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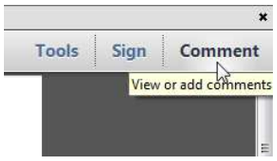

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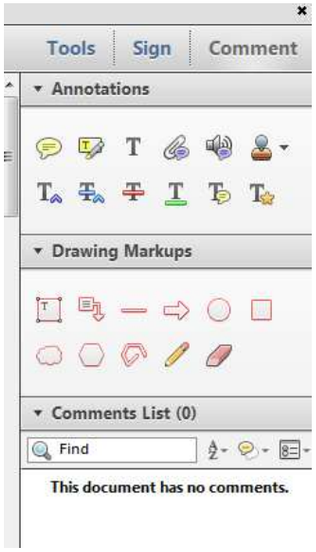

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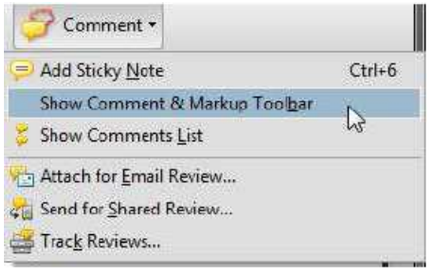

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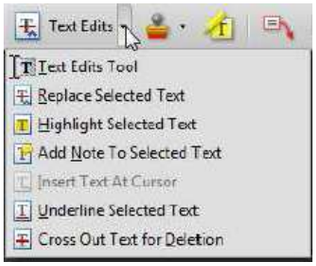

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Original Research

Do Short-Term Effects Predict Long-Term Improvements in Women Who Receive Manual Therapy or Surgery for Carpal Tunnel Syndrome? A Bayesian Network Analysis of a Randomized Clinical Trial

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Abstract

Objective. The purpose of this study was to develop a data-driven Bayesian network approach to understand the potential multivariate pathways of the effect of manual physical therapy in women with carpal tunnel syndrome (CTS).
Methods. Data from a randomized clinical trial (n = 104) were analyzed comparing manual therapy including desensitization maneuvers of the central nervous system versus surgery in women with CTS. All variables included in the original trial were included in a Bayesian network to explore its multivariate relationship. The model was used to quantify the direct and indirect pathways of the effect of physical therapy and surgery on short-term, mid-term, and long-term changes in the clinical variables of pain, related function, and symptom severity.
Results. Manual physical therapy improved function in women with CTS (between-groups difference: 0.09; 95% CI = 0.07 to 0.11). The Bayesian network showed that early improvements (at 1 month) in function and symptom severity led to long-term (at 12 months) changes in related disability both directly and via complex pathways involving baseline pain intensity and depression levels. Additionally, women with moderate CTS had 0.14-point (95% CI = 0.11 to 0.17 point) poorer function at 12 months than those with mild CTS and 0.12-point (95% CI = 0.09 to 0.15 point) poorer function at 12 months than those with severe CTS.
Conclusion. Current findings suggest that short-term benefits in function and symptom severity observed after manual therapy/surgery were associated with long-term improvements in function, but mechanisms driving these effects interact with depression levels and severity as assessed using electromyography. Nevertheless, it should be noted that between-group differences depending on severity determined using electromyography were small, and the clinical relevance is elusive. Further data-driven analyses involving a broad range of biopsychosocial variables are recommended to fully understand the pathways underpinning CTS treatment effects.
Impact. Short-term effects of physical manual therapy seem to be clinically relevant for obtaining long-term effects in women with CTS.

Keywords: Bayesian Networks, Carpal Tunnel Syndrome, Machine Learning, Manual Therapy

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Introduction

Carpal tunnel syndrome (CTS) is the most prevalent entrapment neuropathy of the upper extremity. Although there is no consensus on which treatment option should be applied as first-line management, surgery and conservative treatment are approaches commonly recommended by clinical practice guidelines.[1,2] This lack of consensus reflects the finding that differences between conservative and surgical treatment are smaller than expected, and most patients want to avoid surgery.[3]

Recent theories support that CTS involves peripheral and central sensitization processes, suggesting that conservative treatment should also include interventions targeting the central nervous system in addition to the peripheral nervous system.[4] A randomized clinical trial conducted by Fernández-de-las-Peñas et al showed that manual physical therapy intervention including desensitization maneuvers of the central nervous system obtained better short-term and similar long-term effects on pain intensity (numerical pain rating scale) and related function (Boston Carpal Tunnel Questionnaire) compared with carpal tunnel surgery in women with CTS.[5] An economic analysis of the same trial revealed that this manual physical therapy approach was equally effective clinically but less costly compared with surgery.[6]

