# CAPÍTULO 16

## STUDY DESIGNS AND STATISTICAL APPROACHES FOR BILATERAL CARPAL TUNNES SYNDROME: AN OVERVIEW

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**ABSTRACT: Background:** Pathologies with bilateral involvement, such as carpal tunnel syndrome (CTS), are relatively common in clinical practice. However, some published data are misleading, as many articles consider only one hand in data analysis. **Objectives:** This article aims to briefly propose a study design and

statistical approach for data analysis of bilateral CTS. **Method:** Statistical reporting. **Results:** Although the results of clinical and surgical interventions are usually reported by randomized clinical trials, the main guidelines do not offer recommendations on how to proceed in cases of interventions in patients with bilateral conditions. Additionally, crossover trials may be an alternative, particularly when comparing different interventions in these patients. Considering the statistical approach, traditional tests are not suitable for bilateral conditions, and result in an overestimation of the results. In contrast, regression models, mixed effects analysis, generalized estimating equations, and multilevel modeling analysis are more reliable. Furthermore, in the case of crossover trials, an ANOVA suitable for crossover design should be chosen with normally distributed data of two groups, while a variance-balanced design is the ideal choice for three or more treatments and Cochran's Statistics. **Conclusions:** When considering the comparison of different therapeutic intervention/rehabilitation techniques in patients with CTS or other peripheral nerve pathologies, the choice of the most appropriate study design and statistical analysis will provide more reliable evidence.
**KEYWORDS:** Carpal tunnel syndrome; statistical methods; crossover trial; rehabilitation; surgical treatment.

## 1 | INTRODUCTION

Bilateral Carpal tunnel syndrome (CTS) has clinical implications and therapeutic results that differ from unilateral NM compression (DEC; ZYLUK, 2018). In addition, the presence of bilateral symptoms generates an interrelationship between the outcome measures, which, if not properly considered in the interpretation of the data, causes an effect of repetition of information, which can bias the statistical analysis (SONG; HAAS; CHUNG, 2009). However, despite the high prevalence of bilateral CTS, there is lack of studies that demonstrate the best way to manage these cases, both in relation to clinical (OSTERGAARD; MEYER; EARP, 2020) and surgical treatment (PETERS; PAGE; COPPIETERS; ROSS *et al.*, 2016).

Even the main guidelines for randomized clinical trials (RCTs), researchers lack guidance on how to work with pathologies of bilateral involvement (MOSELEY; ELKINS, 2018; SHAMSEER; HOPEWELL; ALTMAN; MOHER *et al.*, 2016), both in relation to the allocation of participants and the statistical analyzes that should be implemented, considering the interdependence of the data produced by bilaterality (PADUA; PASQUALETTI; ROSENBAUM, 2005). The allocation of patients with bilateral CTS should be made by individual and not by affected hand. At traditional statistical tests, when analyzing results by wrist and not by individual, lead to an overestimation of results due to repetition of information (BAUER; GOTTFREDSON; DEAN; ZUCKER, 2013). Therefore, it is necessary to use more reliable statistical models to manage the repetition of data resulting from the inclusion of the same participant more than once. Therefore, this study aims to discuss aspects related to study designs for the allocation of participants with bilateral CTS and their respective statistical analysis.

## 2 | CARPAL TUNNEL SYNDROME (CTS)

CTS is a compressive neuropathy of the upper limbs, representing 90% of peripheral compressive neuropathies, and is the most common neuropathy in the general population (ALESSIA; DIX; ASEM; MALA *et al.*, 2020). It has been reported that CTS affects 10% of the global population, with 3 to 4 new cases per 1.000 inhabitants per year (BURTON; CHEN; CHESTERTON; VAN DER WINDT, 2018).

In the United States, the prevalence of CTS is nearly 5%, with an incidence of 1 to 3 cases per 1.000 inhabitant (IBRAHIM; MAJID; CLARKE; KERSHAW, 2009). CTS has a higher incidence in women aged 45–65 years and tends to be bilateral in 60%–65% of cases (TADJERBASHI; ÅKESSON; ATROSHI, 2019). Additionally, there is an increase in the prevalence and severity of this pathology with aging (CHAPMAN, 2017).

Clinical signs of CTS, such as pain, numbness, and tingling at the median nerve of the upper limbs, may be associated with muscle weakness and atrophy, with a marked impairment of manual abilities and health-related quality of life (BURTON; CHEN; CHESTERTON; VAN DER WINDT, 2018).

It has been reported that surgical treatment of CTS carries an annual cost of more than 2 billion dollars (MILONE; KARIM; KLIFTO; CAPO, 2019). In Brazil, the estimated cost of CTS surgeries at the Unified Health System is nearly 30 million reais (MAGALHÃES; FERNANDES; ALKMIM; ANJOS, 2017).

The main factors associated with CTS are older age, sex, obesity, diabetes mellitus, rheumatic arthritis (PADUA; CORACI; ERRA; PAZZAGLIA *et al.*, 2016), and manual labor, particularly jobs that require manual strength and physical activity (BECKER; SCALCO; PIETROSKI; CELLI *et al.*, 2014).

