Peripheral nerve damage : diagnosis and prediction of recovery

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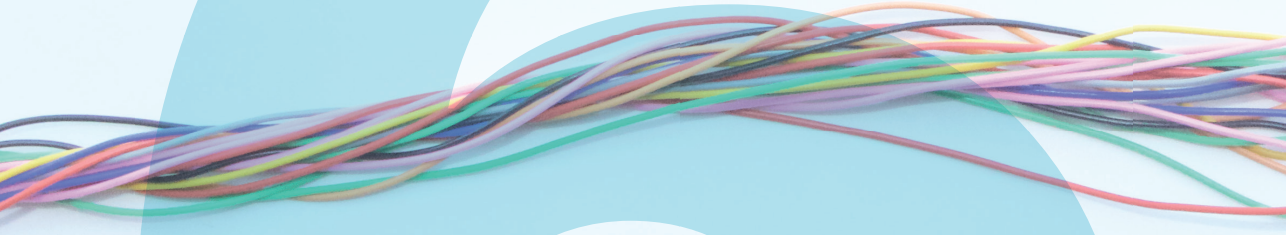

Outcome of carpal tunnel release and the relation with depression

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ABSTRACT

Purpose: To examine the relation between depressive symptoms and outcome of carpal tunnel release (CTR).

Methods: Prospective study in a general hospital with data collection at baseline, three and 12 months after CTR. We quantified depressive symptoms using the Center for Epidemiologic Studies Depression (CES-D) scale and performed multivariable analyses on three outcome measures: 1) CTS symptoms (Boston Carpal Tunnel Questionnaire -BCTQ), 2) palmar pain and 3) patient satisfaction, focusing on preoperative CES-D and BCTQ score, sex, age, alcohol use, diabetes and severity of nerve conduction abnormalities.

Results: We included 227 patients. Preoperatively, patients with depression had a higher BCTQ score than patients without depression. After one year, depressed patients had a higher BCTQ score, had more palmar pain and were less satisfied. CES-D decreased from baseline to one year by a median of 2 points. This correlated with the decrease in BCTQ score. Multivariable analyses showed that preoperative depression had a small but statistically significant influence on palmar pain, but not on postoperative BCTQ score or satisfaction.

Conclusions: Depression is not an independent predictor of residual CTS symptoms or patient satisfaction one year after CTR. Depressive symptoms in patients with CTS decrease after CTR, along with a decrease in CTS symptoms. The causality of this relationship is unknown. Patients with CTS and depression may expect a somewhat higher degree of palmar pain after CTR, the clinical relevance of which is small.

INTRODUCTION

Depression and chronic pain commonly occur together as mutually reinforcing conditions.[1] This co-occurrence has important consequences, as assessing the success of surgical treatment can be complicated by the presence of concomitant depressive symptoms:[2] preoperative depression has been shown to be an independent predictor of postoperative persistence of pain after knee arthroplasty,[3] lumbar spinal stenosis surgery[4] and lumbar discectomy.[5]

In carpal tunnel syndrome (CTS) the relation between depressive symptoms and the outcome of surgery is of particular interest, as depression and CTS are both highly prevalent conditions, specifically among women.[6,7] Although surgical carpal tunnel release (CTR) has a good to excellent outcome in 70-90% of patients,[8-10] the absolute number of patients with a poor outcome is still substantial, due to the high prevalence of CTS.[7] An unfavourable outcome can be due to persistent or recurrent CTS or to pain related to the scar.[11] Unfortunately, the relationship between depression and the outcome of CTR is not well understood. Whereas some studies reported no effect of depression on outcome of CTS,[12,13] others stated that depression affects scar pain[14] or patient satisfaction and perceived disability.[15,16] These seemingly conflicting results are probably caused by differences in study designs, e.g. a retrospective design,[15] a small number of patients[13,15] and a relatively short follow-up.[12,14]

We therefore conducted a prospective, observational study to explore the results of CTR in both depressed and non-depressed patients and to determine the relation between depression and the results of CTR. We used three established outcome measures: 1) residual CTS symptoms, 2) post-operative palmar pain and 3) patient satisfaction. Additional factors that may affect the outcome of CTR include age, sex, diabetes mellitus, alcohol use, severity of CTS symptoms, and severity of NCS abnormalities.[12-20] Hence, these factors were analysed to study their individual influence on surgical outcome and to adjust for their potential confounding effect.