Whereas both treatments are effective, understanding the potential pathways, or "why" a treatment is effective, could be of benefit to clinicians and patients. When treatment was ineffective, a pathway analysis would reveal where a hypothesized variable broke down and potentially where the intervention needs to be strengthened or where clinicians should intercede with more personalized management. To the best of our knowledge, there is only 1 path analysis in a cross-sectional cohort including people with CTS.[7] This study reported that function partially mediated the effects of depression levels and the relationship of symptom severity to pain.[7] No previous studies have investigated the mediating mechanisms by which different treatments influence short- to long-term clinical outcomes in individuals with CTS.

Fernández-de-las-Peñas et al[7] used structural equation modeling for path analysis. Structural equation modeling is ideal for investigating the validity of a hypothesized structural path model of disease mechanism. However, structural equation modeling does not consider whether there could be competing path models that better explain the disorder. For example, it is well-established that experimentally inducing pain can result in altered motor function.[8] In addition, although depression can drive pain,[9] pain may also drive the presence of depression levels, as has been shown in individuals with whiplash disorders.[10] Understanding all competing paths will improve our understanding of how interventions provide an effect.

Bayesian networks[11] (BN) are a class of probabilistic models that provides a data-driven approach to derive complex pathways of effects, which may or may not include structural assumptions in the form of prior knowledge. This approach has previously been used to investigate the pathways of effect for some musculoskeletal disorders, including whiplash[12] and postoperative cervical radiculopathy.[13] Because several pathways of effect could have underpinned the benefits of physical therapy and surgery in individuals with CTS, this study aimed to use BN to explore the pathways of the effect of manual physical therapy and surgery for women with CTS treated in the previous randomized clinical trial.[5] We hypothesize that the influence of early charge in symptom severity measured by pain intensity will mediate long-term change in function.[7]

Methods

Study Design

A preplanned secondary analysis was conducted alongside a randomized clinical trial with a 1-year evaluation primary end-point performed in an urban hospital in Madrid, Spain.[5] Full details of the clinical trial, participants, interventions, and primary results of the clinical outcomes were previously reported.[5] The design was approved by the Hospital Universitario Fundación Alcorcón Ethics Committee (PI01223-HUFA12/14) and the clinical trial was prospectively registered (ClinicalTrials.gov: NCT01789645).

Participants

Full details of participant selection are published in the original trial.[5] Briefly, women with pain and/or paresthesia in the median nerve distribution, positive Tinel or Phalen signs, and deficits of sensory or motor median nerve conduction on electrodiagnostic examination[14] were included. They were excluded if patients had any of the following: motor or sensory deficits in the ulnar/radial nerves; hand surgery; use of steroid injections for CTS; multiple diagnoses on the upper extremity, such as cervical radiculopathy; previous neck, shoulder, or upper extremity trauma; systemic diseases causing CTS, such as diabetes mellitus; underlying medical conditions altering pain perception, such as fibromyalgia; or pregnancy. Participants signed a written informed consent form before their inclusion.

Randomization and Interventions

Participants were randomly assigned to receive either manual physical therapy or surgery as previously described.[5] Those allocated to the manual therapy group received three 30-minute treatment sessions that included desensitization maneuvers of the central nervous system once per week. Briefly, the desensitization maneuvers included soft tissue mobilization techniques targeting 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 lumbrical muscles. Additionally, lateral glides were applied to the cervical spine, and tendon and nerve gliding exercises targeting the median nerve were also applied.[5] The basis for applying these manual therapy approaches is based on current neurosciences suggesting a main neurophysiological effect on the peripheral and central nervous systems.[15] In fact, cadaveric[16] and in vivo[17] studies support that nerve-biased manual therapies are able to decrease intraneural edema of the median nerve at the carpal tunnel. This decrease in intraneural edema would reduce the nociceptive median nerve barrage from the periphery to the central nervous system.[18] A recent clinical trial has demonstrated that application of soft-tissue interventions (eg, diacutaneous fibrolysis) targeting anatomical sites of the upper extremity applied in the original clinical trial[5] is effective for decreasing mechanosensitivity in CTS, suggesting an effect on the nervous system of these approaches.[19] 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.[5] Those randomly allocated to the surgery group underwent open or endoscopic release of the carpal tunnel pragmatically applied on the basis of surgeon and patient preferences.[20] Patients allocated to this group also received the same educational session for performing the tendon/nerve gliding exercises as the manual physical therapy group.[5]

Variables Included in the BN

Clinical outcomes on the original trial were assessed at baseline and at 1, 3, 6, and 12 months after the intervention.[5] The primary outcome was pain intensity assessed with an 11-point numerical pain rating scale (0 = no pain, 10 = maximum pain). In the original trial, the mean intensity of pain and the worst level of pain experienced in the preceding week were independently assessed, but in the current BN, the worst pain score was used. Secondary outcomes included the functional status and symptom severity subscales of the Boston Carpal Tunnel Questionnaire.[21] Each scale is scored from 1 to 5, with higher scores indicating poor function or more symptom severity.