Treatment for CTS may be clinical or surgical, the choice of which is based on disease severity. The use of clinical therapies is indicated for the treatment of CTS with mild or moderate impairment (HUISSTEDE; FRIDEN; COERT; HOOGVLIET *et al.*, 2014). Therapeutic approaches include modification of daily life activities, low-level laser therapy, ultrasound therapy, stretching, and myofascial manipulation (ARMAGAN; BAKILAN; OZGEN; MEHMETOGLU *et al.*, 2014; CHANG; HSIEH; HORNG; CHEN *et al.*, 2014; FUSAKUL; ARANYAVALAI; SAENSRI; THIENGWITTAYAPORN, 2014). However, surgical treatment of this neuropathy is indicated when severe involvement of the median nerve is observed during clinical evaluation or electroneuromyography (CHA; SHIN; AHN; BEOM *et al.*, 2016). Open or endoscopic surgery can also be used, despite several studies indicating no statistical difference when comparing the outcomes of both techniques in this patient group (VASILIADIS; GEORGOULAS; SHRIER; SALANTI *et al.*, 2014). The high incidence of CTS in both developed and developing countries, as well as the clinical features and negative impact of the disease, demonstrates the relevance of this topic, which is confirmed by several published articles involving different aspects of the management of such cases

(DE OLIVEIRA FILHO; DE OLIVEIRA, 2017).

## 3 | STUDY DESIGNS IN BILATERAL CTS

Although CTS is mostly bilateral, insufficient studies have used samples composed exclusively of this population. Individuals with bilateral CTS have peculiar clinical characteristics that influence both the therapeutic results (LARSEN; SØRENSEN; CRONE; WEIS *et al.*, 2013) and data analysis. Moreover, statistical methods that do not consider each hand as an interrelated event overestimate the outcome (PADUA; PASQUALETTI; ROSENBAUM, 2005).

The results of clinical and surgical interventions are usually reported in randomized clinical trials. Considering the need for improvement in the methods of randomized clinical trials, guidelines such as Consolidated Standards of Reporting Trials – CONSORT (SHAMSEER; HOPEWELL; ALTMAN; MOHER *et al.*, 2016) and Physiotherapy Evidence Database - PEDro (MOSELEY; ELKINS, 2018), and Hooked on Evidence (SCHREIBER; STERN, 2005) the latter two being developed specifically for rehabilitation studies. However, there is no recommendation in these guidelines on how to deal with bilateral conditions, which are relatively common in medical practice.

Crossover trials may be an alternative to randomized double-blind studies. Crossover designs are useful for studies where the patients receive a prespecified sequence of treatments during consecutive periods of time for evaluation (TUDOR; KOCH; CATELLIER, 2000). The patients' outcomes are measured during each period and the patients serve as their own control, assuming similar conditions for evaluation across treatment periods for each patient (JOHNSON, 2010). Additionally, it is possible to implement a washout period between consecutive periods so that the preceding treatment does not influence the response to the next treatment, allowing any residual effects of treatments to be minimized (SEDGWICK, 2014). Briefly, the crossover trial is a "within subject" study design, which seems to be a reliable option, particularly for research studies that aim to compare different interventions in the same individuals. The crossover design has numerous advantages that investigators may wish to use for early-stage trials. The strength of this design is that the interventions under investigation are evaluated within the same patients, thus eliminating between-subject variability (MACLURE, 1991). Furthermore, this trial design permits head-to-head trial opportunities, and patients receiving multiple treatments can express preferences for or against treatments (MILLS; CHAN; WU; VAIL *et al.*, 2009).

Crossover studies are extremely popular for the study of new and developmental drugs ( (BROWN JR, 1980)) and are most appropriate in studies where the effects of the treatment(s) are short-lived and reversible, and are best suited to trials related to symptomatic conditions or diseases (CLEOPHAS, 1990; ELBOURNE; ALTMAN; HIGGINS; CURTIN *et al.*, 2002).

## 4 | STATISTICAL ANALYSIS IN BILATERAL CTS

CTS is usually a bilateral pathology, in which the dominant hand has a worse severity status. Statistical approaches that do not consider the bilateral interdependence of the data do not consider the real physio-pathological expression of CTS. CTS has a complex pathology, with clinical implications on both sides, involving both the central and peripheral nervous systems instead of a simple compression that affects the median nerve in both hands (MAEDA; KETTNER; KIM; KIM *et al.*, 2016).

However, some of the published literature regarding these cases is misleading for several reasons. First, many articles about clinical or surgical interventions only consider one hand in the data analysis, even if the patient reports pain in both hands (PETERS; PAGE; COPPIETERS; ROSS *et al.*, 2016). Moreover, many studies do not consider the effect of repeated information, which may introduce bias in the data analysis if a proper statistical approach is not applied (SONG; HAAS; CHUNG, 2009). Additionally, some studies have described bilateral data instead of considering bilateral information in the statistical analysis (PADUA; PASQUALETTI; ROSENBAUM, 2005).

