

# Oral Benfotiamine 300 mg Versus Intramuscular Thiamine in Diabetic Patients with Peripheral Neuropathy

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## Abstract

**Aim:** This is a prospective, pilot, open-label, interventional, comparative, randomized study, enrolled 60 patients with type 2 diabetes mellitus (T2DM) to assess the effect of different doses of oral vitamin B containing Benfotiamine 300 mg versus intramuscular B vitamins containing water-soluble Thiamine HCl.

## Methods

Patients  $\geq$  18 years with T2DM with Peripheral Neuropathy, divided into 3 groups; A & B (Benfotiamine 300 mg) and group C (Thiamine HCl), which were sub-divided to include patients with HbA1c less or more than 8%. Patients were evaluated at baseline, after 2.5 hours, six days, and two weeks.

## Results

Blood vitamin B1 increased from baseline to after 2.5 hours (T2) by 57%, 79% and 33% in group A, B and C respectively, with statistically significant difference in each group (p value < 0.001). Vitamin B1 continued to increase after six days (T6) in patients of groups A & B by 98% and 165% respectively, while dropped in patients of group C from 33% at T2 to 6% at T6, with p-value  $\leq$  0.001 between the three groups. Diabetic Neuropathic Symptom Score (DNS) decreased in mean value in all groups after 14 days of treatment by 64.4%, 53.7% and 48.6% in group A, B and C respectively, indicating improvement of peripheral neuropathy.

**Safety:** There was no AE or SAE reported during the study.

**Conclusion:** Oral Benfotiamine 300 mg is safe and more effective than intramuscular Thiamine HCl, in increasing vitamin B1 blood level in patients with diabetic peripheral neuropathy, which in turn relieves peripheral neuropathy.

Clinical Trial Registration Number: NA

**Keywords:** Benfotiamine, Bioavailability, Thiamine, Diabetic Peripheral Neuropathy

**Abbreviations:** Adverse Event (AE), Advanced Glycation End products (AGE), Analysis of Variance (ANOVA), Alanine Transaminase (ALT), Body Mass Index (BMI), Case Report Form (CRF), Diabetic Neuropathic Symptom score (DNSS), Diacylglycerol (DAG), Dipeptidyl Peptidase 4 Inhibitor (DPP-4 I), Good Clinical Practice (GCP), Informed Consent Form (ICF), Intent to Treat (ITT), Institutional Review Board (IRB), Ministry of Health (MOH), National Institute of Diabetes and endocrinology (NIDE), Nuclear Factor kappaB (NF- $\kappa$ B), Per Protocol (PP), Protein Kinase C (PKC), Research and health Development (RHD), Serious Adverse Event (SAE), Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), Transient Ischemic Stroke (TIA)

## Introduction

Diabetes could be considered a state of Thiamine deficiency. Plasma levels of Thiamine in patients with diabetes were reported to be 76% less compared to the healthy population [1], which leads to a wide range of clinical signs and symptoms affecting mainly the nervous and vascular systems [2]. Diabetes with peripheral neuropathy is a multifactorial and complex entity in which various factors, besides hyperglycemia, play an essential role [3]. These factors are the main drivers for diabetes with peripheral neuropathy in T2DM, including but not limited

to oxidative stress, vascular, and metabolic factors [4]. National data in Egypt confirmed that 29.3% of Egyptian patients with diabetes, suffer from peripheral neuropathy [5]. Several studies revealed that diabetic peripheral neuropathy is more common in T2DM than T1DM and is more prevalent in females than males [5].