Accordingly, we included 21 variables in the BN. The 21 variables were categorized into baseline patient characteristics, treatment group, and clinical outcomes. Baseline patient characteristics included age (years), duration of the symptoms (years with pain), area (pain extent assessed with digital pain draws), electromyography (EMG, classified as minimal, moderate, or severe), and depression levels (assessed with the Beck Depression Inventory, with scores ranging from 0 to 21 and higher scores suggesting higher depression levels). Treatment group included the randomized allocation to treatment (1 = manual therapy, 2 = surgery) from the original clinical trial. Clinical outcomes included pain intensity, function, and symptom severity collected at baseline and at 3, 6, and 12 months after the intervention (3 outcomes × 4 times = 12 variables).

Approach to Data Analysis

BN Analysis

All analyses were performed in R software using the "bnlearn" package,[22] with codes and results included in a public online repository (https://bernard-liew.github.io/2020_cts_bn/2-bn_analysis.html). The BN is a graphical modeling technique[11] that can leverage either data alone or data combined with expert prior knowledge to learn multivariate pathway models. Building a BN model using a data-driven approach involves 2 stages: (1) structure learning (ie, identifying which arcs are present in the graphical model); and (2) parameter learning (ie, estimating the parameters that regulate the strength and the sign of the corresponding relationships).

As previously mentioned, BN can easily include prior knowledge, sourced from the literature and experts, during the model building process. In the BN framework, prior knowledge can be included in the model as blacklist and whitelist arcs. Blacklist arcs are those that contravene known biological/physical mechanisms. In the current study, we imposed the following blacklist: arcs cannot point backward in time (eg, pain at 12 months cannot influence pain at 6 months); no variables can influence group, because group allocation was random; and no other variables can influence baseline patient characteristics.

We made use of model averaging to reduce the potential of including spurious relationships in the BN using bootstrap resampling (B = 200) and performing structure learning on each of the resulting samples using the hill-climbing algorithm. We computed an "average" consensus directed acyclic graph by selecting those arcs that had a frequency of >50% in the bootstrapped samples to create a sparse and interpretable network.[23] AQ6

To determine the validity of the trained model, validation was performed using nested 10-fold cross-validation. This approach splits the training set into 10 approximately equal folds, trains the model on 9 folds using bootstrap resampling (as described above), and evaluates the model's performance on the 10th fold. Model performance was defined as the Pearson correlation coefficient between the predicted and observed values of each continuous variable. The strength of correlation was categorized as negligible ($|r| \leq 0.30$), low ($|r| = 0.31$–0.50), moderate ($|r| = 0.51$–0.70), high ($|r| = 0.71$–0.90), and very high ($|r| = 0.91$–1.0).[24] The greater the model predictive performance, the greater the correlation between predicted and observed values of the modeled variables. Nested 10-fold cross-validation reduces validation optimism, because a model would perform well on the data it was exactly trained on.

Conditional Probability Queries

The derived averaged BN model is considered an "expert system," which means that we can elicit a sample of realizations of the modeled variables under specific conditions. For each conditional probability query, we sampled 10^4 realizations of the variables of interest to obtain precise probability estimates. We used a technique known as belief updating, which estimates the posterior probability of an event happening on the basis of the available evidence for the values of certain variables. We adopted a specific method of belief updating known as logic sampling.[11]

Results

From the baseline, 120 women were included in the original trial, and after trimming missing values, 104 women (52 in each group) were included in this BN. Of the 52 participants allocated to manual physical therapy, 15 were classified as having minimal CTS, 20 were classified as having moderate CTS, and 17 were classified as having severe CTS, according to EMG data. For participants allocated to surgery, 9 were classified as having minimal CTS, 26 were classified as having moderate CTS, and 17 were classified as having severe CTS, according to the EMG data (Fig. 1). Figure 1 also illustrates the mean and SD of each variable included in the BN analysis at each follow-up time point.

