated by steroid injection who subsequently have surgery as a negative response to injection may be disputed as injections are often used to provide short-term relief where surgery may be delayed due to waiting lists. However the additional effect of surgery is likely to result in a greater perceived change (when using GROC) and lower symptoms (when using CTS-6) and would lead to a bias in models of outcome from steroid injection.

Despite local clinical commissioning policies[14] which advocate conservative treatment first, the proportion of participants having a steroid injection in the first 6 months was only 9% and in

contrast to 52% proceeding directly to surgery. This may be due, in part, to some patients having had symptoms for some time or receiving a steroid injection prior to referral for NCS and enrolment in our study. However, whilst three quarters of the surgically treated patients reported a symptom duration greater than 6 months, only 19% reported having had a prior injection. A more likely explanation is that these patients did not seek treatment until their symptoms were severe or functionally limiting, thus making them eligible for direct referral to surgery under local polices.

Conclusions

This large prospective cohort study has identified several independent predictor variables for outcome from surgery and steroid injection for CTS not previously studied. Higher health utility, fewer comorbidities, being less anxious and a lower symptom severity at the outset were independent significant predictors for better outcome from surgery. In patients treated by steroid injection a shorter duration of symptoms, not having had a prior injection and a lower symptom severity at the outset were significant independent predictors for better outcome.

Our study is an important first step in developing prognostic models which, subject to further external validation, could be used to stratify care for CTS. The routine inclusion of patient-reported measures of health-related quality of life, psychological status and comorbidity alongside disease-specific symptom scores could help inform shared decision-making about best treatment and likely prognosis.

Tables:

Table 1: Clinical and sociodemographic characteristics of surgically treated grouped by Global Rating ofChange (slightly improved, much better and cured=success)

Table 2: Generalised Estimation Equation (GEE) Modelling of Global Rating of Change Outcome from surgery (n=445)

Table 3: Clinical and sociodemographic characteristics of patients treated by injection grouped by GROC

Table 4: Generalised Estimation Equation (GEE) Modelling of Global Rating of Change Steroid Injection Outcome (n=150 injections)

Table 5: Summary of independent factors predicting a better outcome from surgery and steroid injection

Figures

Figure 1: STROBE flowchart

Supplementary Tables

Table 1: Generalised Estimation Equation Modelling of Positive Global Rating of Change Outcome (GROC≥4) from surgery (n=445 procedures)

Table 2: General Linear Modelling of symptom severity outcome from surgery at 18 months (n=406)

Table 3: General Linear Modelling of symptom severity outcome from steroid injection at 18 months (n=102 patients treated with injection)

Table 1: Clinical and sociodemographic characteristics of surgically treated grouped by Global Rating of Change

variables	*Score range*	Failure (N=43)	Success (N=412)
Age yrs		62.2 (12.9)	62.3 (12.2)
Body mass index		27.6 (4.9)	28.6 (5.5)
Drink (Units)		5.1 (11.8)	4.7 (6.8)
Comorbidity Score	*(0 to 36)*	5.5 (4.1)	5.2 (4.1)
EQ-5D-3L Utility	*(0 to 1)*	0.56 (0.30)	0.65 (0.26)
MHQ Total Score	*(0 to 100)*	54.0 (25.7)	59.7 (22.3)
CTS-6	*(1 to 5)*	3.1 (0.9)	3.1 (0.8)
HADS – Anxiety	*(0-21)*	7.5 (5.0)	5.9 (4.3)
HADS – Depression	*(0 to21)*	6.0 (4.8)	4.4 (3.9)
NCS Grade	*(1 to 6)*	3.6 (1.5)	3.7 (1.3)
Sex	*Male*	30 (70%)	263 (64%)
	Female	13 (30%)	149 (36%)
Work Status	*Working*	21 (49%)	184 (45%)
	Non-working	22 (51%)	228 (55%)
Smoking Status	*Non-smoker*	21 (49%)	217 (53%)
	Ex-Smoker	15 (35%)	161 (39%)
	Current Smoker	7 (16%)	33 (8%)