The primary biochemical pathways that resulted in the pathogenesis of hyperglycemia-induced vascular damage are the hexosamine pathway of glucose metabolism, the formation of advanced glycation end products (AGEs), and the diacylglycerol

(DAG)–protein kinase C (PKC) pathway with the common feature of overproduction of superoxide by the mitochondrial electron transport chain. All are activated by the increased availability of the glycolytic metabolites, glyceraldehyde-3-phosphate and fructose 6-phosphate. [1], [6]

Benfotiamine is a lipid-soluble form of Thiamine that can block the three pathways of hyperglycemic damage, as well as hyperglycemia-associated nuclear factor-kappaB (NF-κB) activation by increasing transketolase activity, the rate-limiting enzyme of the non-oxidative branch of the pentose phosphate pathway, which converts glyceraldehyde-3-phosphate and fructose-6-phosphate into pentose-5-phosphates and other sugars [1], [6]. Benfotiamine completely prevents macro and microvascular endothelial dysfunction and oxidative stress in patients with T2DM, by reducing AGEs and dicarbonyl (methylglyoxal) formation [7]. Additionally, Benfotiamine prevents the polyol pathway by decreasing aldose reductase activity, sorbitol, and intracellular glucose concentrations, protecting endothelial cells from glucose-induced damage [1], [6].

The pharmacokinetics and bioavailability study of Benfotiamine compared to thiamine hydrochloride showed higher bioavailability of Thiamine from an oral dose of Benfotiamine compared to an oral dose of thiamine hydrochloride. [8]

The management of diabetic peripheral neuropathy depends mainly on glycemic control and specific medications such as anticonvulsants, Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), tricyclic antidepressants, and B vitamins used empirically in patients with diabetes suffering from peripheral neuropathy.

As injections are perceived more efficacious and have a rapid onset of action, a pilot comparative study took place to assess the efficacy of oral vitamin B with Benfotiamine (lipid-soluble thiamine) versus intramuscular vitamin B with the water-soluble Thiamine HCl in increasing blood levels of Vitamin B1.

## Materials and Methods

This pilot is a single-center, interventional, comparative, three arms, randomized, open-label, prospective phase IV study. It was conducted in the National Institute of Diabetes and Endocrinology (NIDE) outpatient clinics in Egypt (Teaching Hospital). It compares the efficacy and safety of oral vitamin B with the lipid-soluble vitamin B1 - Benfotiamine 300 mg, versus intramuscular B vitamins with the water-soluble thiamine HCl 150 mg “as commercially available in Egypt” in increasing blood levels of vitamin B1 in patients clinically diagnosed with diabetes and suffering from peripheral neuropathy, after three weeks of washout of any previous vitamin B1 intake in any form.

The study enrolled 68 Egyptian patients with T2DM with peripheral neuropathy, distributed into three groups. Group A included 25 patients receiving one tablet daily of Milga Advance® with the lipid-soluble Benfotiamine 300 mg. Group B included 22 patients receiving two tablets daily of Milga Advance® with

the lipid-soluble Benfotiamine 300 mg. In comparison, Group C included 21 patients receiving one intramuscular ampoule, twice weekly, of multivitamin B with B1 in the form of water-soluble thiamine HCl 150 mg, as stated in its leaflet and as usually prescribed by Egyptian diabetologists. Each group was subdivided into 2 sub-groups; 50% with HbA1c up to 8 % and the second sub-group with HbA1c between 8.1 % & 10 %. Sixty patients completed the study.

Assessments were carried out along baseline (blood level of vitamin B1) at baseline, after 2.5 hours and (Diabetic Neuropathic Symptom Score (DNS), six days from baseline (blood level of vitamin B1), and two weeks from baseline (DNS).

### Inclusion criteria

Egyptian male and female patients, aged ≥ 18 years with T2DM, treated for diabetic peripheral neuropathy, willing to sign an ICF, and ready to comply with the protocol for the duration of the study

### Exclusion Criteria

Patients with markedly uncontrolled hyperglycemia (HbA1c more than 10 %), with any uncontrolled endocrine disorder rather than T2DM, who are taking Vitamin B1 in any form in the past three weeks, with chronic liver disease defined by serum levels of Alanine aminotransferase, or alkaline phosphatase above three times upper limit of the normal value, with chronic renal disease (S. creatinine above 2 mg/dl), on renal Dialysis, or with a Malignancy history during the past three years were excluded. In addition, patients with stroke, including Transient Ischemic Attack (TIA), or whom with diabetes and have foot infection, amputation (non-traumatic, even minor), and gangrene, with malabsorption presented by but not limited to symptoms of anemia, weight loss, muscle wasting, receiving drugs that interfere with the metabolism and decreasing the effectiveness of oral Vitamin B1, such as antacids, oral contraceptives, phenytoin, nitro antibacterial, 5-fluorouracil, pregnant and breastfeeding women were also excluded from the study.