Figure 2 shows the averaged BN consensus model learned from 200 networks constructed from the data, with arcs appearing in >50% of the networks kept. The average correlations across all 10 folds between the observed values and between the values predicted by our BN for all variables are included in the eTable (available at https://academic.oup.com/ptj). An advantage of the BN model is that it enables the reader to query different elements of the system to fully understand the interaction between the variables. By systematically removing individual variables from the model, the impact of that variable on the remaining variables in the AQ7

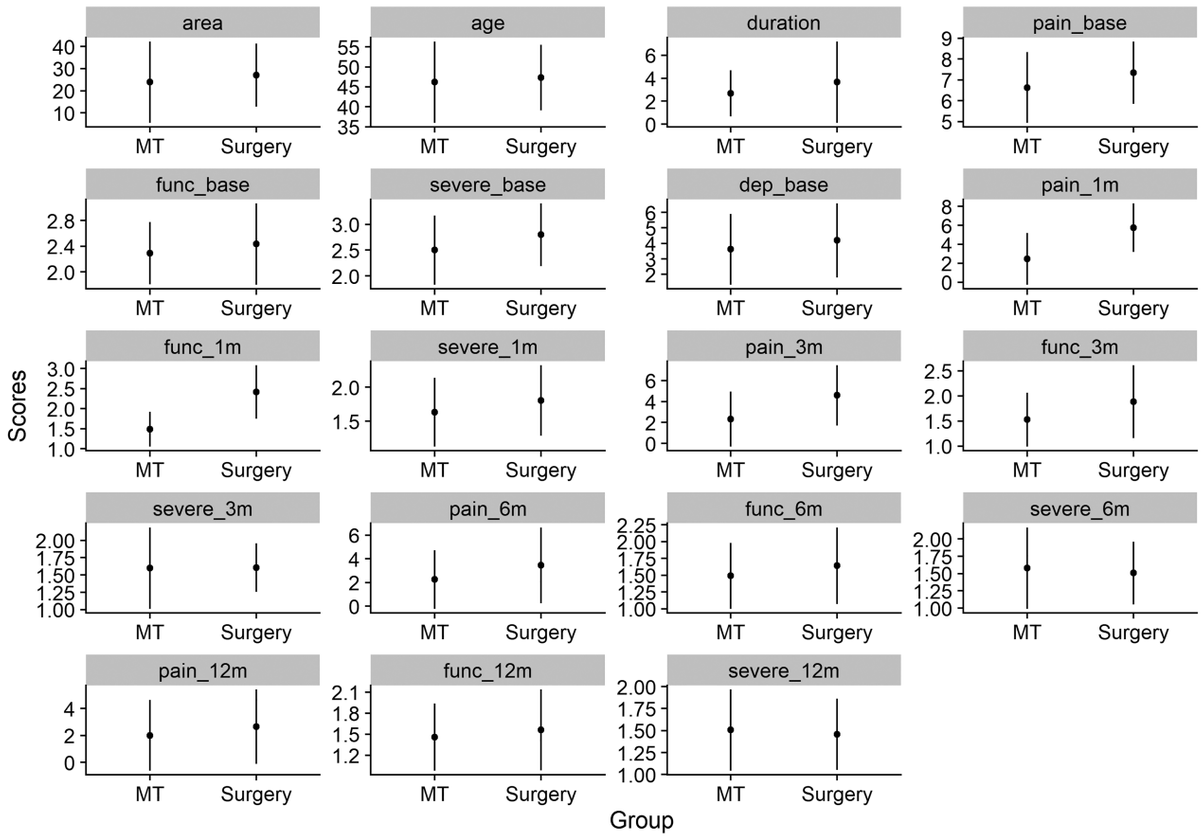

Figure 1. Mean with error bars representing 1 SD of the values of each modeled variable in the Bayesian network. Values of each outcome are based on their main scores: area is expressed in arbitrary units, age and duration are expressed in years, pain is expressed on an 11-point numerical pain rate scale (0–10 points), function and severity are expressed as 0 to 5 points, and depression is expressed as scores from 0 to 21. _1m = values at 1-month follow-up; _3m = values at 3-month follow-up; _6m = values at 6-month follow-up; _12m = values at 12-month follow-up; _base = values at baseline; dep = total score on the Beck Depression Inventory for depression symptoms; func = function subscale of the Boston Carpal Tunnel Questionnaire; severe = symptom severity subscale of the Boston Carpal Tunnel Questionnaire.

model becomes clearer. For simplicity, the magnitude of the relationship between variables is reported using β coefficients, which are interpreted as a 1-unit change in the independent variable resulting in a β-unit change in the dependent variable. Because the BN model was complex with multiple interconnected ~~variables~~, we explore in more detail below 4 findings that were of most relevance to understanding the mechanisms of the interventions. It can be observed that 4 independent variables influenced function at 12 months: treatment group, baseline pain intensity, symptom severity at 1 month, and EMG classification (Fig. 2).

