

Add on effect of benfotiamine over pregabalin among patients with carpal tunnel syndrome in tertiary care specialty clinic – a randomized controlled trial

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Abstract

Introduction: Carpal Tunnel syndrome is a common entrapment neuropathy involving the median nerve across the transverse carpal ligament. The diagnosis is clinical and confirmed by neurophysiological evaluation. Management varies from conservative as well as surgical. Since most of the patients prefer medical management we decided to compare the efficacy of benfotiamine, a neuro protective agent and pregabalin, a third generation anticonvulsant drug used for symptom relief.

Aim: The study was conducted to compare the efficacy of pregabalin in combination with benfotiamine, and pregabalin as monotherapy in the management of carpal tunnel syndrome (CTS).

Materials and Method: Fifty eight patients with CTS, who were diagnosed clinically and confirmed by nerve conduction study, were included through convenience sampling method. They were allocated to two groups: (i) treatment with pregabalin(n=30) and (ii) treatment with pregabalin in combination with benfotiamine (n=28) by simple randomization method. Symptom severity and functional status of these enrolled patients were compared before the intervention at recruitment and 12 weeks after the intervention using Boston Carpal Tunnel Syndrome Questionnaire (BCTQ).

Result: The mean difference in symptom severity scale (SSS) and functional status scale(FSS) scores between two treatment groups were analyzed by intention to treat method. Statistically significant differences were observed after 12 weeks of treatment in the FSS and SSS in both the groups, compared to the baseline. Patients who received combination treatment had higher scores after 12 weeks in the FSS as well as the SSS compared to pregabalin group [12 weeks score in SSS: pregabalin: 0.33±0.29, pregabalin+benfotiamine group: 2.16±0.58, p=0.0001, mean reduction in FSS: pregabalin: 0.14± 0.25, pregabalin+benfotiamine group: 1.81±0.24, p=0.0001].

Conclusion: Combining benfotiamine with pregabalin is found to be effective in the conservative management of Carpal Tunnel Syndrome due to the different modalities of action. The long term efficacy of these drugs needs to be studied.

Keywords: Carpal Tunnel Syndrome, Pregabalin, Benfotiamine, Boston Carpal Tunnel Syndrome Questionnaire (BCTQ).

Introduction

Carpal tunnel syndrome (CTS) is an entrapment neuropathy of the median nerve⁽¹⁾ at the wrist with the clinical features of pain, numbness, tingling sensation along the median side of the palm and weakness of thumb abduction along with a positive Tinel's sign. The symptoms are at their worst during sleep at night and early morning which often disturbs the patient. The symptoms are also accelerated by driving a two wheeler, manual work at workplace and performing household work like washing dishes and rinsing the linen. Certain patient population such as with stroke and Parkinson's disease has CTS of the normal hand. Other treatment options carried out by various specialists for CTS include techniques like laser therapy, wrist splinting, ultrasound therapy, botulinum toxin and patient oriented programmes like work modification with restriction of activity.⁽²⁾

Various treatment options, both conservative and surgical, have been suggested for CTS. Conservative treatments available are (a) symptomatic e.g. pharmacological agents that are effective in patients with neuropathic pain which include anticonvulsants like pregabalin and gabapentin as well as tricyclic antidepressants; and (b) pathogenetically oriented

treatments like alpha lipoic acid, benfotiamine, aldose reductase inhibitor like epalrestat orally and linseed oil as topical application. Surgical treatment is considered in patients who do not respond to conservative measures and also show evidence of progressive nerve injury.⁽³⁾

The symptom severity reflects the degree of interference with the daily routines of the patient. The patient's pain leads to excessive health resource utilization. The intensity of symptoms like pain, numbness interferes with the daily activities.^(4,5) Conservative treatment is the initial treatment prescribed by most neurologists. However, current conservative treatment options cannot reduce symptom severity when they are administered separately. Therefore, new conservative combination treatments are the need of the hour.⁽⁶⁾ This concept provoked us to plan and organize the study.