### Evaluation Parameters (Diabetic Neuropathy Symptom Score)

Four questions were asked to each patient about the unsteadiness in walking, numbness, burning, aching pain, tenderness in legs or feet, and prickling sensations.

Each question gets 1 point to calculate the total symptom score. The total maximum abnormal symptom score is 4.

### Clinical Grouping

One hundred three patients were screened, out of which only 68 were enrolled in the study. Patients were chosen through a computer-assisted randomization listing according to the level of HbA1c (8 %) or below and more than 8 % to form the three study groups with a balanced ratio of 1:1:1. (Figure 1);

Eight patients were dropped out due to loss of follow up, while 60 patients completed the study without any non-compliance

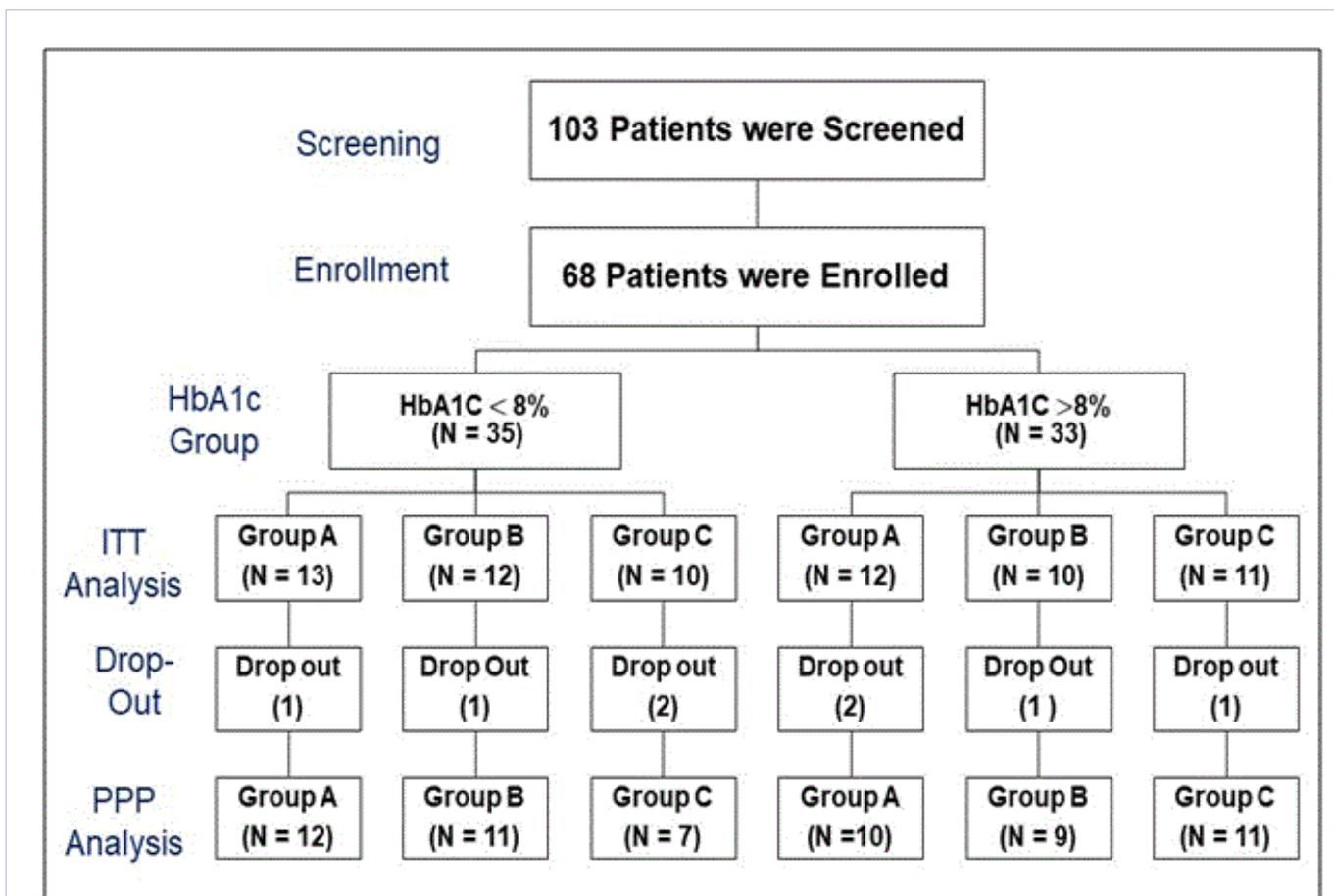


Figure 1 : Patients' disposition during the study

Group A: Received one oral tablet daily of Vitamin B with Vitamin B1 as Benfotiamine

Group B: Received twice-daily oral vitamin B with Vitamin B1 as Benfotiamine

Group C: Received an intramuscular injection twice weekly of Vitamin B with Vitamin B1 as Thiamine

### Statistical Analysis

The medium effect size was used in this study for 20 patients in each group (20 Group A, 20 Group B, and 20 Group C). The total sample was 60 patients, according to Whitehead AL et al. to estimate a sample size for a pilot study.

All enrolled patients were included in the safety analyses, intent to treat (ITT). Patients who completed the study were included in efficacy analysis, as per protocol (PP), and all tests were performed on a 5% level of significance.

Normality was done by Kolmogorov-Smirnov test, reliability by Cronbach's alpha test, and validity test. Correlations were used between values before analyzing the data to choose the appropriate statistics and significance tests.

Statistics used in this study are the Chi<sup>2</sup> test for unpaired categorical variables, paired t-test for estimating the change in numerical variables throughout the study visits, Wilcoxon Signed Ranks test for non-parametric variables, one-way Analysis of Variance (ANOVA) test for estimating the comparison between the subgroups for the numerical variables and using Kruskal Wallis

test for non-parametric variables. The unpaired t-test estimating the change in numerical variables between subgroups using Mann-Whitney test for non-parametric variables and a P-value less than 0.05 was considered to be statistically significant.

### Results

#### Demographic Data at Baseline Visit

The number of females was more than the number of males in all study groups, especially in Group C, with a statistically significant difference between the three treatment groups with HbA1c < 8 % (p-value = 0.039), as presented in [Table 1]

The mean age of patients in all groups ranged between 47.09 to 55.53 years. There was no statistically significant difference in mean age between the 3 treatment groups with HbA1c < 8 (p-value = 0.309) and HbA1c > 8 % (p-value = 0.369), as presented in [Table 1]