METHODS

Design, setting and participants

This study concerned a prospective observational study in the general care setting of the Alrijne hospital in Leiden, the Netherlands. All adult patients scheduled for CTR were eligible for participation, except for patients undergoing revision surgery. CTR was performed if both clinical symptoms and nerve conduction studies (NCS) were consistent with CTS. The clinical diagnosis was made by one of four experienced neurologists and was based on typical signs and symptoms. The electrophysiological diagnosis was based on the CTS guidelines of the Dutch Society of Neurology.[21] In case of bilateral CTR, the interval between surgery of the two sides generally was no longer than three months We only included data concerning the first CTR of these patients. From March 2012 until July 2014 eligible patients were enrolled non-consecutively when a research nurse was present. The study was approved by the medical ethics committee of Leiden University Medical Centre. All participants provided written informed consent. Procedures followed were in accordance with the Fortaleza Declaration of 2013.

Measurements

The following baseline variables were recorded: sex, age, the presence of diabetes mellitus, assessed through the use of antidiabetic medication and alcohol intake, expressed in number of glasses per week.

NCS were performed in all cases, comprising motor and sensory nerve conduction tests according to the CTS guidelines of the Dutch Society of Neurology.[21] All measurements were performed with a hand temperature of at least 30 °C. We selected the difference between sensory nerve conduction velocity (CV) of the ulnar and median nerve after stimulation at the level of the wrist and recording at the fourth digit as a marker for the severity of NCS abnormalities.[22] The results were divided in three categories: mild (CV difference between ulnar and median nerve <10 m/s), moderate (CV difference ≥10 and <20 m/s) or severe (difference >20 m/s or sensory nerve action potentials of the median nerve absent).

Patients filled out questionnaires at three points in time: within two weeks prior to surgery, three months post-surgery ± two weeks and one year post-surgery ± four weeks. The first questionnaires were filled out by the patient together with a trained research nurse. The postoperative questionnaires were self-administered.

CTS symptoms were measured using the first part of the Boston Carpal Tunnel Questionnaire (BCTQ) which includes 11 questions concerning severity, frequency and duration of pain and tingling at night and daytime, numbness and loss of dexterity. Each question provides five response choices, from 1 (no symptoms) to 5 (most severe/often); the mean of 11 responses is calculated as the BCTQ score, ranging from 1 to 5.[23] Depressive symptoms were quantified using the Center for Epidemiologic Studies Depression Scale (CES-D), a commonly used validated questionnaire based on the diagnostic and statistical manual of mental disorders, fifth edition (DSM-V).[24] The 20 items on this questionnaire measure various aspects of depression such as depressed mood and feelings of worthlessness and helplessness. Each item has four response choices, from 0 to 3, quantifying depressive symptoms over the past week. The scores ranges from 0-60, with a higher score representing more severe symptoms.[25-27] A clinically relevant depression is defined as CES-D ≥16.[25,28] The presence and severity of scar pain and proximal palm pain were measured by the Palmar Pain Scale, a scale developed and validated specifically for pain after CTR.[29] This scale consists of two items. The first concerns the severity of pain at the scar and/or the proximal palm. The five responses vary from no pain (0) to most severe (4). The second item concerns activity limitations because of pain, with six responses from no limitation (0) to most severe (5). We calculated the sum of these items resulting in a range of 0 to 9. Finally, to determine whether patients were satisfied with the results of surgery, we asked whether their symptoms had been relieved on a seven-point scale: 1) completely resolved, 2) improved considerably, 3) improved somewhat, 4) no change, 5) worsened somewhat, 6) worsened considerably and 7) symptoms have become much worse.