Effect of Treatment Group on Function at 12 Months

On the basis of simulated data from the model, function at 12 months was 0.09 point (95% CI = 0.07 to 0.11 point) lower in the manual therapy group (suggesting better function) than in the surgery group (t (9998) = 8.44; $P < .001$) (Fig. 3). From Figure 2, group had a direct effect on function at 12 months but also an indirect effect via its influence on function at 1 month. When we simulated a scenario in which the arc for function at 1 month was removed by fixing the value of the 1-month function regression coefficient in the local distributions to 0, function at 12 months was 0.03 point lower in the manual therapy group (suggesting better function) than in the surgery group (t (9998) = 3.38; $P = .001$). This finding suggests that almost one-third of the influence of treatment group on function at 12 months was attributed to its direct effect and that the remaining two-thirds of the influence was attributed to the treatment group effect on function at 1 month.

Influence of Baseline Pain on Function at 12 Months

Baseline pain intensity was significantly associated with function at 12 months. A 1-point increase in pain worsened function at 12 months by 0.008 point (t (9998) = 2.39; $P = .017$) (Fig. 4). As shown in Figure 2, baseline pain intensity influenced function at 12 months via its impact on baseline depression levels. When we simulated a scenario in which baseline depression was made independent from baseline pain intensity, the latter no longer had a significant association with function at 12 months (t (9998) = 1.30; $P = .195$).

Influence of Symptom Severity at 1 Month on Function at 12 Months

Symptom severity at 1 month was significantly associated with function at 12 months. A 1-point increase in symptom severity at 1 month worsened function at 12 months by 0.15

