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Title Page

Perceived Pain Extent is not associated with Physical, Psychological or Psychophysical Outcomes in Women with Carpal Tunnel Syndrome

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Abstract

Objective: Our aims were; 1, to investigate whether perceived pain extent, assessed from the pain drawing, relates to clinical, psychological and psychophysical outcomes in women with CTS; 2, to assess differences in pain extent depending on the presence of median or extra-median symptoms; and, 3, to investigate differences in pain extent according to severity (minimal, moderate or severe) or laterality (unilateral or bilateral) of CTS.

Methods: One hundred and forty (n=140) women with CTS completed pain drawings which were subsequently digitized allowing pain extent to be calculated. Clinical features including pain intensity (Numerical Pain Rating Scale, 0-10) and disability (Boston Carpal Tunnel Questionnaire), psychological features including depression (Beck Depression Inventory-BDI), and psychophysical (pressure pain and thermal pain thresholds) variables were assessed. Spearman rho correlation coefficients were used to reveal the correlations between pain extent and other outcomes. Differences in pain extent according to severity (minimal, moderate, severe) or laterality (unilateral, bilateral), and the presence of extra-median symptoms were also evaluated.

Results: No significant associations were identified between pain extent and clinical, psychological or psychophysical outcomes. Women with extra-median symptoms (88%) exhibited larger ($P<.001$) pain extent (total: $24.2\pm13.5\%$) than those women with median symptoms (12%, total: $12.2\pm6.9\%$). Pain extent was not significantly different depending on the severity or laterality of the symptoms.

Conclusions: Pain extent in the upper extremity was not associated with clinical, psychological or psychophysical variables and was not related to the severity or laterality of the symptoms in women with CTS.

Key words: carpal tunnel syndrome, pain area, pressure pain, sensitization.

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Perceived Pain Extent is not associated with Physical, Psychological or Psychophysical Outcomes in Women with Carpal Tunnel Syndrome

Introduction

Carpal tunnel syndrome (CTS) is the most common nerve entrapment of the upper extremity with a prevalence rate ranging from 6.3% to 11.7% depending on the diagnostic criteria applied (1). Women are more frequently affected by CTS than men (ratio 2:1) (2). The societal burden of CTS is substantial since patients often take time off from their work (3). The overall cost associated with CTS in the United States of America alone exceeds \$2 billion annually (4).

Although CTS is traditionally considered as a peripheral neuropathy of the median nerve at the carpal tunnel, increasing evidence suggests that CTS is a heterogeneous pain disorder involving central and peripheral sensitization mechanisms (5). Some studies have reported that women with CTS exhibit widespread pressure pain hypersensitivity (6), bilateral thermal pain hyperalgesia (7), and enhanced wind-up in extra-median nerve territories (8) as manifestations of altered nociceptive processing. These sensory deficits are not associated with electrodiagnostic findings suggesting that sensitization is not related to the damage of the median nerve but rather can be present from the onset of the condition (9). A recent study confirming the hypothesis of altered central pain processing in CTS has shown that patients not only exhibit increased pain facilitation but that they also have reduced endogenous pain inhibition (10). Nevertheless, other studies have not found widespread sensory changes in patients with CTS without concomitant neck pain suggesting that there might be subgroups of subjects with CTS with varying levels of sensitivity (11). This hypothesis was supported by a recent study identifying a subgroup of women with CTS exhibiting higher pain sensitivity (12).

111 Pain drawings capture a graphic representation of the location and distribution of symptoms
112 in people with pain by asking them to draw where they perceive their pain on a body chart. It is
113 accepted that an expanded distribution of pain represents a clinical sign of central sensitization (13).
114 In fact, some studies have reported the presence of pain spreading to extra-median areas (14) and to
115 the upper extremity (15) as a potential manifestation of central sensitization in patients with CTS.
116 Importantly, spreading of pain symptoms is not associated with the results of nerve conduction
117 studies (16).