Surgical approach

Open CTR was performed by one of three experienced neurosurgeons applying the same technique under local anesthesia with xylocaine and epinephrine.[30] In short, the patient is in supine position with the arm resting on a hand table. A longitudinal palmar incision of +/- 2 cm. is made along the thenar crease to the level of the distal wrist crease. The subcutaneous tissue is dissected bluntly and the palmar fascia is split. The fat tissue between the palmar aponeurosis and the transverse carpal ligament is detached at the radial side and mobilized to the ulnar side. The ligament is incised distally until fat on top of the median nerve is visible. Proximally, the ligament is cut into the volar forearm fascia which is further proximally sectioned subcutaneously under direct vision. Hand movement without load is encouraged immediately following surgery. The hand is held in a sling for two days upon which progressive use is encouraged.

Statistical analysis

Patients who filled in questionnaires at all three points in time were labelled 'participants'. Patients who filled in questionnaires preoperatively, but not postoperatively were labelled 'non-participants'.

Preoperative data were compared between participants and non-participants and depressed and non-depressed patients either using the two-sample t-test (normally distributed data) or the Mann-Whitney U test (not-normally distributed data) or the chi-square test (categorical data). Significance was defined as $p<0.05$. The BCTQ score and CES-D score on the three different points in time were compared using the Friedman test and the Wilcoxon signed rank test (post-hoc) for paired data. The palmar pain sum score and patient satisfaction at three months and at one year were compared using the Wilcoxon signed rank test. Only data from the participants were included. In patients with bilateral CTR we only used data concerning the first CTR.

We used multivariable linear regression to explore the influence of seven predictors (preoperative CES-D score, age, sex, presence of diabetes mellitus, alcohol intake, preoperative BCTQ score, and severity of NCS abnormalities) on each of the following three outcome measures: CTS symptoms (BCTQ score), palmar pain (sum score) and patient satisfaction; each in a separate regression analysis. In addition, we analysed the influence of these factors on CES-D score one year after surgery, using the same model. We chose to investigate diabetes mellitus and alcohol consumption because they are common causes of neuropathy. Previous studies on the effect of diabetes mellitus on CTR present conflicting results [31-34] and we found only one study on the effect of alcohol.[16] Preoperative symptom severity (BCTQ score) and NCS were included because they reflect the clinical and electrophysiological severity of CTS.[14,16-18] We analysed the influence of the variables on the outcome after one year only, and not at three months, because symptoms including palmar pain continued to decrease from three to 12 months post surgery (figure 1). The measurements at one year are therefore more likely to reflect an end stage than the measurements after three months.

To account for missing values, we applied a 5-fold multiple imputation for which we included the seven preoperative variables and the three postoperative outcome variables as well as the CES-D postoperatively. Results of the multiple regression analysis were expressed as beta coefficients along with a p-value. When the corresponding p-value is <0.05, beta coefficients represent the unique contribution of each variable to the prediction of the outcome. A generalized linear model was selected as the appropriate model for our analysis, as the number of included patients was sufficient to resolve any concerns on distribution of the data. Finally, we analysed the correlation between outcome of the BCTQ and the CES-D score from baseline to one year after CTR using the Pearson correlation coefficient.

RESULTS

Baseline characteristics

During the inclusion period 1023 patients underwent CTR. A total of 345 patients filled in questionnaires preoperatively. Of these, 227 patients filled in questionnaires at all three points in time ('participants'). The remaining 118 patients were either lost to follow-up or declined long term participation ('non-participants'). Participants and non-participants did not differ in sex distribution (74% women and 67% women respectively, p = 0.16), median preoperative CES-D score: score 3 (1-8) and 4 (0-10) respectively, p = 0.44, or median preoperative BCTQ score: 2.7 (2.3-3.2) and 2.7 (2.4-3.2) respectively, p = 0.62. Participants were 5 years older than non-participants: median age 58 (49-73) and 53 (43-61) respectively, p < 0.05. The preoperative CES-D score of the participants was low, indicating low depression ratings. Nonetheless, 23 patients (11.2 %) had signs of a clinically relevant depression using a CES-D cutoff ≥16. [25,28] Patients with depression had a higher preoperative median BCTQ score than patients without depression, but showed no other differences at baseline (table 1). Seventy-seven patients (33.9%) underwent bilateral CTR, of whom only data of the first CTR were used.