Table 1: Patients' characteristics at baseline visit between the three treatment groups						
Patients' Characteristics	HbA1c < 8 %			HbA1c > 8 %		
	Group A 13	Group B 12	Group C 10	Group A 12	Group B 10	Group C 11
Male, N (%)	6 (46.2%)	5 (41.7%)	0 (0.0%)	4 (33.3%)	5 (50.0%)	1 (9.1%)
Female, N (%)	7 (53.8%)	7 (58.3%)	10 (100%)	8 (66.7%)	5 (50.0%)	10 (90.9%)
<i>p-value</i> *	<b>0.039</b>			<b>0.12</b>		
Mean age (SD) years	53.1 (10.55)	53.36 (12.35)	47.09 (7.59)	55.53 (9.83)	49.7 (7.95)	49.98 (14.01)
<i>p-value</i> **	<b>0.309</b>			<b>0.369</b>		
Mean pulse/Min (SD)	73.85 (5.21)	76.00 (5.41)	73.60 (6.64)	72.67 (5.30)	74.70 (4.81)	73.82 (5.19)
<i>p-value</i> **	<b>0.543</b>			<b>0.650</b>		
Mean temperature (°C) (SD)	37.09 (0.10)	37.13 (0.11)	37.13 (0.11)	37.05 (0.07)	37.15 (0.10)	37.09 (0.07)
<i>p-value</i> **	<b>0.550</b>			<b>0.020</b>		
Mean weight (Kg) (SD)	77.85 (14.68)	93.00 (13.74)	95.00 (23.73)	88.67 (15.44)	85.00 (14.24)	94.27 (17.05)
<i>p-value</i>	<b>0.042</b>			<b>0.420</b>		
Mean height (cm) (SD)	162.54 (8.02)	164.83 (9.07)	159.80 (4.83)	160.92 (7.10)	163.30 (6.99)	158.09 (3.91)
<i>p-value</i> **	<b>0.323</b>			<b>0.172</b>		
Mean BMI (Kg/m <sup>2</sup> ) (SD),	29.60 (6.18)	34.34 (5.02)	37.04 (8.31)	34.09 (4.38)	31.78 (4.27)	37.62 (6.17)
<i>p-value</i> **	<b>0.031</b>			<b>0.039</b>		
Mean HbA1c (%) (SD)	6.67 (0.84)	7.14 (0.67)	7.3 (0.66)	9.2 (0.45)	8.86 (0.53)	8.91 (0.58)
<i>p-value</i> **	0.112			0.253		
Mean ALT (IU) (SD)	26.38 (9.38)	27.75 (20.74)	24.60 (7.49)	24.33 (17.89)	24.50 (4.72)	28.55 (7.45)
<i>p-value</i> **	0.872			0.648		
Mean RBS (mmol/L) (SD)	7.48 (2.02)	9.09 (2.95)	6.99 (2.14)	11.41 (4.78)	11.49 (4.91)	14.63 (5.25)
<i>p-value</i> **	0.111			0.24		
Mean S. Creatinine (mg/dL) (SD)	1.03 (0.32)	1.07 (0.17)	0.95 (0.16)	1.03 (0.19)	1.08 (0.22)	0.99 (0.24)
<i>p-value</i> **	0.563				0.665	

\* Chi<sup>2</sup> test used to find a statistical difference in categorical variables between the three groups at each point  
\*\* ANOVA test used to find a statistical difference in numerical variables between the three groups at each point

**Primary Endpoints**

The blood level of Vitamin B1 in the three groups after 2.5 hours of treatment compared to baseline.

The blood level of vitamin B1 was almost doubled from baseline (T0) to after 2.5 hours (T2), with a highly statistically significant difference in groups A & B (p-value < 0.001). While it was slightly increased in patients in group C, (p-value = 0.001). There was statistically significant difference between 3 treatment groups in patients with HbA1c < 8 % (p-value = 0.041), and no statistically significant difference (p-value = 0.312) in patients with HbA1c > 8 % [Table 2].

**Secondary Endpoints**

The difference in the blood level of Vitamin B1 in the three groups between baseline and after six days of treatment

The blood level of vitamin B1 continued to increase after six days (T6) in patients with HbA1C less or more than 8 in group A & B with highly statistical significance between baseline and T6 (p-value < 0.001), while dropped in patients of group C without statistical significance (p-value= 0.419), with HbA1c less and more than 8%, as presented in [Table 2].

**Neuropathic pain after two weeks of treatment using Diabetic Neuropathic Symptom Score (DNS) versus baseline**

The median DNS decreased from baseline to after 14 days of treatment in all three treatment groups, with a statistically significant difference in the same group of patients, but without statistical significance between the 3 treatment groups, as presented in [Table 2].