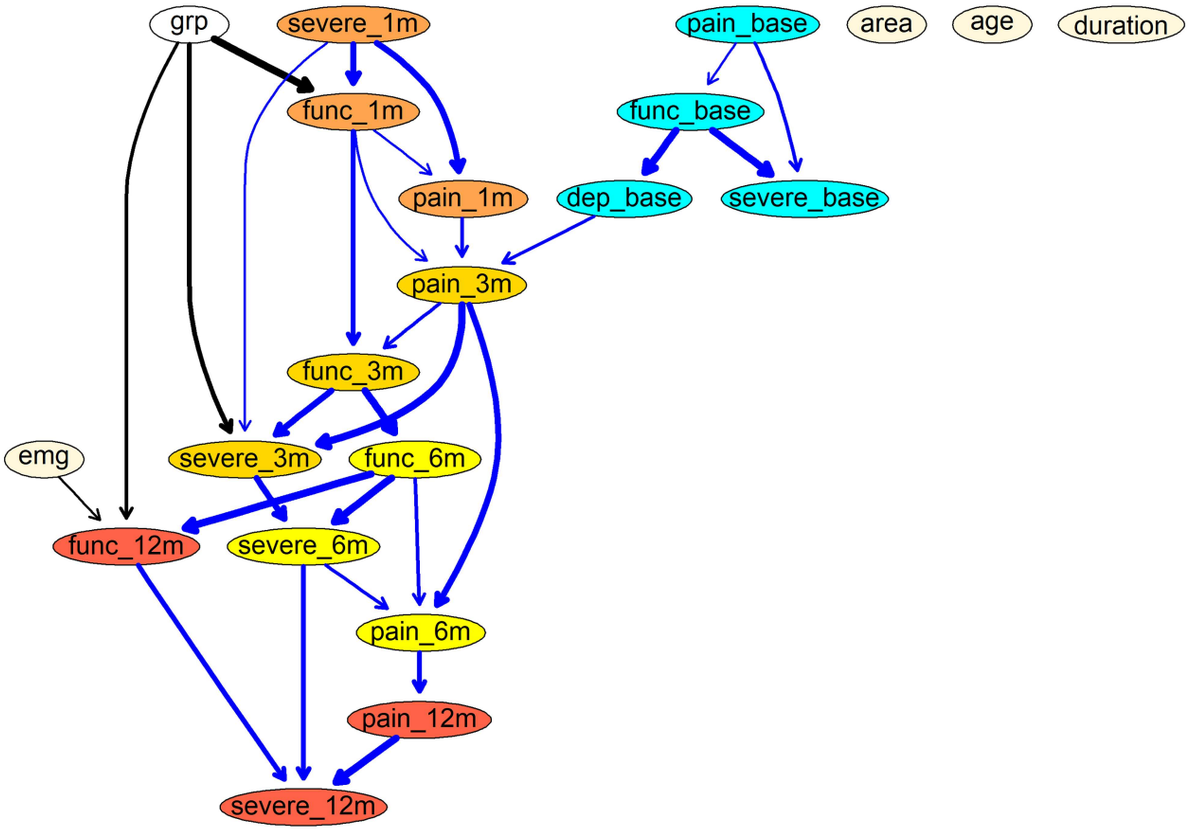

Figure 2. Directed acyclic graph (DAG) underlying the consensus Bayesian network learned from the variables. For continuous variables, blue-colored arcs reflect positive β coefficient values relating "parent" to "child" variables. For categorical variables, arcs were colored black. The thickness of the arcs reflects the proportion of times each arc was found in the 200 Bayesian network models built; only arcs with a proportion of >0.5 were included in the final averaged consensus network. _1m = values at 1-month follow-up; _3m = values at 3-month follow-up; _6m = values at 6-month follow-up; _12m = values at 12-month follow-up; _base = values at baseline; dep = total score on the Beck Depression Inventory for depression symptoms; func = function subscale of the Boston Carpal Tunnel Questionnaire; severe = symptom severity subscale of the Boston Carpal Tunnel Questionnaire.

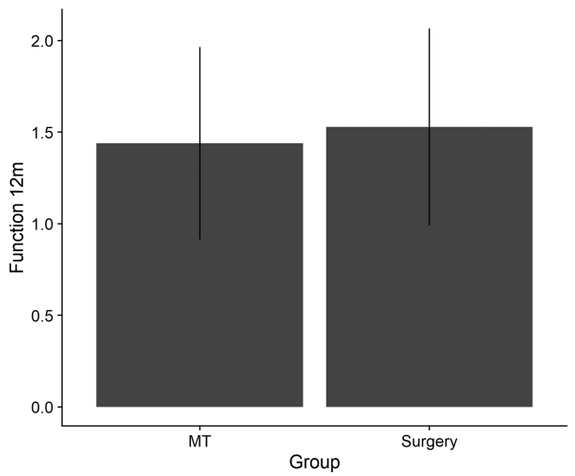

Figure 3. Mean with error bars representing 1 SD of the posterior samples (10^4) of the relationship between group (manual therapy [MT] vs surgery) and function at 12 months.

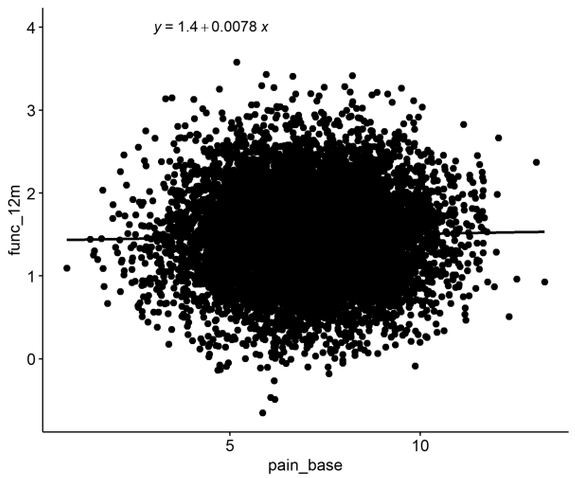

Figure 4. Posterior samples (10^4) of the relationship between baseline pain intensity (pain_base) and function at 12 months (func_12m).

point (t (9998) $t = 14.57$; $P < .001$) (Fig. 5). Although symptom severity at 1 month influenced function at 12 months via multiple pathways, a common point of effect was its effect on function at 6 months. When we simulated a scenario in which symptom severity at 1 month was made independent from function at 6 months, there was no longer a significant

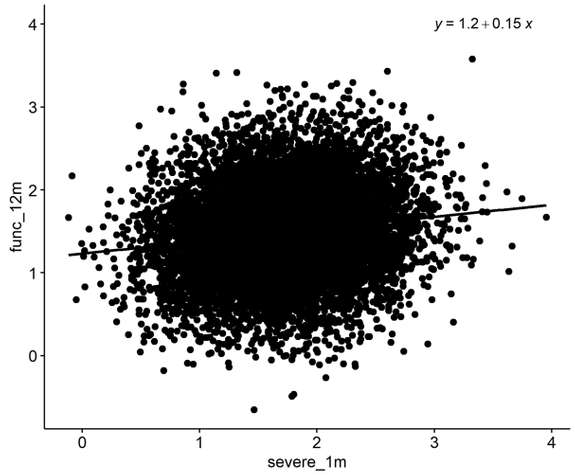

Figure 5. Posterior samples (10^4) of the relationship between symptom's severity at 1 month (severe_1m) and function at 12 months (func_12m).