Table 1. Baseline characteristics of all study participants and a comparison of these characteristics between patients with and without depression at baseline.

	Study participants n = 227	No depression at baseline n = 182	Depression at baseline n = 23	p-value	Missing data
Preoperative CES-D score	3 (1-8)	3 (0-6)	20 (17-22)	n.a.	22 (9.7%)
Age (years)	58 (49-73)	58 (49-72)	52 (42-66)	0.14	0
Sex (female)	167 (74.0%)	136 (74.7%)	15 (65.2%)	0.33	0
Preoperative BCTQ score	2.7 (2.3-3.2)	2.7 (2.3-3.1)	3.3 (2.6-3.5)	<0.05	6 (2,6%)
Alcohol intake (glasses/week)	2.0 (0.0-7.0)	2.0 (0.0-7.0)	1.0 (0.0-5.3)	0.64	13 (5.7%)
Diabetes mellitus; present	16 (7.2%)	11 (6.2%)	2 (9.1%)	0.46	5 (2.2%)
NCS abnormality:*mild	13 (5.7%)	9 (5.1%)	2 (9.1%)	0.07	9 (4.0%)
moderate	71 (31.3%)	57 (32.6%)	12 (54.4%)		
severe	134 (59.0%)	109 (62.3%)	8 (36.4%)		

Continuous data are presented as median (25^{th}-75^{th} percentile). BCTQ = Boston Carpal Tunnel Questionnaire, CES-D = Center for Epidemiologic Studies Depression Scale, NCS = nerve conduction studies, n.a. = not applicable.
* These data do not add up to 100% because of missing data (n=9).

Figure 1

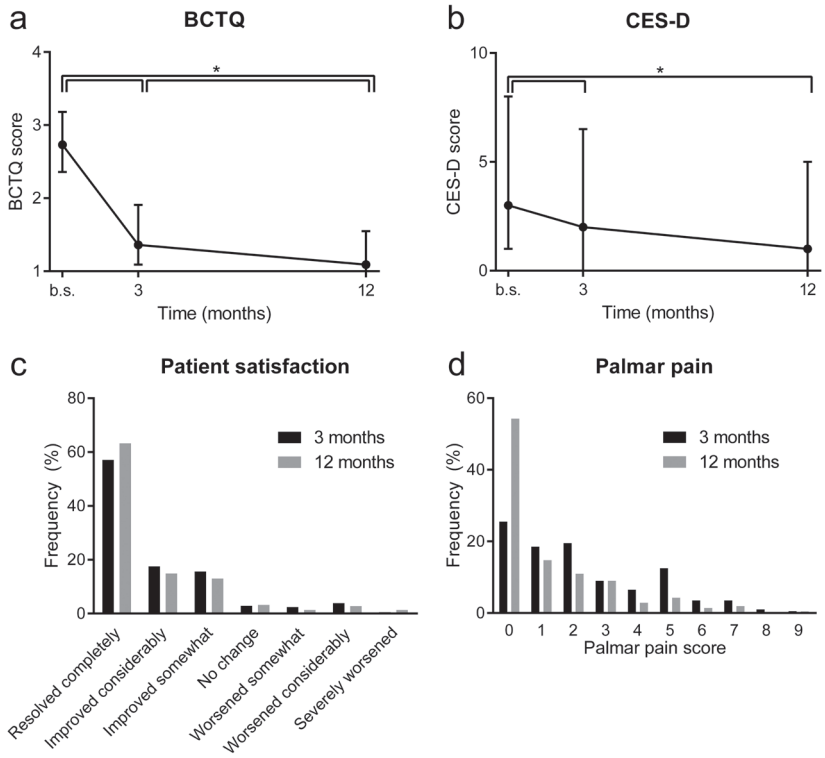

Figure 1: Long-term results of carpal tunnel release. Figure 1a shows the median scores on the Boston Carpal Tunnel Questionnaire (BCTQ) with the 25th and 75th percentile (interquartile range)indicated by vertical bars. Figure 1b shows the median score on the CES-D (Center for Epidemiologic Studies Depression Scale) with the interquartile range indicated by vertical bars. Figure 1c shows patient satisfaction postoperatively. Satisfaction grades did not differ significantly between three and twelve months postoperatively (p = 0.37). Figure 1d shows the frequency of palmar pain. Significant changes at different points in time are marked by *. b.s. = before surgery.