118 There is preliminary evidence suggesting that enlarged pain areas are associated with more
119 severe pain, higher pressure pain hypersensitivity, higher disability or poorer psychological health
120 in different chronic pain conditions such as painful knee osteoarthritis (17,18), whiplash-associated
121 disorders (19) and fibromyalgia (20). Pain drawings may also assist clinicians in identifying people
122 with CTS exhibiting higher pain sensitivity or more severe clinical features. Zanette et al found that
123 subjects with CTS suffering from extra-median distribution of the symptoms reported higher pain
124 intensity (14); however, this study did not investigate the size of the painful area nor the presence of
125 concomitant symptoms in the upper extremity. No previous study has investigated if the size of the
126 painful area (i.e. pain extent) is associated with clinical, psychological and psychophysiological
127 outcomes in CTS. Thus, the aims of this study were: 1, to examine whether pain extent, extracted
128 from pain drawings, was associated with clinical features, depression, widespread pressure pain
129 hypersensitivity, or thermal pain hyperalgesia in women with CTS; 2, to determine the presence of
130 median and extra-median symptoms from the pain drawings and to investigate the differences in
131 pain extent between individuals with median or extra-median symptoms; and, 3, to investigate the
132 differences in pain extent according to severity (minimal, moderate, severe) or laterality (unilateral
133 or bilateral) of CTS.

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136 **Methods**

137 **Participants**

138 Women with signs and symptoms compatible with CTS presenting at a local regional Hospital
139 in Madrid (Spain) were screened for eligibility criteria (21). To be eligible, patients had to exhibit
140 both clinical and electrophysiological findings of CTS including pain and paresthesia in the median
141 nerve distribution, increasing symptoms during the night, and both a positive Tinel sign and
142 positive Phalen sign. The electro-diagnostic examination had to reveal deficits of sensory and motor
143 median nerve conduction according to the American Association of Electrodiagnosis (AAEM), the
144 American Academy of Neurology (AAN), and the American Physical Medicine and Rehabilitation
145 Academy (AAPM&R) guideline (22). Specifically, findings from the exam that were needed to
146 confirm the diagnosis included: 1. median nerve distal sensory latency of the index finger (>3.60
147 ms) and/or 2. median nerve distal motor latency (>4.20 ms). Sensory and motor conduction studies
148 of the radial and ulnar nerves were also conducted to exclude multiple neuropathy. Patients were
149 classified as minimal, moderate or severe CTS according to international guidelines (22).

150 Individuals were excluded if they exhibited any of the following criteria: 1. motor or sensory
151 deficits in the ulnar or radial nerves; 2. older than 65 years; 3. previous surgery or steroid injections
152 in the hand; 4. multiple diagnoses on the upper extremity (e.g., cervical radiculopathy); 5. cervical,
153 shoulder, or upper extremity previous trauma; 6. any systemic disease causing CTS (e.g. diabetes
154 mellitus, thyroid disease); 7. diagnosis of fibromyalgia syndrome; 8. pregnancy; or, 9. male gender.
155 All participants signed the informed consent prior to their inclusion in the study. The local human
156 research committee (PI01223-HUFA12/14) approved the study which was conducted according to
157 the declaration of Helsinki.

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162 **Pain Drawings**

163 All participants were instructed to complete a pain drawing indicating their pain location
164 and extent on four different paper body charts of the hand and upper extremity: one reporting a
165 palmar view of hand, one reporting a dorsal view of hand, one reporting a frontal view of the upper
166 extremity and the last one reporting a dorsal view of the upper extremity. The four body charts were
167 printed on an A4 sheet and participants were instructed to colour, using a pencil, every part of the
168 body chart where they perceived pain symptoms. Participants were asked to report the pain that
169 they usually experienced. Subsequently pain drawings on the paper body charts were copied onto a
170 digital body chart by 2 trained operators using an image analysis software (Inkscape version 0.91).
171 This procedure for digitizing pain drawings has shown high reliability (23,24). Pain extent was then
172 computed using custom software developed with Matlab[®] and previously tested (25). The software
173 calculates the amount of the pixels included on each pain drawing and any pain drawn outside of
174 the body chart borders was not included in the analysis. Calculations were based on the number of
175 pixels resulting from the size of the palmar and the dorsal view of the hand (palmar hand: 47175
176 pixels, dorsal hand: 41105 pixels) and the size of the frontal and the dorsal view of the upper
177 extremity (frontal arm: 9980 pixels, dorsal arm: 10228 pixels) separately. Pain extent was expressed
178 as the percentage of the total body chart area where the patient experienced pain (number of pixels
179 with pain / total of pixels of the anatomical area x 100). Pain frequency maps were generated for the
180 four different body charts bilaterally to illustrate where pain was most frequently perceived in the
181 enrolled patients. Pain frequency maps were hence obtained by superimposing all the pain drawings
182 performed on the same body chart from all participants.