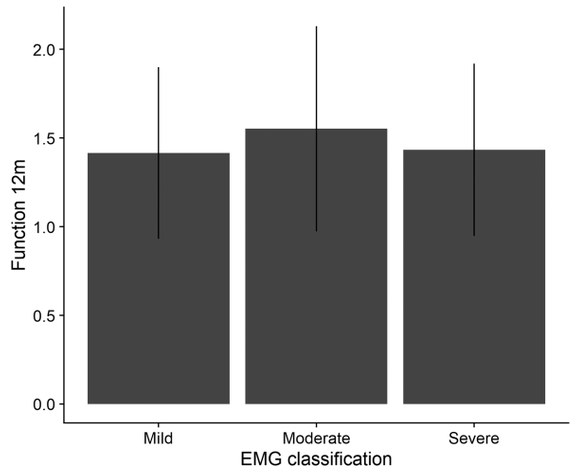

Figure 6. Mean with error bars representing 1 SD of the posterior samples (10^4) of the relationship between electromyography classification and function at 12 months.

association between symptom severity at 1 month and function at 12 months (t 9998) = −0.79; P = .429).

Influence of EMG Classification on Function at 12 Months

On the basis of simulated data from the model, there was a significant effect of EMG classification on function at 12 months (F (2, 9997) = 70.86; P < .001) (Fig. 6). A post hoc Tukey honestly significant difference test found that people with moderate CTS had a 0.14-point (95% CI = 0.11 to 0.17 point; P < .001) poorer function than those with mild CTS and a 0.12-point (95% CI = 0.09 to 0.15 point; P < .001) poorer function than those with severe CTS. There was no difference in function at 12 months between severe CTS and mild CTS (P = .39).

Discussion

This study presents the first longitudinal investigation, to our knowledge, to adopt a data-driven modeling approach to quantify the probabilistic pathways of effect underpinning manual physical therapy or surgery for women with CTS. We found that allocation to a manual physical therapy group directly improved long-term function compared with surgery. We also observed that baseline pain intensity influenced the effect of the treatment and was mediated by depression symptoms. Lastly, we found that early improvements (approximately 1 month) in function (mediated by treatment) and symptom severity influenced the effect of physical therapy and surgery on pain and related disability in women with CTS. These findings are worth discussing in further detail.

Effect of Treatment Group on Function at 12 Months

Allocation to the manual physical therapy treatment group had a direct effect on function at 12 months but also an indirect effect via its influence on function at 1 month. The indirect effect may be associated with the recovery time associated with CTS surgery. On average, it takes 4 to 6 weeks before the surgery heals to a point at which patients may report improvement of symptoms. During this time, patients are asked to avoid heavy lifting and repeated movements of their wrist and are placed in a protected protocol to allow the surgical approach to healing. In fact, although there are different types of surgeries, some more invasive than others, the time required to heal will likely always result in a delayed recovery compared with a conservative approach. The slower improvement in function observed in the surgery group mostly at 1 and 3 months seems to be related to the tissue healing recovery process needed after the surgical intervention.

Influence of Baseline Pain on Function at 12 Months

We feel there is an intuitive relationship between pain-related symptoms and disability and that the higher level of baseline symptoms is likely related to the severity of the pathology. This relationship has been explored and validated in numerus studies including individuals with musculoskeletal pain conditions. Higher baseline pain intensity is a predictor for low back pain[25] and neck pain[26] at 12 months and also at 12 months after distal radius fracture.[27] In people with neuropathic pain, baseline leg pain intensity has been also associated with surgery in individuals with sciatica.[28] The review by Mallen et al[29] indicated that higher baseline pain intensity is a negative prognostic factor for a number of musculoskeletal pain conditions, including the spine, shoulder, neck, hip, knee, and elbow. To our knowledge, we are the first to report on the predictive capacity of baseline pain intensity for women with CTS. In addition, it was previously observed that worse function or higher symptom severity, assessed with the Boston Carpal Tunnel Questionnaire, is a predictive of outcome for a better response to conservative therapy.[30] We did not identify that baseline function or symptom severity scores influenced long-term outcomes in our study.