Outcome three months and one year after CTR

The median BCTQ score was significantly lower after surgery than before, with a median value of 1.4 points after three months (p <0.05) and 1.1 points after one year (p <0.05) (Figure 1a). The improvement on the BCTQ from baseline to one year did not differ between patients with depression and patients without depression at baseline, p = 0.67). The median CES-D score decreased three months after surgery from a median score of 3 to 2 (p = <0.05), but did not significantly decrease any further from three to 12 months postoperatively (p = 0.32) (figure 1b). One year after surgery, the majority of patients reported that their symptoms had resolved completely (figure 1c). A substantial proportion of the patients (74.5%) reported some degree of palmar pain three months after surgery, which declined to 45.6% one year after surgery (p <0.05) (figure 1d). Patients with a depression at baseline had a significantly less favourable score on all outcome parameters (table 2).

Table 2. Outcome at twelve months for patients with and without depression at baseline.*

Outcome one year after surgery	No depression at baseline n=182	Depression at baseline n=23	p-value	Missing data
BCTQ	1.1 (1.0-1.6)	1.4 (1.2-2.1)	<0.05	10/1
Palmar pain score = 0	101 (58.4%)	6 (27.3%)	<0.05	13/1
Patient satisfaction			<0.05	7/1
Resolved completely	116 (66.9%)	10 (45.5%)		
Severely worsened	2 (1.1%)	1 (4.5%)		

Depression is defined as ≥16 points on the Center for Epidemiologic Studies Depression Scale (CES-D). BCTQ = Boston Carpal Tunnel Questionnaire. BCTQ is presented as median (25^{th}-75^{th} percentile). * CES-D is missing at baseline for 22 patients.

Predictors of outcomes one year post surgery

In the multivariable analysis, preoperative CES-D score was found to be not related to the BCTQ score one year after surgery. The preoperative BCTQ score proved to be a significant predictor of the BCTQ score after one year with a beta coefficient of 0.139 meaning that an increase of preoperative BCTQ score of one point leads to an increase of postoperative BCTQ score of 0.14 points (table 3). A greater preoperative CES-D score was a predictor of more palmar pain after one year, although with a small beta coefficient of 0.075 (table 3). Neither CES-D nor any of the other preoperative variables in the model was an independent predictor of patient satisfaction (table 3).

Table 3: Multivariable analysis of the influence of preoperative variables on the outcome of carpal tunnel release one year after surgery as measured with three different outcome measures: CTS symptoms (BCTQ score), palmar pain (sum score) and patient satisfaction.

