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A pilot clinical trial comparing efficacy and safety of tramadol versus prednisone along with therapeutic ultrasound as adjuvant therapy in Chinese patients with carpal tunnel syndrome diagnosed by ultrasonography

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Abstract: The primary objective of the present clinical trial was to evaluate efficacy and safety of tramadol versus prednisone in Chinese patients with carpal tunnel syndrome (CTS) diagnosed by ultrasonography. A total of 60 patients' diagnosed with moderate CTS based on a clinical and electrophysiological parameters were enrolled in this clinical trial. The patients were randomly assigned to one of two groups in allocation ratio of 1:1. Test group was given controlled release Tramadol (100 mg every 12 hours) and Reference Group received Prednisone 20 mg once daily for 2 weeks (14 days). Ultrasound therapy (UT) was given as adjuvant therapy in both the group. CTS were evaluated before and after treatment through clinical findings, Boston Carpal Tunnel Questionnaire, visual analog scale (VAS) and electrophysiological data. The results were evaluated with Student's *t* test and chi-squared. A statistically significant difference was observed between both the treatment group regarding Durkan's test, Phalen's test, VAS and electrophysiological data after treatment. Improvement in patients treated with tramadol was significantly higher compared to prednisone group in all clinical and electrophysiological parameters. The Boston Questionnaire showed better results in tramadol groups, with a significant improvement in the symptom severity scale (SSS; $p<0.005$) and functional status scale (FSS; $p<0.005$). The results of this clinical trial suggest that treatment of CTS with tramadol along with UT as adjuvant therapy was associated with a significant improvement of clinical and electrophysiological parameters compared to Prednisone.

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Keywords: Carpal tunnel syndrome, prednisone, tramadol, Chinese, pain.

INTRODUCTION

Carpal tunnel syndrome is a one of most frequent neurological disorder which causes several discomfort such as pain, lack of feeling (numbness), and abnormal dermal sensation which results in denervation of muscle (Middleton, 2014; Boonhong, 2019; Mulroy, 2019; Klokkari, 2018; Blanquero, 2019) It is due to the compression of the median nerve in the passage through the carpal tunnel in the wrist. It is diagnosed with clinical criteria and electrophysiological studies, which are objective and quantitative, and have been recognized to be highly sensitive and specific for the assessment of nerve function in CTS patients (Blanquero, 2019; Zwolińska, 2019). There are several non-surgical treatment options available for the patients who experienced mild to moderate signs of carpal tunnel syndrome (CTS), which includes steroid and non-steroid drugs (Klokkari, 2018). Also, the effect of therapeutic exercise has been reported in published articles (Faig-Martí, 2017; Klokkari, 2018; Blanquero, 2019). CTS therapies can be conservative or surgical, but it remains unclear to physicians when it needs treatment, if the severity is low and how to make a decision regarding surgical treatment (Blanquero, 2019; Klokkari, 2018; Zwolińska, 2019). Surgical treatment is indicated in severe cases (Klokkari, 2018). In general, conservative management of CTS includes avoiding all provoking factors, correcting potential medical illnesses that can determine CTS (hypothyroidism or diabetes), use of wrist splints, non-steroidal anti-inflammatory drugs, corticosteroids, and vitamin B12.

In a randomized, double-blind, placebo-controlled clinical trial of patients with mild to moderate CTS, effectiveness of low-dose, short-term oral prednisone in ameliorating the pain and other symptoms of carpal tunnel syndrome (CTS) was reported (Herskovitz, 1995). In this published clinical trial, Prednisone, in doses of 20 mg daily for the first week and 10 mg daily for the second week, resulted in significant improvement in global symptom scores. The effect was rapid, but gradually waned over 8 weeks of observation. This approach may provide a treatment alternative in the short-term, conservative management of CTS. Tramadol is a centrally acting synthetic opioid analgesic that has a dual mechanism of action, binding to mu-opioid receptors and weakly inhibiting the neuronal reuptake of norepinephrine and serotonin (Matzon-Hand, 2017). Tramadol appears to be equally effective in managing postoperative pain following carpal tunnel