Pregabalin is structurally similar to gamma-amino butyric acid (GABA) and has been used in chronic neurogenic pain such as post-herpetic neuralgia,^(7,8) diabetic peripheral neuropathy and fibromyalgia.⁽⁹⁾ The mechanism of action of pregabalin, which is an alpha 2 delta Ca channel ligand is that it decreases the release of many neurotransmitters such as substance P,

norepinephrine, and glutamate.⁽¹⁰⁾ Benfotiamine (S-benzoylthiamine-O-monophosphate), which is a derivative of synthetic thiamine is considered in our study since it is well tolerated without allergic reactions unlike other vitamin preparations even at high doses, with a higher bioavailability compared to thiamine,⁽⁹⁾ with added properties like anti-inflammatory, antioxidant and neural protective activities to prevent the progression of neuropathy.⁽¹¹⁻¹³⁾

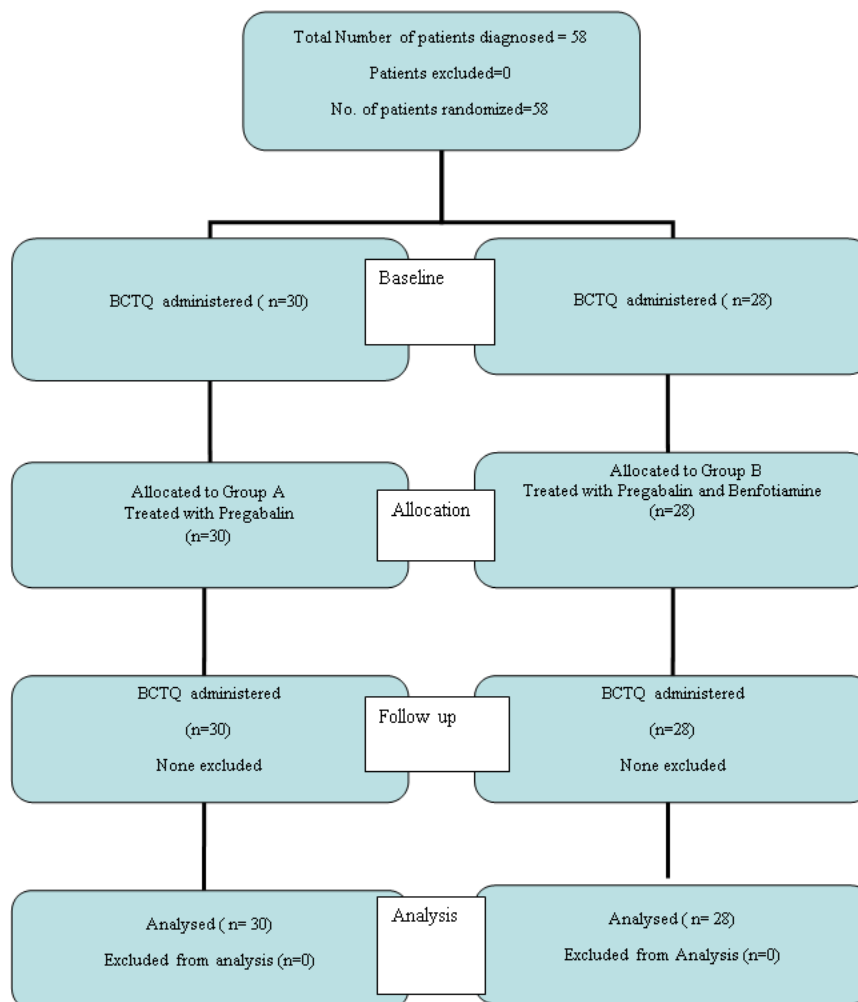
Since neuropathy is common in diabetics, and based on efficacy and safety data, drugs like benfotiamine and alpha lipoic acid were considered first choices among pathogenetically oriented treatments of diabetic neuropathy. The mechanism of action of benfotiamine which is a lipophilic thiamine diphosphate prodrug, is that it exerts its efficacy in neuropathy through its capability as an anti-oxidant. The DNA protective effects of benfotiamine have been found to be effective in diabetic neuropathy. Similar efficacy was observed in neurodegenerative disorders like Alzheimer's disease.⁽¹⁴⁾ Since diabetic neuropathy responded well to benfotiamine, it was decided to consider benfotiamine as a treatment modality for carpal tunnel syndrome.