	Beta-Coefficient	Standard Error	95% Confidence Interval	P-value
Outcome = CTS symptoms (BCTQ), R^2 = 0.06				
Preoperative depression (CES-D)	0.005	0.0068	-0.008 - 0.019	0.44
Sex (female)	-0.162	0.0988	-0.356 - 0.032	0.10
Age	0.002	0.0031	-0.004 – 0.008	0.49
Diabetes mellitus	-0.170	0.1585	-0.482 - 0.142	0.28
Alcohol use (glasses per week)	-0.010	0.0076	-0.025 - 0.005	0.16
Preoperative symptoms (BCTQ)	0.139	0.0669	0.008 - 0.270	<0.05
NCS abnormality: moderate#	-0.071	0.1768	-0.417 - 0.276	0.69
severe #	-0.155	0.1794	-0.509 - 0.199	0.39
Outcome = palmar pain, R^2 = 0.11				
Preoperative depression (CES-D)	0.075	0.0310	.014 - .136	<0.05
Sex (female)	-0.409	0.5054	-1.415 - 0.597	0.42
Age	-0.012	0.0131	-.038 - 0.013	0.34
Diabetes mellitus	-0.970	0.7242	-2.390 - 0.451	0.18
Alcohol use (glasses per week)	-0.043	0.0383	-.118 - .033	0.27
Preoperative symptoms (BCTQ)	0.601	0.3175	-.024 - 1.226	0.06
NCS abnormality: moderate#	-0.361	0.8148	-1.958 - 1.236	0.66
severe #	-0.998	0.7958	-2.560 - 0.564	0.21
Outcome = patient satisfaction, R^2 = 0.07				
Preoperative depression (CES-D)	0.007	0.0187	-0.031 - 0.045	0.71
Sex (female)	0.029	0.2810	-0.530 - 0.589	0.92
Age	0.008	0.0075	-0.006 - 0.023	0.27
Diabetes mellitus	-0.463	0.4059	-1.260 - 0.333	0.25
Alcohol use (glasses per week)	-0.021	0.0218	-0.065 - 0.022	0.33
Preoperative symptoms (BCTQ)	0.222	0.1692	-0.110 - 0.554	0.19
NCS abnormality: moderate#	0.123	0.4777	-0.818 - 1.064	0.80
severe #	-0.487	0.4524	-1.377 - 0.403	0.28

CES-D = Center for Epidemiologic Studies Depression Scale. #Index = mild nerve conduction studies (NCS) abnormality

Depressive symptoms after one year

One year after surgery, 16 patients were depressed (CES-D ≥16). The only predictor of depressive symptoms one year after surgery was the level of depressive symptoms at baseline (table 4). The decrease in BCTQ and CES-D score from baseline to one year were significantly correlated, but with a low Pearson correlation coefficient (Pearson 0.268, $p<0.05$).

Table 4: Multivariable analysis of the influence of preoperative variables on depressive symptoms one year after surgery as measured with the CES-D (Center for Epidemiologic Studies Depression Scale).

	CES-D after one year, $R^2 = 0.40$			
	Beta-Coefficient	**Standard Error**	**95% Confidence Interval**	**P-value**
Preoperative depression (CES-D)	0.581	0.0600	0.462 – 0.699	<0.05
Sex (female)	-0.523	0.9257	-2.340 – 1.293	0.57
Age	-0.003	0.0277	-0.058 – 0.051	0.90
Diabetes mellitus	0.673	1.8603	-3.109 – 4.454	0.72
Alcohol use (glasses per week)	-0.053	0.0721	-0.195 – 0.088	0.46
Preoperative symptoms (BCTQ)	-0.576	0.6187	-1.790 – 0.637	0.35
NCS abnormality: moderate#	2.704	1.7281	-0.687 – 6.094	0.12
severe #	-0.696	0.8579	-2.378 – 0.985	0.42

BCTQ = Boston Carpal Tunnel Questionnaire . #Index = mild nerve conduction studies (NCS) abnormality.

DISCUSSION

Depression and residual CTS symptoms (BCTQ score after one year)

Our multivariable analysis showed that depression was not an independent predictor of residual CTS symptoms after one year. This is in accordance with a prospective study on 97 patients with clinically proven CTS that found no association between preoperative depression scores, assessed using the Hospital Anxiety and Depression scale (HADS), and the BCTQ at six months respectively.[12] The only predictor for more severe postoperative residual CTS symptoms was a higher preoperative severity of CTS symptoms . This is in line with a prospective study on 523 hands.[19] The small difference of 0.3 points in postoperative BCTQ score between depressed and non-depressed patients we found, has little or no clinical importance. [33] Furthermore, it was not related to depression and was partially due to the somewhat higher BCTQ score at baseline.