183 Pain drawings involving the thumb (with or without the thenar eminence), index, and
184 middle fingers (either palm or dorsum) were considered as median distribution; whereas symptoms
185 involving the little and/or the ring finger were considered as an extra-median distribution. Further,
186 any pain drawn including the upper extremity, excluding the hand, was considered as extra-median
187 distribution.

188 **Self-reported Clinical Measures**

189 A 10-cm Numerical Pain Rating Scale (26) (NPRS; 0: no pain, 10: maximum pain) was used
190 to assess the average intensity of hand pain, and worst and lowest level of hand pain experienced in
191 the preceding week. The Spanish validated version (27) of the Boston Carpal Tunnel Questionnaire
192 (28) (BCTQ) was used to assess the hand pain related-disability. It includes a functional status scale
193 assessing the ability to perform eight common hand-related tasks, and a symptom severity scale
194 assessing pain severity, numbness and weakness at night and during the day. Each item is answered
195 on a 5-point scale (1: no complaint; 5: severe complaint) with higher scores indicating greater
196 related-disability. This questionnaire is valid, reliable, and responsive for individuals with CTS
197 (29).

198 **Psychological Measures**

199 Patients completed the Beck Depression Inventory (BDI-II) to obtain a measure of their
200 level of depressive symptoms. This questionnaire consists of 21-item self-reported items assessing
201 affective, cognitive, and somatic symptoms of depression (30). The BDI-II is easily adapted in most
202 clinical conditions for detecting symptoms of depression (31).

203 **Psychophysical Measures**

204 In the current study, we also evaluated sensitivity to pressure and thermal pain to assess
205 nociceptive gain processing. Pressure pain thresholds (PPT), the minimal amount of pressure where
206 a sense of pressure first changes to pain, were measured bilaterally with an electronic algometer
207 (Somedic AB©, Farsta, Sweden) over the median, ulnar and radial nerves, the articular pillar of C5-
208 C6 joint, carpal tunnel, and tibialis anterior (6). The pressure was applied at an approximate rate of
209 30 kPa/sec. Participants were instructed to press the stop switch when the sensation changed from
210 pressure to pain. The mean of three trials was calculated and used for the analysis. A 30-second rest
211 period was provided between each trial to avoid temporal summation (32). The order of the
212 assessment was randomized between participants. The reliability of algometry is high (33,34).

213 Thermal pain thresholds were assessed bilaterally with a Thermotest System (Somedic AB©
214 Farsta, Sweden) over the carpal tunnel or thenar eminence (7). Patients were instructed to press a
215 hand-controlled stop switch when the sensation changed from heat/cold to heat/cold pain (heat or
216 cold pain threshold, HPT/CPT respectively). The mean of 3 trials at each region was calculated and
217 used for the analysis. A rest of 5 seconds was allowed between trials. The order of the assessment
218 was randomized. A systematic review concluded that the reliability of thermal pain thresholds on
219 the hand is high (35).

220 **Sample Size Calculation**

221 The sample size was calculated using Ene 3.0 software (Autonomic University of Barcelona,
222 Spain). The sample calculation was based on detecting significant moderate correlations ($r=0.3$)
223 between the studied variables with an alpha level (α) of 0.05, and a desired power (β) of 95%. This
224 generated a sample size of at least 135 subjects.

225 **Statistical Analysis**

226 Distribution of the data was tested with the Shapiro-Wilk test and non-normally distributed
227 data were observed. Since no side-to-side differences in PPTs, HPTs or CPTs were found, the mean
228 of both sides was used in the analysis. For the first objective, Spearman's correlation coefficients
229 were computed to reveal the associations between pain extent with all clinical, psychological and
230 psychophysical outcomes. Correlation was considered weak when $r_s < .3$, moderate when $.3 < r_s < .7$,
231 and strong when $r_s > .7$ (36). Statistical analysis was performed using R version 3.2.2. Significance
232 was set to $\alpha=.05$ and the Bonferroni correction was applied (α -adjusted=.003) to account for
233 multiple testing (37). For the second objective, a non-parametric Wilcoxon Rank Test was used to
234 evaluate the differences in pain extent between those with median and extra-median symptoms.
235 Finally, for the third objective, a non-parametric Kruskal-Wallis Test was used to evaluate the
236 differences in pain extent accordingly to severity (minimal, moderate or severe) or laterality (left,
237 right or bilateral).