Biochemical property of benfotiamine in relation to neuro transmission is theoretically proven. However, its effect among carpal tunnel syndrome which is an entrapment neuropathy is not explored. Therefore the present study was performed to identify whether benfotiamine has an added efficacy when combined with pregabalin in the conservative management of carpal tunnel syndrome.

Materials and Method

The study was conducted in the outpatient clinic of the neurology department in a tertiary care teaching hospital. These patients were managed either conservatively with medications or referred for surgical exploration based on the standard treatment

guidelines.⁽¹⁵⁾ As a routine, all these patients with carpal tunnel syndrome were advised to come for the follow up visit on monthly basis. 58 patients with carpal tunnel syndrome, diagnosed both clinically and confirmed with nerve conduction study by the neurologist (principal investigator) were recruited for the study over a period spanning eight months. Before recruitment, patients with diabetes mellitus, hypothyroidism, arthritis, obvious structural defects (patients who need surgical exploration) and vasculitic painful polyneuropathy were excluded from the study. After obtaining informed consent and institutional ethical committee clearance, patients were randomized into pregabalin and combination group. Simple randomization was done and the randomization sequence was prepared by the person who is not involved in the study. According to the randomization sequence consecutively the patients received prescriptions. Patients randomized under group A (n=30) received pregabalin at a dose of 75mg at night and those who were randomized under group B (n=28) received pregabalin 75mg at night along with benfotiamine at a dose of 100mg twice a day. As patients were advised to receive the medications from the routine pharmacy where usually they collect medications, allocation concealment was not possible. Since the patients knew whether they are consuming one tablet or two tablets patients were not blinded. For the same reason, the treating physician also was not blinded. However, the person who is assessing the treatment outcome and the person analyzing the data were blinded. None of the patients recruited were lost to follow up and all of them were available for final outcome assessment at the end of 12 weeks. There has been no deviation from the protocol. They were seen once in every four weeks. Before initiation and after twelve weeks of treatment, all of the patient's were evaluated with Boston Carpal Tunnel Syndrome Questionnaire (BCTQ).⁽¹⁶⁾



Evaluations: All of the patient's symptom severity and functional status were evaluated at baseline and after the 12 weeks treatment by a blinded investigator with Boston Carpel Tunnel Syndrome Questionnaire. The Boston Questionnaire evaluates the severity, frequency, time and kind of symptoms and the functional status, how the syndrome affects the quality of daily life.

There are 11 questions in symptom severity scale addressing pain intensity during the day and night, time of pain during the day, dormancy, weakness, tingling sensation at night, frequency of the nocturnal tingling sensation, and skill. It is a five point scale where 1 means no symptoms, 2- mild symptoms, 3- moderate symptoms, 4- intense symptoms, and 5-severe symptoms.

FSS is also a five point scale which focuses on evaluating difficulty in 8 areas of functional activities like writing, buttoning clothes, holding a book while reading, holding a telephone, housekeeping, opening a jar, carrying groceries, bathing and dressing. Each activity corresponds to the increasing difficulty, where 1 denotes no difficulty, 2 little difficulty, 3 moderate

difficulty, 4 intense difficulty, and 5 cannot perform the activity at all due to hand and wrist symptoms.

Patients are allowed to choose only one alternative in each question based on their symptom severity and degree of functional difficulty. The answers are rated by the patients based on their symptoms within 24 hours, for the last two weeks.

Statistical Analysis: Socio demographic characteristics of the patients are summarized in the form of mean \pm SD and proportions. Symptom severity scale and Functional status scale at baseline and at 12 weeks based on pregabalin and combination treatments are summarized as mean \pm SD and median with Inter Quartile Range (IQR). Based on the intention to treat analysis, the median score in SSS and FSS were compared in both the groups. These FSS and SSS scores between two groups at baseline and at 12 weeks were compared using non parametric Mann Whitney U test. Similarly, The 12 weeks change in FSS and SSS was analyzed by Wilcoxon signed rank test.