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release compared with opioids (Matzon-Hand, 2017). Pro-inflammatory cytokines play an important role in the pathophysiology of neuropathic pain syndromes (Kraychete, 2009). In patients with CTS, plasma levels of TNF-+/- and IL-6 were higher than in healthy volunteers. Plasma levels of TNF-+/- was significantly decreased after treatment with tramadol (100 mg every 12 hours). Since, there is no direct clinical trial evaluating the efficacy of tramadol in CTS patients. Based on the analgesic and anti-inflammatory properties of tramadol, we therefore hypothesized that tramadol would be effective in ameliorating the pain and other symptoms of CTS. Ultrasound therapy (UT) was found effective adjuvant therapy for CTS (Bartkowiak, 2019; Roh, 2019). Effect of UT is mainly because of its thermal and non-thermal properties. Thermal effect of UT is mainly because when sound waves infiltrate the body tissue and creates quivering; this produces heat which helps in pain relief. Numerous clinical studies have shown that UT treatment has some beneficial effect among CTS patients (Bartkowiak, 2019; Roh, 2019). However, several other high quality evidences have shown that there are inadequate studies conducted to support the UT treatment.

Since, there is no clinical trial evaluating the efficacy and safety of tramadol versus prednisone along with UT as adjuvant therapy in Chinese patients with CTS is available. We, therefore designed the present clinical trial to evaluate efficacy and safety of tramadol versus Prednisone along with UT as adjuvant therapy in Chinese patients with CTS diagnosed by ultrasonography.

MATERIALS AND METHODS

Clinical trial design and participants

In this preliminary clinical trial, the patients who had aged more than 18 years but less than 65 years who were diagnosed with moderate severity of CTS based on clinical and electrophysiological parameters were enrolled. Also, the subject who had electrophysiological evidence of CT was eligible in the present clinical trial. Moreover, subject with positive signs and symptoms of a Phalen's (sensation of tingling, numbness, or pain in the fingers) or Tinel's (sensation of tingling or "pins and needles") were also eligible. The subject with age less than 18 years old and suffering from lifestyle related medical disease for example T2DM, kidney failure, rheumatoid arthritis and diabetes mellitus, and hypothyroidism. Also, the female subjects with pregnancy or who underwent any kind of wrist trauma or any kind of surgical procedure in past were also excluded during screening. Written informed consent was taken from each patient and ethics committee approval was obtained from institutional ethics committee of Jining Medical University.

Study treatment and efficacy assessment

The patients were randomly assigned to one of two groups in allocation ratio of 1:1. Test group was given controlled release tramadol (100 mg every 12 hours) and Reference Group received prednisone 20 mg once daily for 2 weeks (14 days). Ultrasound therapy (UT) was given as adjuvant therapy in both the group. Controlled release formulation of tramadol has the potential to provide patients increased control over the management of their pain, fewer interruptions in sleep and improved compliance. In carpal tunnel syndrome, plasma levels of TNF-α is significantly higher than in healthy volunteers. Tramadol (100 mg every 12 hours) was found effective in patients with carpal tunnel syndrome by decreasing plasma levels of TNF-α (Kraychete *et al*., 2009). In order to get desired therapeutic effect, tramadol (100 mg every 12 hours) was considered.

The severity of symptoms and functional impairment of the patients were assessed using a Spanish translation of Levine's questionnaire (Levine, 1993; Rosales, 2002) before and after treatment. This tool has good validity, reliability and responsiveness (Sambandam, 2008) and is recommended as an assessment instrument for research in CTS. The symptom severity scale (SSS) refers to the first 11 questions and the functional status scale (FSS) refers to the last 8 questions of this questionnaire. A clinical examination including Durkan's test (Durkan, 1991) and Phalen's test (Phalen, 1966) was performed at these two time points, and the presence of paresthesia was also recorded. A second ENG was also carried out to evaluate any changes in electrophysiological data.

Data regarding the physical examination and nerve conducting parameters was collected from the subject of both the group. The following physical examination and nerve conducting parameters were evaluated before and after treatment in treatment in both the groups: Filament test, motor latency and sensory latency.

Safety assessment

In this clinical trial, adverse events were assessed, and recorded during the study period. Standard laboratory tests were performed at the baseline visit and during the study period. Treatment-emergent adverse events (TEAEs) is defined as AEs that started or worsened in severity on or after the first dose of treatment and no later than 30 days after the date of last study treatment administration. Study treatment-related SAE collected later than 30 days after the last dose of fruquintinib was considered as TEAE. Treatment-related TEAEs or SAEs were any event that was considered to be causally related to the study treatment according to the physician's subjective judgment. Serious adverse evets will be followed until recovery, death or lost follow-up if a casual relation with the investigational drug cannot be ruled out.