To consider the continuous or categorical characteristics between interdependent groups, the use of traditional tests, such as the t-test, chi square test, ANOVA, Kruskal–Wallis, and Mann–Whitney test, are unsuitable for bilateral conditions, and create an overestimation of the results (WINTERS; WINTERS; AMEDEE, 2010). Additionally, the description of only one hand for the analysis, or the inclusion of both hands from the same individual creates an artificial increase in the sample size, which predisposes the results to a type I error (SONG; HAAS; CHUNG, 2009).

A better option to analyze the repeated data arising from bilateral pathologies would be the use of regression models (ALI; BHASKAR, 2016) and the analysis of mixed effects (ZEGER; LIANG, 1992). Additionally, the generalized estimating equation (GEE) is a less used but still suitable option that is found in some statistical software; the GEE allows the results from both hands to be grouped and the models to be compared considering the correlations between observations for everyone (Johnson, 2010). Additionally, multilevel modeling analysis is a method that analyzes data with multilevel variability. Multilevel models can connect dependent observations that lay bilateral characteristics (DIEZ-ROUX, 2000).

Furthermore, while crossover trials are supposed to reduce the standard errors for treatment comparisons, a problem may occur if there are carryover or residual effects from a treatment given in one period to a treatment given in a subsequent period. Carryover exists when a treatment (or intervention) “A” is given in the first period and continues to affect treatment “B”, which is given in the subsequent period (JOHNSON, 2010).

For the analysis of more complicated designs and further investigation of carryover effects, as well as interactions involving treatment effects, models that address conditional distributions of responses within patients can be applied. This potential source of bias is akin

to confounding in an epidemiological study and implies that, to some extent, the analysis of data from a crossover trial will inevitably rely more on assumptions and modeling, and less directly on the randomization, than a conventional parallel group study (JONES; KENWARD, 1989).

A crossover trial has a special type of repeated measures design, and the variance-covariance structure of the repeated measures should be taken into consideration when analyzing the collected data.

Crossover data are examples of repeated measurements. Consequently, a key concept in the design and analysis of crossover trials is between-subject and within-subject information. Between-subject information is contained in the total (or mean) of the measurements from a subject, while within-subject information is contained among all differences in the measurements from a subject (JONES; KENWARD, 1989). Statistical analysis of data repeated in the same individuals because of bilateral involvement is done by a specific ANOVA for crossover design (Tudor et al., 2000)

In cases with three or more treatments, there will be more than one possible contrast between the treatment effects. In such situations, a variance-balanced design is the ideal choice because the variance of every estimated pairwise comparison is equal to the same constant value, such as in the Williams design (ISAAC; DEAN; OSTROM, 2001) The Williams design also possess a combinatorial balance in the sense that every treatment follows every other treatment (except itself) the same number of times, and is a special case of sequentially counterbalanced Latin squares (WILLIAMS, 1949).

Additionally, the analysis of non-normal crossover data falls into the class of analyses of non-normal clustered or dependent data. Such analyses are more complex than those for continuous data based on a linear model (KENWARD; JONES, 2007). There are two main reasons for this. First, there is no single “natural” choice of multivariate model in such settings for which to parallel the multivariate normal linear model. Second, for most problems in this class, it is appropriate to assume a non-linear relationship between the mean or expectation of an observation and the linear predictor with various fixed effects [(KENWARD; JONES, 2007; MOLENBERGHS; VERBEKE, 2005). Therefore, a straightforward nonparametric method can be used for the comparison of treatments in situations where one can assume that neither carryover nor period effects are present (TUDOR; KOCH; CATELLIER, 2000). In such cases, Mantel-Haenszel statistics or Cochran analyzes can be used if the response variable is dichotomous. It is based on Mantel–Haenszel statistics with the respective patients as strata, within which the association between treatments and ordinal outcomes is assessed (Tudor et al., 2000). In addition, the dichotomous response variable is comparable to Cochran’s statistics (STOKES; DAVIS; KOCH, 1995).

## 5 | CONCLUSIONS

Although randomized controlled trials are the primary choice for comparing different interventions, considering the frequent bilateral condition in CTS, crossover trials may be another suitable option, particularly when comparing different interventions in these patients. Considering the statistical approach, traditional tests are not suitable for bilateral conditions and result in an overestimation of the results. Regression models, mixed effects analysis, generalized estimating equations, and multilevel modeling analysis are more reliable methods for this condition.

In the case of crossover trials an ANOVA that is suitable for the crossover design should be chosen. However, when there are three or more treatments, a variance-balanced design is the ideal choice, whereas Cochran's statistics may be chosen for dichotomous response variables.

Therefore, when considering the comparison of therapeutic interventions or different rehabilitation techniques in patients with CTS or other peripheral nerve pathologies, the choice of the most appropriate study design and statistical analysis will provide more reliable evidence.

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