Has Diabetes	*Yes*	5 (12%)	49 (12%)
	No	38 (88%)	363 (88%)
Variables cont'd	***Score range***	***Failure (N=43)***	***Success (N=412)***
Income category	*£15-21.5K*	4 (9%)	59 (14%)
	£21.5-34.9K	8 (19%)	88 (21%)
	£35-50K	3 (7%)	43 (10%)
	>£50K	2 (5%)	21 (5%)
	Rather not say	18 (42%)	107 (26%)
Bilateral Disease	*Yes*	31 (72%)	284 (69%)
	No	12 (28%)	128 (31%)
Duration Category	*<3 months*	3 (7%)	21 (5%)
	3-6 months	6 (14%)	67 (16%)
	6-12 months	8 (19%)	102 (25%)
	12-18 months	6 (14%)	56 (14%)
	>18 months	20 (47%)	166 (40%)
Prior Injection	*Yes – Helped*	3 (7%)	55 (13%)
	Yes – Unhelpful	3 (7%)	25 (6%)
	No	37 (86%)	332 (81%)

Values reported as mean (standard deviation) or numbers (percentage)

Legend: MHQ- Michigan Hand Questionnaire; CTS-6 shortened Boston Questionnaire; HADS – Hospital Anxiety and Depression Scale ; NCS – Nerve conduction Studies

Table 2: Generalised Estimation Equation (GEE) Modelling of Global Rating of Change (success ≥3) Outcome from surgery (n=445)

	Univariate		Full Model		Final Model	
Variables	**O.R. (95% C.I.)**	**p-value**	**O.R. (95% C.I.)**	**p-value**	**O.R. (95% C.I.)**	**p-value**
Age	1.00 (0.98, 1.03)	0.935	0.97 (0.93, 1.02)	0.259		
Body Mass Index	1.04 (0.98, 1.11)	0.227	1.05 (0.96, 1.14)	0.284		
Drink (Units)	0.99 (0.94, 1.05)	0.762	1.08 (0.98, 1.19)	0.138		
Comorbidity Score	0.98 (0.91, 1.06)	0.638	0.98 (0.87, 1.10)	0.742		
EQ-5D-3L Utility	**3.17 (1.22, 8.26)**	**0.018**	2.14 (0.24, 19.19)	0.498	**3.17 (1.22, 8.26)**	**0.018**
MHQ Total Score	1.01 (0.99, 1.03)	0.144	0.99 (0.96, 1.01)	0.359		
CTS-6	1.00 (0.65, 1.55)	0.984	0.97 (0.48, 2.09)	0.931		
HADS – Anxiety	**0.93 (0.87, 0.99)**	**0.023**	1.02 (0.90, 1.16)	0.710		
HADS – Depression	**0.92 (0.85, 0.98)**	**0.015**	0.92 (0.77, 1.09)	0.317		
NCS Grade	1.05 (0.82, 1.35)	0.728	1.21 (0.86, 1.69)	0.268		

Income		0.87 (0.72, 1.04)	0.113	0.85 (0.53, 1.35)	0.480		
Duration		0.93 (0.71, 1.22)	0.600	0.89 (0.62, 1.29)	0.547		
Sex	Male	0		0			
	Female	1.30 (0.66, 2.58)	0.455	1.30 (0.52, 3.30)	0.575		
		Univariate		**Full Model**		**Final Model**	
		O.R. (95% C.I.)	**p-value**	**O.R. (95% C.I.)**	**p-value**	**O.R. (95% C.I.)**	**p-value**
Smoking Status	Smoker	0		0			
	Ex-Smoker	2.28 (0.85, 6.14)	0.104	2.00 (0.40, 9.96)	0.398		
	Non-Smoker	2.19 (0.86, 5.58)	0.100	1.38 (0.28, 6.87)	0.691		
Diabetic	No	0		0			
	Yes	0.97 (0.36, 2.56)	0.955	0.97 (0.39, 2.42)	0.753		
Bilateral Disease	No	0		0			
	Yes	1.17 (0.56, 2.43)	0.677	0.94 (0.42, 2.08)	0.956		
Prior Injection	No	0		0			