STATISTICAL ANALYSIS

Since, the present clinical trial designed as pilot trial, thus, no formal sample size calculation was performed.

Table 1: Patient characteristics of enrolled patients

Characteristics	Tramadol (N=30)	Prednisone(N=30)
Age		
Mean (SD)	49.3 (2.1)	51.2 (1.1)
Gender, n		
Male	20	19
Female	10	11
Ethnicity, n		
Han (Chinese)	28	27
Not Han (Chinese)	2	3
Marital status, n		
Yes	26	25
No	4	5
Employment status, n		
Employed	22	19
Non-Employed	8	11
Smoking status, n		
Smoker	29	28
Non-Smoker	1	2
Hand Involvement, n		
Unilateral	16	18
Bilateral	14	12
Education level, n		
Graduate or above	30	29
Below Graduate	0	1
Financial status (in US dollar per month), n		
Less than 5,000 USD	3	4
More than 5,000 USD	27	26

Abbreviations: N=number of planned patients; n=number of patients; UT=therapeutic ultrasound therapy; PT=standard paraffin therapy

Table 2: Summary of outcome after treatment in subjects with CTS

Characteristics	Tramadol (N=30)	Prednisone(N=30)	P value
Positive Phalen's test, n	6	13	<0.005*
Positive Durkan's test, n	12	19	<0.005*
Visual Analogue Scale, Mean (SD)	2.16 (1.1)	4.69 (1.2)	<0.005**
Functional status scale, Mean (SD)	1.06 (0.6)	2.89 (0.2)	<0.005**
Symptom severity scale, Mean (SD)	1.31 (0.3)	3.23 (0.4)	<0.005**
Sensitive latency, Mean (SD)	4.59 (0.5)	3.12 (1.2)	<0.005**
Sensitive peak amplitude, Mean (SD)	12.12 (2.3)	8.62 (1.2)	<0.005**
Sensitive speed, Mean (SD)	39.06 (2.1)	41.39 (2.5)	<0.005**
Motor latency, Mean (SD)	5.19 (1.1)	4.35 (1.3)	<0.005**
Motor peak amplitude, Mean (SD)	6.16 (2.4)	7.69 (2.2)	<0.005**

Abbreviations: N=number of planned patients; n=number of patients. *Chi square test; ** t test

However, 60 patients were required to have an 80% chance of detection, as significant at the 5% level, an increase in the primary outcome measure pain score from 2.2 cm in the control group to 3 cm in the experimental group. Thus, a total of 60 patients with confirm diagnosis of CTS were planned to be included in this study. Safety parameters were described in frequency table. Patient reported outcome were analyzed and effectiveness of tramadol versus prednisone was compared statistically using paired and unpaired t test if data were parametric in nature. Non-parametric test was used if data were non-parametric in nature. Categorical data were analyzed using chi-squared. Descriptive statistics was used for describing demography and disease characteristics. Data analysis was performed using graph pad prism software, version 07.

Table 3: Summary of outcome of physical examination and nerve conducting experiment in subjects with CTS

Variables	Tramadol (N=30)	Prednisone (N=30)	P value Between group comparison
Filament test results			
Baseline, Mean (SD)	26 (2.5)	26.7 (3.2)	<0.05**
After treatment, Mean (SD)	20.2 (1.1)	24.5 (1.6)	
P value (Within group comparison)	<0.05*	<0.05*	
Motor latency			
Baseline, Mean (SD)	6.5 (2.5)	6.6 (1.5)	<0.05**
After treatment, Mean (SD)	3.1 (1.9)	5.5 (1.2)	
P value (Within group comparison)	<0.05*	<0.05*	
Sensory latency			
Baseline, Mean (SD)	5.8 (2.5)	5.6 (1.5)	<0.05**
After treatment, Mean (SD)	2.6 (1.3)	3.7 (1.2)	
P value (Within group comparison)	<0.05*	<0.05*	

Abbreviations: N=number of planned patients *Paired t test; ** unpaired t test

RESULTS

Patient characteristics

The majority of patients in both groups had involvement of bilateral hands. Majority of enrolled subject were men and of Han (Chinese) ethnicity. Most of subject in both the groups were married. Majority of subjects had graduate or post-graduate degree, with majority of subjects having monthly income of more than 5000 USD. In general, both groups were well balanced in terms of baseline demography and disease characteristics. The patient demography and clinical characteristics of all enrolled patients are shown in Table 1.