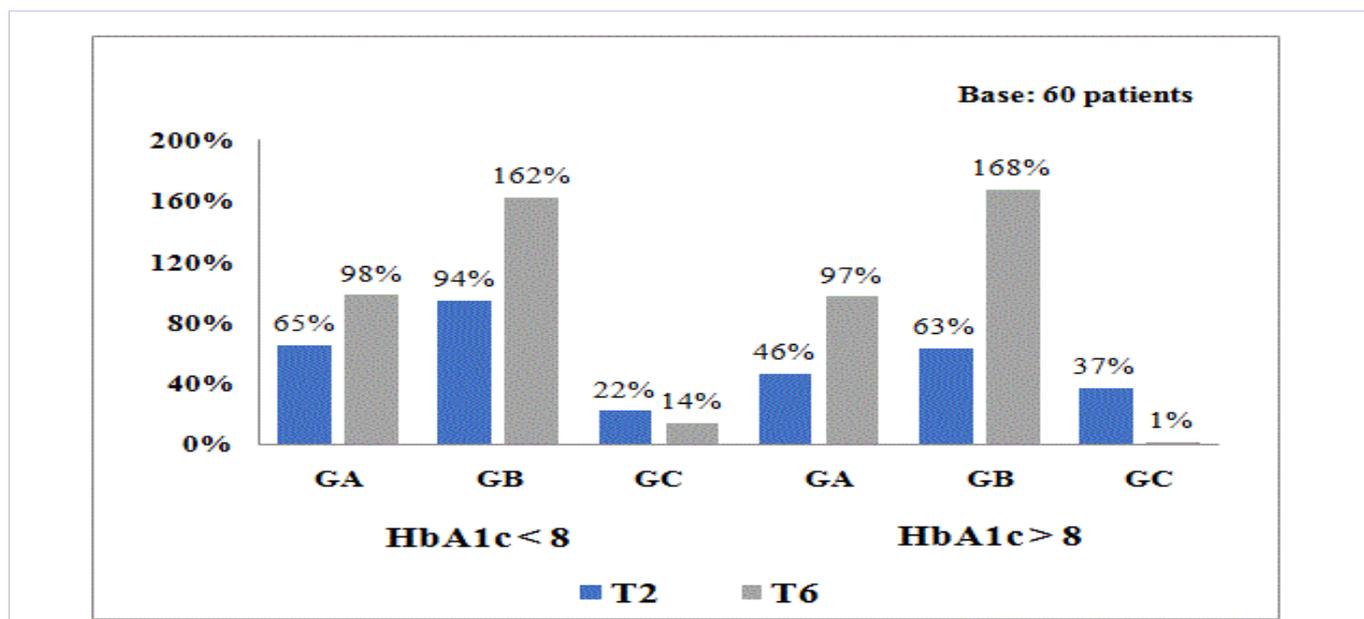


Figure 2 : %Change between Baseline, (T2) and (T6) in the 3 treatment groups with different HbA1c

**Vital signs**

There was no statistically significant difference at baseline visit in mean pulse between treatment groups. However, there was a statistically significant difference in mean temperature between the three groups with HbA1c > 8 % (p-value = 0.020).

**Body Weight and Body Mass Index (BMI)**

There was a statistically significant difference at baseline visit in the mean BMI between the 3 treatment groups with HbA1c < 8 %; (p-value = 0.031), and HbA1c > 8 %; (p-value = 0.039).

**Laboratory tests**

Lab tests (HbA1c, ALT, RBS, and S. Creatinine) at baseline visit of the three treatment groups showed no statistically significant differences.

**Medical History for Enrolled Patients**

Most patients of the three treatment groups with HbA1c less or more than 8% had hypertension with no statistically significant

Table 2: Evaluation Parameters; blood vitamin B1 level at baseline, after 2 hours & after 6 days									
	HbA1c < 8 %			HbA1c > 8 %				Overall	
N	G (A) 12	G (B) 11	G (C) 7	G (A) 10	G (B) 19	G (C) 11	G (A) 22	G (B) 20	G (C) 18
Mean T0 µg/L	75.62	61.94	84.27	71.36	71.76	84.04	73.68	66.37	83.26
Mean T2 µg/L	124.78	120.08	102.51	104.38	116.92	114.71	115.51	118.66	111.08
%Change	65%	94%	22%	46%	63%	37%	57%	79%	33%
p-value*	<b>0.001</b>	<b>&lt; 0.001</b>	0.212	<b>&lt; 0.001</b>	<b>0.001</b>	<b>0.002</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>	<b>0.001</b>
p-value**	<b>0.041</b>			<b>0.312</b>			<b>0.027</b>		
Mean T6 µg/L	149.81	162.16	96.42	140.81	192.43	84.93	145.72	175.78	89.39
%Change	98%	162%	14%	97%	168%	1%	98%	165%	6%
p-value*	<b>&lt; 0.001</b>	<b>0.001</b>	0.116	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>	0.927	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>	0.419
p-value**	<b>0.006</b>			<b>&lt; 0.001</b>			<b>&lt; 0.001</b>		
Median DNS1	2.00	2.00	2.00	2.00	2.00	3.00	2.00	2.00	2.50
Median DNS2	1.00	1.00	0.00	0.50	1.00	2.00	1.00	1.00	1.00
%Change	-50.0%	-50.0%	-100%	-70.0%	-50.0%	-33.3%	-50.0%	-50.0%	-60.0%
p-value*	<b>0.004</b>	<b>0.002</b>	<b>0.011</b>	<b>0.007</b>	<b>0.007</b>	<b>0.038</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>	<b>0.001</b>
p-value**	0.847			0.186			0.328		