Result

Patients were randomly assigned to two groups (pregabalin, pregabalin in combination with

benfotiamine). Out of 58 patients with carpal tunnel syndrome, 25(43%) were beedi rollers and the rest of the patients were from diverse occupational background (Table 1, Fig. 1). Though number of males and females participated in the study are same as 29 the distribution within the assigned group are not similar. The baseline mean score for FSS and SSS were similar in both the groups ($p=0.1$) (Table 2). At the end of 12 weeks patients who were on combination treatment with benfotiamine had significantly lower FSS and SSS

compared to pregabalin group ($p=0.0001$) (Table 3). Also, patients on combination treatment had significantly high reduction in FSS and SSS from the baseline ($p=0.0001$) (Table 4). All the patients had sedation during the first week of starting treatment with pregabalin. This was considered to be beneficial to the patients who had sleep disturbance as the main complaint due to the pain, tingling and numbness of the hands. None of the patients complained of adverse reactions to benfotiamine.

Table 1: Patient demographics and clinical characteristics at baseline

Occupation		Group A (N=30)	Group B (N=28)
		N (%)	N (%)
Beedi rollers		8 (26.7)	17 (60.7)
Clerk		2 (6.6)	1 (3.6)
Manual laborer		5 (16.7)	4 (14.3)
Driver		-	1 (3.6)
Farmer		4 (13.3)	2 (7.1)
Housewife		9 (30.0)	-
Engineer		2 (6.6)	3 (10.8)
Gender	Male	7 (23.3)	22 (78.6)
	Female	23 (76.7)	6 (21.4)

Table 2: Comparison of scores of symptom severity and functional status of Group A and Group B at baseline

Index	Summary	Group A (n=30)	Group B (n=28)	P value*
Symptom severity score	Mean (SD)	3.1 (0.4)	3.3 (0.5)	-
	Median (IQR)	3 (2.6-3.5)	3.6 (2.6-3.6)	0.1
Functional status score	Mean (SD)	2.6 (0.6)	2.8 (0.2)	-
	Median (IQR)	2.9 (2.5-3)	3 (2.5-3)	0.1

*P value by Mann whitney U test IQR – Inter Quartile range

Table 3: Comparison of scores of symptom severity and functional status of Group A and Group B after 3 months of treatment

Index	Summary	Group A (n=30)	Group B (n=28)	P value
Symptom severity score	Mean (SD)	2.7 (0.2)	1.1 (0.2)	-
	Median (IQR)	2.7 (2.6-3)	1 (1-1.1)	<0.00001
Functional status score	Mean (SD)	2.5 (0.5)	1.0 (0.1)	-
	Median (IQR)	2.5 (2.5-3)	1 (1-1)	<0.00001

*P value by Mann whitney U test IQR – Inter Quartile range

Table 4: Difference in symptom severity and functional status of Group A and Group B after 3 months of treatment from the baseline

Index	Summary	Group A (n=30)	Group B (n=28)	P value
Difference in Symptom severity score	Mean (SD)	0.33 (0.29)	2.17 (0.58)	-
	Median (IQR)	0.36 (0.0-0.64)	2.6 (1.55-2.64)	<0.00001
Difference Functional status score	Mean (SD)	0.14 (0.25)	1.8 (0.24)	-
	Median (IQR)	0 (0-0.16)	2 (1.5-2)	<0.00001