Efficacy

CTS were evaluated before and after treatment through clinical findings, Boston Carpal Tunnel Questionnaire, visual analog scale (VAS) and electrophysiological data. The results were evaluated with Student's *t* test and Chi-square. A statistically significant difference was observed between both the treatment group regarding Durkan's test, Phalen's test, VAS and electrophysiological data after treatment. Improvement in patients treated with tramadol was significantly higher compared to prednisone group in all clinical and electrophysiological parameters. The Boston Questionnaire showed better results in tramadol groups, with a significant improvement in the symptom severity scale (SSS; $p < 0.005$) and functional status scale (FSS; $p < 0.005$). The results of this clinical trial suggest that treatment of CTS with Tramadol is associated with an improvement of clinical and electrophysiological parameters. The outcome of CTS based questionnaire is summarized in Table 2.

In both the treatment group, statistical significant difference in filament test was observed. Similar trend of statistical significant difference was observed for motor latency and sensory latency for within group comparison. On comparing Tramadol vs Prednisone, we observed that there was statistical significant difference in all the physical examination and nerve conducting parameters such as filament test, motor latency and sensory latency. The outcome of physical examination and nerve conducting experiment in subjects with CTS is summarized in Table 3.

Both the study treatment was well tolerated. None of study treatment caused any kind of serious adverse events.

DISCUSSION

Since there is no clinical trial evaluating the efficacy and safety of tramadol versus prednisone in patients with moderate severity of CTS patients is available. Thus, the present clinical trial is the first clinical trial designed to evaluate efficacy and safety of tramadol versus prednisone in Chinese patients with CTS diagnosed by ultrasonography. In the present clinical trial, it has been observed that the reduction in function score after tramadol treatment was significantly greater as compared to prednisone group. On comparing symptom and pain severity score after treatments, reduction in pain severity after tramadol treatment was significantly greater as compared to prednisone. Similar reduction in symptom severity score was found between both the treatments. Our clinical trial results are consistent with Herskovitz *et al* (Herskovitz, 1995), which was conducted in CTS patients, and shown that tramadol was found more effective in improving sign and symptoms when compared with prednisone treatment among patients with moderate CTS.

The favorable effect of tramadol compared to prednisone possibly due to potential anti-inflammatory properties of tramadol, which has been shown in earlier study. Plasma

levels of TNF-+/- was significantly decreased after treatment with tramadol (Kraychete, 2009). Earlier, tramadol has been used in combination with several modalities of treatment in management of musculoskeletal disorders. Numerous clinical trials showed that tramadol treatment has some beneficial effect among CTS patients. However, none was conducted in China; the present clinical trial is the first clinical trial in Chinese patients with CTS. However, several other high quality evidences shows that there is inadequate studies conducted to support the tramadol treatment recommendation in patients with CTS, when compared to other modalities of treatment for CTS. The present clinical trial results suggest use of tramadol in Chinese patients with moderate severity of CTS. However, there is need of additional research to be conducted to compare the efficacy of tramadol than other available gold standard therapy. Also, long terms safety related information should be generate after the use of tramadol in Chinese patients with CTS. The greater effectiveness of tramadol compared to prednisone is possibly due to its analgesic and anti-inflammatory property. It acts by reducing pain and inflammation. In contrast, prednisone has only anti-inflammatory effect for reducing sign and symptoms in patients with CTS.

Overall, both the clinical trial treatment was well tolerated. None of study treatment caused any kind of serious adverse events. Overall, tramadol and prednisone appeared efficacious and have a manageable safety profile and well tolerated in the treatment population. Since this clinical trial was designed as pilot clinical trial with small sample size, thus a large clinical study with appropriate sample size warranted. Since the study was conducted at single study center, thus, the finding of this trial could not generalize to all Chinese patients with CTS. We, therefore encourage conducting multi-centric trial across China in order to generalize the finding in Chinese population. The effect of therapeutic exercise in comparison with tramadol or prednisone has not been evaluated in the present study as it was not the pre-defined objective of this study, thus, it is not known whether therapeutic exercise would be better than tramadol/prednisone or not. A separate study evaluating the effect of therapeutic exercise versus tramadol/prednisone in patients with CTS is warranted, to confirm if exercise is an better alternative than drug or not.