T0: Blood level of vitamin B1 at the baseline visit, T2: Blood level of vitamin B1 at 2.5 hours from baseline, T6: Blood level of vitamin B1 at six days from baseline, DNS1: Diabetic neuropathic symptom score at baseline and DNS2: Diabetic neuropathic symptom score at two weeks from baseline  
 p-value\*: For the difference in the Blood level of Vitamin B1 in the same group, Using Paired t-test  
 p-value\*\*: For absolute Change of Blood level of Vitamin B1 between 3 groups, Using ANOVA test  
 p-value\*: For the difference in Median DNS in the same group, Using Wilcoxon Signed Ranks Test  
 p-value\*\*: For absolute Change of Median DNS between 3 groups, Using Kruskal Wallis Test

**Vital signs**

There was no statistically significant difference at baseline visit in mean pulse between treatment groups. However, there was a statistically significant difference in mean temperature between the three groups with HbA1c > 8 % (p-value = 0.020).

**Body Weight and Body Mass Index (BMI)**

There was a statistically significant difference at baseline visit in the mean BMI between the 3 treatment groups with HbA1c < 8 %; (p-value = 0.031), and HbA1c > 8 %; (p-value = 0.039).

**Laboratory tests**

Lab tests (HbA1c, ALT, RBS, and S. Creatinine) at baseline visit of the three treatment groups showed no statistically significant differences.

**Medical History for Enrolled Patients**

Most patients of the three treatment groups with HbA1c less or more than 8% had hypertension with no statistically significant difference between the three treatment groups, and only one

patient from Group C with HbA1c < 8 had thyrotoxicosis.

**Concomitant Medications**

Most enrolled patients in the study took concomitant medications for hypertension during the three visits of the study, with no statistically significant difference between concomitant medications in the three treatment groups. (p-value = 0.447).

**Diabetes mellitus treatment**

Patients used either insulin or oral hypoglycemic medications (Biguanides, Dipeptidyl Peptidase 4 Inhibitor (DPP4-I) + Biguanides, and Sulfonylurea) showed no statistically significant difference in vitamin B1 blood level at T2 and T6, or in DNS2 in the three treatment groups, A, B and C, as presented in [Table 3]

**Adverse Events**

No adverse (AE) or serious adverse events (SAE) were reported during the study in patients of the three treatment groups.