Yes-Helped	2.05 (0.61, 6.90)	0.247	2.00 (0.38, 10.58)	0.415
Yes-Unhelpful	0.93 (0.27, 3.24)	0.911	0.82 (0.15, 4.41)	0.815

Legend: MHQ- Michigan Hand Questionnaire; CTS-6 shortened Boston Questionnaire; HADS – Hospital Anxiety and Depression Scale ; NCS – Nerve Conduction Studies

Table 3: Clinical and sociodemographic characteristics of patients treated by injection grouped by Global Rating of Change

Variables	*Score range*	*Failure (N=86)*	*Success (N=64)*
Age		60.8 (12.2)	61.0 (11.3)
Body Mass Index		28.8 (5.9)	29.3 (8.3)
Drink (Units)		3.6 (5.6)	5.3 (6.3)
Comorbidity Score	*(0 to 36)*	5.1 (3.6)	5.9 (4.3)
EQ-5D-3L Utility	*(0 to 1)*	0.61 (0.31)	0.69 (0.25)
MHQ Total Score	*(0 to 100)*	63.7 (23.0)	66.9 (21.1)
CTS6	*(1 to 5)*	2.7 (0.86)	2.7 (0.85)
HADS – Anxiety	*(0-21)*	6.5 (5.0)	6.9 (4.7)
HADS – Depression	*(0 to21)*	4.4 (3.9)	4.8 (3.7)
NCS Grade	*(1 to 6)*	2.7 (1.4)	2.5 (1.3)
Sex	Male	59 (69%)	45 (70%)
	Female	27 (31%)	19 (30%)
Work Status	Working	38 (44%)	33 (52%)
	Non-working	48 (56%)	31 (48%)
Smoking Status	Non-smoker	46 (53%)	35 (55%)
	Ex-Smoker	31 (36%)	21 (33%)
	Current Smoker	9 (10%)	8 (13%)

Has Diabetes	Yes	6 (7%)	8 (13%)
	No	80 (93%)	56 (87%)
Variables (cont'd		***Failure (n=86)***	***Success (n=64)***
Income Category	*<£15K*	19 (22%)	14 (22%)
	£15-21.5K	11 (13%)	14 (22%)
	£21.5-34.9K	17 (20%)	17 (27%)
	£35-50K	4 (5%)	4 (6%)
	>£50K	8 (9%)	2 (3%)
	Rather not say	27 (31%)	13 (20%)
Bilateral Disease	Yes	54 (63%)	45 (70%)
	No	32 (37%)	19 (30%)
Duration Category	*<3 months*	1 (1%)	3 (5%)
	3-6 months	15 (17%)	25 (39%)
	6-12 months	23 (27%)	13 (20%)
	12-18 months	13 (15%)	5 (8%)
	>18 months	34 (40%)	18 (35%)
Prior Injection	Yes – Helped	25 (29%)	6 (9%)
	Yes – Unhelpful	4 (5%)	0
	No	57 (66%)	58 (91%)

Values reported as mean (standard deviation) or numbers (percentage)

Legend: MHQ- Michigan Hand Questionnaire; CTS-6 shortened Boston Questionnaire; HADS – Hospital Anxiety and Depression Scale ; NCS – Nerve conduction Studies

Table 4: Generalised Estimation Equation (GEE) Modelling of Global Rating of Change outcome for Steroid Injection (n=150 injections)