Influence of Symptom Severity at 1 Month on Function at 12 Months

Previous studies evaluated whether early change in symptoms is related to long-term outcomes. Rundell et al[31] investigated if 3-month outcomes including back and leg pain could predict 12-month back and pain, disability, and patient satisfaction;

they reported that the 3-month data were stronger predictors than the baseline counterparts. Walston and McLester[32] reported that early changes in reports of low back pain within the first 23 to 30 days predicted long-term changes and were reflective of those who benefited from physical therapy. Other studies examining changes in pain during much shorter terms found benefits in a sustained between-session treatment. Early responses from the second to fourth treatment visits were able to correctly predict 80.4% of the discharge outcomes in patients with chronic low back pain.[33] A better short-term response that occurs from the first treatment to the second treatment is associated with better effects of physical therapist interventions at 6-month follow-up periods in people with low back pain.[34] It is worth noting that all the aforementioned studies lacked a comparative group and used simple correlational statistical measures. To our knowledge, no previous studies have explored early change of pain intensity in women with CTS.

Influence of EMG Classification on Function at 12 Months

We also observed that women with mild or severe EMG findings experienced better long-term function than those with moderate findings. This result was unexpected, because it suggests that more severe EMG findings would lead to better clinical outcomes, at least within the manual physical therapy group. In fact, clinical guidelines recommend conservative treatment mostly for mild to moderate, and, sometimes severe, cases of CTS.[1,2] This premise is based on trials examining therapeutic approaches using the traditional clinical reasoning that CTS is just a localized pathology associated with a peripheral lesion at the carpal tunnel, and, therefore, local interventions are applied. Because the current clinical trial used manual physical therapist interventions considering current nociceptive understanding of CTS, it is possible that this approach would lead to better outcomes albeit in severe CTS. Perhaps this topic is indeed an area of future research because the value of electrodiagnostic findings in predicting functional outcomes is unclear and conflicting.[35,36] Nevertheless, it should be noted that between-group differences depending on EMG severity were small and their clinical relevance is elusive.

Strengths and Limitations

This study had several potential strengths and limitations. First, the analysis was performed on a robustly conducted, randomized clinical trial, with 87% of the original cohort included in the analysis. Secondly, we uncovered surprising pathways of treatment effect, such as long-term effects on related-function being dependent on short-term changes, which have not been previously tested in this pain condition. Despite these strengths, some weaknesses are also present. We note that the method to quantify mechanisms of change is not a singular method but actually consists of 3 progressive levels[37]: association (ie, "How are the variables related?"), intervention (ie, "What would Y be if I do X?"), and counterfactuals (ie, "What if I had acted differently?"). Each ladder provides a potential incremental amount of evidence towards causal inference. The current BN analysis can only act on the first and second rung (via our simulated intervention analysis) of the causation ladder, meaning that we cannot definitively conclude our reported pathways as really causal. Despite an inability to perform counterfactual analysis, the current analysis could be said to provide competing, and potentially more probable, pathways of an effect than those presented in the literature that can be confirmed by future research. A second limitation was the inclusion of only women with CTS. Another limitation of this study was that psychophysical and psychological variables were not included in the BN, because the original clinical trial did not consider them. Newer insights into the mechanisms of effect of treatments offered to manage CTS could be revealed by the inclusion of biopsychosocial variables in future trials. Further, we only collected self-reported pain and related disability as outcomes. Because patients with CTS also exhibit other sensory or motor symptoms, such as weakness, tingling, numbness, and difficulty with grasping and use of small objects, it is possible that these other symptoms could also play a role in this process. Finally, it should be considered that both groups received instructions for performing tendon/nerve gliding exercises as home exercises at demand as secondary and complementary treatment to their primary intervention, such as manual therapy or surgery.

A data-driven BN modeling approach showed that manual physical therapy reduced related disability in women with CTS. Early improvement in function and symptom severity led to long-term improvement in function both directly and via more complex pathways involving baseline pain and depression levels. In addition, the severity of the condition, expressed by EMG data, also had a direct influence on long-term effects on function. Current findings as a whole suggest that short-term benefits in function and symptom severity were associated with long-term improvement in related disability; however, the mechanisms driving the effects interacted with depression levels and EMG severity.

Author Contributions

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Ethics Approval

The design was approved by the Hospital Universitario Fundación Alcorcón Ethics Committee (PI01223-HUFA12/14).

Clinical Trial Registration

The clinical trial was registered at ClinicalTrials.gov: NCT01789645.

Disclosures

The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

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