238 Results

239 Two hundred (n=200) women with diagnosis of CTS between January 2015 and June 2017
240 were screened according to the eligibility criteria. Finally, 140 (70%) women satisfied all the
241 eligibility criteria, agreed to participate, and signed the informed consent. The reasons for exclusion
242 included: previous surgery (n=20), previous steroid injections (n=15), diabetes (n=10), whiplash
243 (n=5), age above 65 (n=5), pain drawings not recognised by the software (n=5). Thirty-seven (26%)
244 reported unilateral symptoms (28 right side, 9 left side), and the remaining 103 (74%) exhibited
245 bilateral symptoms. Thirty-two (23%) presented minimal CTS, 62 (44%) moderate CTS and the
246 remaining 46 (33%) severe CTS. The total pain extent was $22.1 \pm 13.9\%$ across the entire group of
247 women with CTS, whereas pain extent for the hand and arm only was $25.7 \pm 16.1\%$ and $5.8 \pm 10.6\%$,
248 respectively. **Table 1** presents the clinical, psychological, and psychophysical measures of the
249 entire sample. No significant associations were found between the pain extent and clinical,
250 psychological or psychophysical variables in the total sample of women of CTS, except for CPT
251 over the carpal tunnel and pain extent in the upper extremity ($r=0.25$; $P=.002$)

252 Pain frequency maps for women with CTS are illustrated in **Figure 1**. According to the pain
253 drawings, 124 (88%) women exhibited extra-median symptoms and the remaining 16 (12%) women
254 experienced median symptoms. Women with extra-median symptoms exhibited significantly larger
255 ($P<.001$) total ($24.2 \pm 13.5\%$) and hand ($28.4 \pm 15.5\%$) pain extent than those with median symptoms
256 (total: $12.2 \pm 6.9\%$; hand: $13.3 \pm 8.3\%$) as it is depicted in **Figure 2**.

257 The Kruskal-Wallis Test did not find significant differences for the total ($F=1.396$; $P=.251$),
258 hand ($F=1.674$; $P=.197$) or arm ($F=1.050$; $P=.353$) pain extent between women with minimal (total:
259 $26.1 \pm 14.4\%$; hand: $30.9 \pm 16.8\%$; arm: $5.0 \pm 7.0\%$), moderate (total: $21.3 \pm 12.4\%$; hand: $24.9 \pm 14.8\%$;
260 arm: $5.2 \pm 10.2\%$) and severe (total: $22.7 \pm 14.1\%$; hand: $26.1 \pm 15.4\%$; arm: $7.9 \pm 13.1\%$) CTS. In
261 addition, no significant differences in the total ($F=.576$; $P=.563$), hand ($F=.646$; $P=.526$), or upper
262 extremity ($F=.643$; $P=.527$) pain extent were identified between those women with unilateral versus
263 bilateral symptoms.

264 **Discussion**

265 The current study observed that the degree of pain extent was not associated with clinical,
266 psychological or psychophysical variables in women with CTS. Additionally, no difference in pain
267 extent was found depending on the severity or laterality of the symptoms.

268 It has been generally assumed that people with CTS should exhibit pain in the median nerve
269 area; however, we observed that around 80% of our sample experienced extra-median symptoms. In
270 fact, previous studies have reported a prevalence of extra-median symptoms in the hand or proximal
271 upper extremity pain ranging from 40% to 50% (14-16), which is a lower rate than in the current
272 study. Discrepancies in the prevalence of extra-median symptoms between the current and previous
273 studies can likely be explained by the fact that our study is the first to include pain drawings of both
274 the hand and upper extremity for describing extra-median symptoms, since Zanette et al (14) and
275 Mansiz-Kaplan et al (16) only included the hands, whereas Zanette et al (15) only considered upper
276 extremity symptoms. Further, previous studies only evaluated the presence of symptoms, but they
277 did not assess the extent of pain. Thus, this is the first study to report the extent of pain as depicted
278 by a novel method of pain drawing in a sample of women with CTS. In fact, our findings of a non-
279 neuroanatomical distribution of pain in our sample of women with CTS is consistent with previous
280 observations involving spinal nerves during both experimental and clinical studies (38,39).