Decrease of depressive symptoms after CTR

Remarkably, we observed a significant decrease in depressive symptoms from baseline to three months after surgery. A possible explanation for this decrease could be a more postoperative well-being due to the relief of symptoms such as pain and tingling. This hypothesis is supported by the finding that the decrease in BCTQ and CES-D scores were correlated. Another important factor might be that the CES-D includes one question on sleep ('my sleep was restless', options: rarely, some, occasionally, most).[25] Many patients with CTS wake up from their symptoms at night. As surgery relieves these nocturnal complaints in the majority of patients, the decrease in CES-D scores postoperatively is likely to be partially explained by a lower score assigned to this 'sleep question'. In addition, a recent study showed a negative effect of CTS on sleep quality, while poorer sleep quality can negatively

influence the severity of depressive symptoms. [35] The return of a normal sleep pattern after CTR could have led to a lower depression score as well.

Depression and palmar pain

Although post-operative palmar pain is a well-known complication of CTR, data on its prevalence and severity are scarce. The observed decrease of palmar pain from three to 12 months post surgery in our study was in line with the results of the study in which the palmar pain scale was validated.[29] Depressive symptoms were an independent predictor of a higher degree of palmar pain one year after surgery. In accordance with our findings, a prospective study among 83 patients with electrodiagnostically proven CTS found that depression as assessed with the CES-D was a predictor of scar pain, measured on a 10-point ordinal scale three months after surgery.[14] The observed effect in our study was, however, quite small. The beta coefficient of 0.075 indicates that a 16 point increase on the CES-D scale (i.e. an increase from 0 to 16 points, the cut-off point for depression)[25,28] results in an increase in palmar pain of only 1.2 points, on a scale from 0-9. Moreover, our study showed that overall satisfaction was not affected by depressive symptoms. Therefore the clinical relevance of this finding appears to be limited.

Depression and patient satisfaction

Neither depression, nor any of the other preoperative variables we analysed predicted patient satisfaction one year after CTR. The observed difference in satisfaction between patients with and without depression at baseline was not explained by any of the studied variables, especially not by preoperative depressive symptoms. Patient satisfaction was not assessed in the studies mentioned above,[12,14] but two studies that did measure patient satisfaction contrasted with our results.[15,16] One study in 82 patients found a weak but significant correlation between CES- D and patient satisfaction (on a scale from 0-10) with a follow-up of at least two years after CTR.[15] However, this was a retrospective study on a relatively small number of patients. Another study also found that worse preoperative mental health status was predictive of lower satisfaction after 18 months in a group of 188 clinically defined CTS patients. In this study mental health was measured by the mental health subscale of the SF-36 which measures depression and anxiety. Patient satisfaction was scored on a 5-point scale.[16] An NCS-confirmation of CTS was not required and NCS-parameters were not included in the analysis. This may have affected the analysis, as a normal NCS is an independent predictor of a poor surgical outcome.[36] Another explanation for the discrepancy with our findings is that the mental health subscale of the SF-36 differs from the CES-D.

Strengths and limitations

The strengths of this study are its prospective design, the large number of patients with NCS-confirmed CTS, the systematic application of validated, quantitative measures for depression and symptoms of CTS and the long follow-up period. The follow-up period is important as it takes approximately ten months before maximum symptom relief is achieved after CTR.[37] A limitation is the low rate of patients participating as a percentage of the total

study population. Although this might theoretically affect the generalizability of the results we do not feel that this actually was the case, since the overall number of patients that participated is high and reflects the common CTS population. Furthermore, the percentage of patients who did not participate in follow-up was relatively high. However, these patients did not differ from participants on preoperative BCTQ and CES-D scores. Participants were older than non-participants, perhaps because older patients were more willing to fill in time-consuming questionnaires. As our results show no influence of age on the outcome of CTR on any of the three parameters, we do not expect that this difference affects the validity of our conclusions. We could have implemented the presence and severity of diabetes mellitus in more detail, i.e using glucose or HbA1c measurements in addition to medication use, but these measurements were not systematically available. Finally, not all possible variables that could affect the outcome of CTS were included. An example are legal proceedings regarding workers' compensations, which have been associated with worse outcomes.[17] These are very rare in the Netherlands, justifying their omission.

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