CONCLUSION

The results of this clinical trial suggest that treatment of CTS with tramadol is associated with an improvement of clinical and electrophysiological parameters. Tramadol along with UT as adjuvant therapy was found be more effective in improving sign and symptoms associated with CTS as compared to prednisone with UT therapy. Safety profile of tramadol and prednisone was generally similar; with no safety concern has been reported. Since the present clinical trial collected data of only one site, thus, we encourage conducting multi-centric trial across China in order to generalize the finding in Chinese population.

REFERENCE

Bartkowiak Z, Eliks M, Zgorzalewicz-Stachowiak M, Romanowski L (2019). The effects of nerve and tendon gliding exercises combined with low-level laser or ultrasound therapy in carpal tunnel syndrome. *Indian J. Orthop.,* **53**(2): 347-352.

Blanquero J, Cortes-Vega MD, García-Frasquet MA, Sanchez-Laulhe PR, Nieto Diaz de Los Bernardos MI and Suero-Pineda A (2019). Exercises using a touchscreen tablet application improved functional ability more than an exercise program prescribed on paper in people after surgical carpal tunnel release: a randomised trial. *J. Physiother.,* **65**(2): 81-87.

Boonhong J and Thienkul W (2019). Effectiveness of phonophoresis treatment in carpal tunnel syndrome: A randomized double-blind, controlled trial. PM R. doi: 10.1002/pmrj.12171 (Epub ahead of print).

Durkan JA (1991). A new diagnostic test for carpal tunnel syndrome. *J. Bone Joint Surg. Am.,* **73**(4): 535-538.

Herskovitz S, Berger AR and Lipton RB (1995). Low-dose, short-term oral prednisone in the treatment of carpal tunnel syndrome. *Neurology,* **45**(10): 1923-1925.

Klokkari D and Mamais (2018). Effectiveness of surgical versus conservative treatment for carpal tunnel syndrome: A systematic review, meta-analysis and qualitative analysis. *Hong Kong Physiother. J.,* **38**(2): 91-114.

Kraychete DC, Sakata RK, Issy AM, Bacellar O, Jesus RS, Carvalho EM (2009). Proinflammatory cytokines in patients with neuropathic pain treated with Tramadol. *Rev. Bras. Anestesiol.,* **59**(3): 297-303.

Levine DW, Simmons BP, Koris MJ, Daltroy LH, Hohl GG, Fossel AH and Katz JN (1993). A self-administered questionnaire for the assessment of severity of symptoms and functional status in carpal tunnel syndrome. *J. Bone Joint Surg Am.,* **75**(11): 1585-1592.

Middleton SD and Anakwe RE (2014). Carpal tunnel syndrome. *BMJ.,* **349**: g6437

Miller A, Kim N, Zmistowski B, Ilyas AM and Matzon-Hand JL (2017). Postoperative pain management following carpal tunnel release: *A Prospective Cohort Evaluation.,* **12**(6): 541-545.

Mulroy E and Pelosi L (2019). Carpal tunnel syndrome in advanced age: A sonographic and electrodiagnostic study. Muscle Nerve.

Phalen GS. The carpal-tunnel syndrome. Seventeen years' experience in diagnosis and treatment of six hundred fifty-four hands. *J. Bone Joint Surg Am.,* **48**(2): 211-228.

Roh YH, Hwangbo K, Gong HS and Baek GH (2019). Comparison of ultrasound-guided versus landmark-based corticosteroid injection for carpal tunnel syndrome: A prospective randomized trial. *J. Hand Surg. Am.,* **44**(4): 304-310.

Rosales RS, Delgado EB, Díez de la Lastra-Bosch.Evaluation of the Spanish version of the DASH and carpal tunnel syndrome health-related quality-of-life instruments: Cross-cultural adaptation process and reliability. *J. Hand Surg. Am.,* **27**(2): 334-343.

Sambandam SN, Priyanka P, Gul A and Ilango B (2007). Critical analysis of outcome measures used in the assessment of carpal tunnel syndrome. *Int. Orthop.,* **32**(4): 497-504.

Zwolinska J and Kwolek A (2019). Factors determining the effectiveness of conservative treatment in patients with carpal tunnel syndrome. *Int. J. Occup. Med. Environ Health,* **32**(2): 197-215.