281 Larger pain extent (13) and widespread pressure hypersensitivity (6,9) have been associated
282 with stronger levels of sensitization. In the current study, pain extent in women with CTS with
283 extra-median symptoms was larger than that in women with just median symptoms. These findings
284 would agree with the hypothesis that the presence of extra-median symptoms (14-16) and larger
285 pain areas (13) are clinical manifestations of central sensitization. The presence of central
286 sensitization is supported by neuro-physiological studies investigating different quantitative sensory
287 tests in individuals with CTS (5-10). Current results further support spreading of pain as a potential
288 manifestation of sensitization mechanisms in women with CTS. Nevertheless, it should be noted
289 that we did not find any significant association between pain extent and psychophysical outcomes

290 of sensitization, i.e., widespread pressure pain or thermal pain hypersensitivity (except CPT over
291 the carpal tunnel). Current findings would agree with the results previously found in some primary
292 headaches such as migraine (40) or tension-type headache (41) but contrast with those previously
293 reported in painful knee osteoarthritis (18) where larger pain extent was associated with higher
294 pressure pain sensitivity. Similarly, the current study did not find any significant association
295 between pain extent and clinical, psychological, and related-disability outcomes in women with
296 CTS which is also in disagreement with previous findings found on painful knee osteoarthritis (18),
297 whiplash-associated disorders (19), and fibromyalgia (20) where larger pain extent was associated
298 with higher intensity of pain or worse psychological variables. Previous studies suggest the
299 relevance of pain drawing as an adjunct variable for evaluating patients; however, expanded pain
300 drawings seem to be not always associated with psychological state (42), as in the current study.

301 One potential explanation for the discrepancy between studies may be related to the fact that
302 knee osteoarthritis or whiplash-associated disorders are most typically nociceptive pain disorders
303 whereas CTS is a neuropathic pain condition. It has been postulated that central sensitization
304 progressively develops in musculoskeletal pain conditions such as painful knee osteoarthritis (18);
305 whereas it seems that central sensitization is present in individuals with CTS from the beginning of
306 their symptoms independently of electrodiagnostic findings (9). This hypothesis is supported by the
307 results from the current study since pain extent or the presence of extra-median symptoms was not
308 significantly different between women with minimal, moderate or severe CTS or between those
309 with unilateral/bilateral symptoms. Since the electro-diagnostic examination classified women with
310 CTS according to nerve conduction impairments; our results would support the well-known notion
311 that pain features/manifestations are not correlated with potential nerve damage due to compression,
312 even in case of a neurological condition and when considering the pain extent. Further, this
313 assumption would explain the results previously found in women with fibromyalgia syndrome, a
314 condition with a neuropathic component (43), where widespread pressure or thermal hyperalgesia
315 was not associated with pain extent (20). Interestingly, in women with fibromyalgia syndrome (20)

316 and in those with CTS, pain extent was poorly associated with cold pain thresholds, a feature of
317 neuropathic pain (44). It is possible that the association between pain extent and clinical,
318 psychological or psychophysical measures is more complex in neuropathic pain conditions than in
319 musculoskeletal pain disorders, or that pain extent would represent a different component of the
320 pain spectrum in these conditions.

321 Finally, we should recognize that the current study has some potential limitations. First, we
322 only included women with CTS recruited from one urban hospital. Therefore, our results should not
323 be extrapolated to men with CTS. Multi-centre studies including men and women with CTS from
324 the general population would help to strengthen the results. Second, we used sensitivity to pressure
325 or thermal pain and pain extent for investigating central sensitization. We do not know if the use of
326 dynamic, e.g., wind up or conditioned pain modulation, or self-reported, e.g., central sensitization
327 inventory (CSI), outcomes would lead to different results. Finally, the role of other psychological
328 variables, e.g., anxiety, sleep disorders was not either considered. Future studies evaluating the role
329 of pain extent in the clinical evolution or as prognostic factor of treatment in CTS are needed.

330

331 **Conclusions**

332 This study used a reliable procedure to quantify pain extent in women with CTS and found
333 that almost 80% of the patients exhibit extra-median symptoms. Pain extent was not associated with
334 clinical, psychological or psychophysical variables in women with CTS and was not significantly
335 different depending on the severity or laterality of the symptoms. Further research is needed to
336 determine the role of pain extent in the clinical course and treatment prognosis of pain conditions.

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Legend of Figures

Figure 1: Pain frequency maps generated by superimposing the pain drawings of all women with carpal tunnel syndrome (n=140). The colour bar represents the frequency of coloured areas. Dark red indicates the most frequently reported area of pain

Figure 2: Pain frequency maps generated by superimposing the pain drawings of women with carpal tunnel syndrome with median (n=16) or extra-median (n=124) symptoms. The colour bar represents the frequency of coloured areas. Dark red indicates the most frequently reported area of pain.