	Univariate		***Full Model***		***Final Model***	
Variables	O.R. (95% C.I.)	p-value	O.R. (95% C.I.)	p-value	O.R. (95% C.I.)	p-value
Age	1.00 (0.98, 1.03)	0.922	0.99 (0.94, 1.04)	0.654		
Body Mass Index	1.01 (0.97, 1.05)	0.596	1.03 (0.94, 1.14)	0.510		
Drink (Units)	1.05 (1.00, 1.11)	0.074	**1.12 (1.01, 1.23)**	**0.026**	**1.07 (1.00, 1.15)**	**0.037**
Comorbidity Score	1.06 (0.98, 1.14)	0.148	1.07 (0.96, 1.21)	0.220	**1.13 (1.03, 1.25)**	**0.012**
EQ-5D Utility	2.90 (0.90, 9.34)	0.075	14.5 (0.92, 226.5)	0.057	**5.20 (1.16, 23.4)**	**0.037**
MHQ Total Score	1.01 (0.99, 1.02)	0.375	1.01 (0.96, 1.06)	0.721		
CTS6	1.03 (0.70, 1.53)	0.872	1.37 (0.58, 3.26)	0.475		
HADS – Anxiety	1.02 (0.95, 1.09)	0.630	0.92 (0.76, 1.11)	0.366		
HADS – Depression	1.03 (0.94, 1.13)	0.536	1.19 (0.94, 1.51)	0.150		
NCS Grade	0.92 (0.72, 1.18)	0.516	0.90 (0.63, 1.28)	0.554		
Income	0.86 (0.73, 1.02)	0.089	0.90 (0.59, 1.36)	0.609		

Duration		**0.69 (0.53, 0.90)**	**0.007**	**0.65 (0.42, 0.99)**	**0.044**	**0.73 (0.54, 0.98)**	**0.036**
Sex	Male	1.00		1.00			
	Female	0.92 (0.47, 1.81)	0.815	0.69 (0.24, 1.97)	0.484		
		Univariate		***Full Model***		***Final Model***	
		O.R. (95% C.I.)	***p-value***	***O.R. (95% C.I.)***	***p-value***	***O.R. (95% C.I.)***	***p-value***
Work Status	Non-working	1.00		1.00		**1.00**	
	Working	0.74 (0.39, 1.43)	0.373	1.93 (0.65, 5.75)	0.237	**2.20 (1.05, 4.60)**	**0.037**
Smoking Status	Smoker	1.00		1.00			
	Ex-Smoker	0.76 (0.22, 2.63)	0.668	0.58 (0.09, 3.35)	0.523		
	Non-Smoker	0.86 (0.26, 2.77)	0.795	0.59 (0.10, 3.43)	0.559		
Has Diabetes	No	1.00		1.00			
	Yes	1.90 (0.70, 5.18)	0.207	2.03 (0.09, 48.5)	0.661		
ateral Disease	No	1.00		1.00			
	Yes	1.41 (0.71, 3.03)	0.323	2.52 (0.97, 6.59)	0.059		

Prior Injection	No	**1.00**		**1.00**		**1.00**	
	Yes	**0.20 (0.08, 0.50)**	**<0.001**	**0.77 (0.19, 3.07)**	**0.003**	**0.18 (0.07, 0.47)**	**<0.001**

Legend: MHQ- Michigan Hand Questionnaire; CTS-6 shortened Boston Questionnaire; HADS – Hospital Anxiety and Depression Scale ; NCS – Nerve conduction Studies

Table 5: Summary of independent factors predicting a better outcome from surgery and steroid injection

	Surgery	Steroid injection
GROC ≥3 (slightly better)	Higher EQ5D health utility (Lower HADS Anxiety and Depression)	Shorter duration of symptoms No previous steroid injection
GROC ≥4 (much improved)	Lower Comorbidity score Lower HADS Anxiety	N/A
Lower symptom severity (CTS-6) at 18 months	Lower Comorbidity score Lower symptom score at baseline Lower HADS anxiety score	Lower symptom score at baseline

Legend: GROC- global rating of outcome; CTS-6 shortened Boston Carpal Tunnel Questionnaire, HADS – Hospital Anxiety and Depression Scale;

Abbreviations used:

CI – confidence interval

CTS-6 – 6 item carpal tunnel syndrome questionnaire

CTS - carpal tunnel syndrome

EQ5D – EuroQuol 5 dimensions

GROC – global rating of change

HADS – Hospital Anxiety and Depression Scale

NCS – nerve conduction studies

OR – odds ratio

p - probability

SACQ – Self-assessed comorbidity Questionnaire

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Figure 1: STROBE Flow Diagram