*P value by Wilcoxon signed Rank test IQR – Inter Quartile range

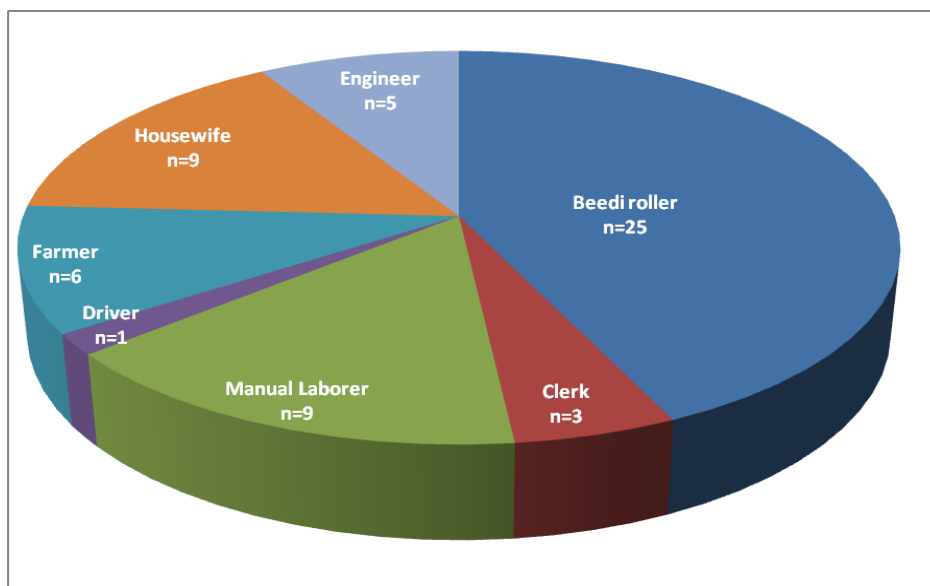


Fig. 1: Frequency distribution of the study population

Discussion

Carpal tunnel syndrome (CTS) is a painful, debilitating condition which has many therapeutic options, but no single treatment modality has been definitely established as superior to any other. CTS is estimated to occur in about 1–4% of the general population and more common in females. The area of dysesthesia is not necessarily restricted in area of distal median nerve and can radiate proximally upto the shoulder. The results from conservative treatments vary, and there is no widespread agreement on the best method of treatment.^(17,18)

Bilateral CTS is common. Subjective symptoms of CTS do not correlate well with NCS data, and certain percentage of patients who present with significant symptoms present to the neurologist with normal electrophysiology.⁽¹⁹⁾ Patients improved with pregabalin therapy at a dose of 75 mg at night without adverse reactions like somnolence, dizziness, pedal edema and weight gain reported in other study populations.⁽²⁰⁻²²⁾ Benfotiamine was added to preserve the nerve function and avoid ongoing nerve damage. None of the patient had nausea, dizziness, stomach ache and weight gain following benfotiamine use.⁽²³⁾ Benfotiamine when combined with pregabalin effectively relieved the intensity of the symptoms and improved the quality of life of the patients by improving their functional status. The combination treatment significantly resulted in a high level of treatment satisfaction.

In our study population beedi rollers were found to be more vulnerable to carpal tunnel syndrome but the exact causation needs detailed basic research. Beedi rollers form a major group of subsets who are reported to have health hazards involving multiple organ systems including malignancy²⁴ however, none of the previous studies have highlighted neuropathies including carpal tunnel syndrome in these patients. To

the best of our knowledge, the present study is the first research to evaluate the effects of combination of pregabalin and benfotiamine on CTS.

Limitations of the study

This study has the following limitations: 1) Since, we did not find any similar randomized trial done earlier which compares the efficacy of pregabalin and benfotiamine compared to pregabalin, sample size was not calculated a priori. 2) Post hoc calculation of power was found to be 90% for all the measures including the change in mean score between baseline to 12 weeks.

Conclusion

Combining benfotiamine with pregabalin has been found to be effective in the conservative management of carpal tunnel syndrome which needs to be evaluated in larger populations from varying backgrounds.

Recommendations of the study

The results of the study indicate the need to combine pathogenetically oriented treatment modalities with symptomatic treatment in the conservative management of carpal tunnel syndrome. This could be the initial treatment of carpal tunnel syndrome before contemplating surgical management.

Conflicts of interest

There are no conflicts of interest.

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Nil

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