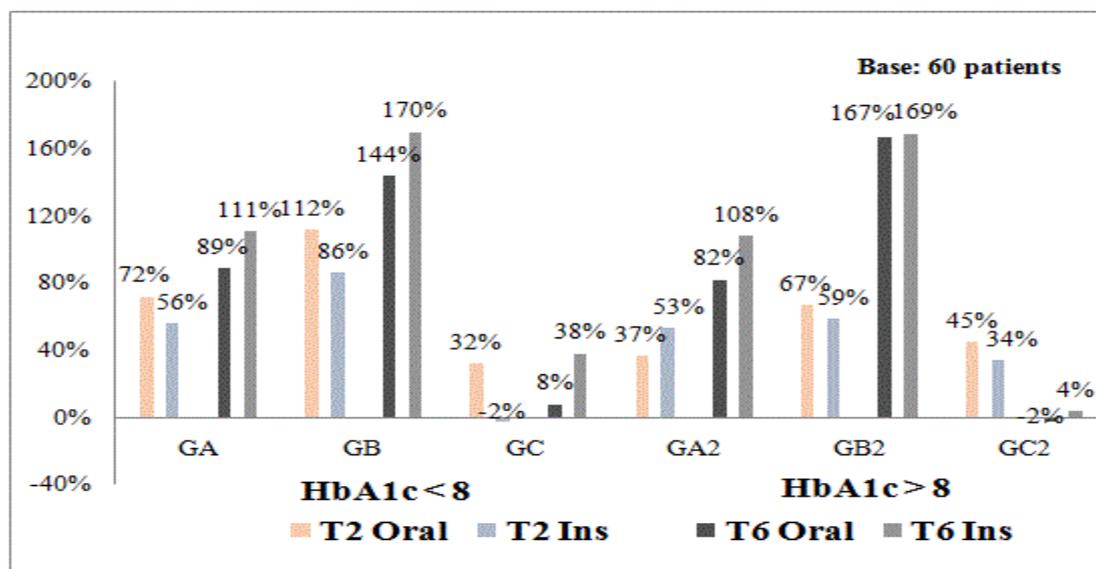


Figure 3 : %Change between Baseline, (T2) and (T6) in the 3 treatment groups using either insulin or oral with different HbA1c

Table 3: Effect of oral hypoglycemic medications and insulin on endpoint parameters (Vitamin B1)

N	HbA1c < 8 %						HbA1c > 8 %					
	Group A		Group B		Group C		Group A		Group B		Group C	
	Oral 7	Ins. 5	Oral 4	Ins. 7	Oral 5	Ins. 2	Oral 4	Ins. 6	Oral 5	Ins. 4	Oral 6	Ins. 5
Mean T0 µg/L	76.3	74.7	53.2	66.9	89.5	61	72.8	70.4	62.5	83.4	80.9	87
Mean T2 µg/L	130.8	116.3	112.8	124.2	117.9	59.6	99.7	107.5	104.6	132.4	117.7	116.9
%Change	72%	56%	112%	86%	32%	-2%	37%	53%	67%	59%	45%	34%
p-value*	0.017	0.023	0.008	0.001	0.005	0.982	0.083	0.005	0.021	0.008	0.010	0.095
p-value**	0.571		0.875		0.301		0.445		0.651		0.677	
Mean T6 µg/L	144.2	157.7	130.1	180.5	101.3	84.1	132.7	146.2	167	224.2	80.3	90.4
%Change	89%	111%	144%	170%	8%	38%	82%	108%	167%	169%	-2%	4%
p-value*	0.012	0.003	0.045	0.012	0.420	0.076	0.074	0.002	0.007	0.018	0.921	0.842
p-value**	0.561		0.449		0.336		0.530		0.337		0.818	
Median DNS1	2.0	2.0	2.0	3.0	2.0	1.5	1.5	2.5	2.0	2.0	2.5	3.0
Median DNS2	1.0	1.0	1.0	1.0	0.0	0.5	0.0	1.0	0.0	1.5	0.0	2.0
%Change	-50%	-50%	-50%	-67%	-100%	-67%	-100%	-60%	-100%	-25%	-100%	-33%
p-value*	0.039	0.034	0.046	0.020	0.034	0.157	0.063	0.041	0.034	0.083	0.102	0.157
p-value**	0.716		1.000		0.527		1.000		0.180		0.307	

p-value\*: For the difference in the Blood level of Vitamin B1 in the same group for patients who received either insulin or oral hypoglycemic, Using Paired t-test

p-value\*\*: For absolute Change of Blood level of Vitamin B1 in the same group between oral hypoglycemic and insulin, Using Unpaired t-test

p-value\*: For the difference in Median DNS in the same group for patients who received either insulin or oral hypoglycemic, Using Wilcoxon Signed Ranks Test

p-value\*\*: For absolute Change of Median DNS in the same group between oral hypoglycemic and insulin, Using Mann-Whitney Test

## Discussion

The difference in the blood levels of Vitamin B1 in the three treatment groups between baseline and after 2.5 hours of treatment

Vitamin B1 (thiamine) has been used in neuropathy management for patients with diabetes for decades [8]. The absorption rate of water-soluble thiamine from the intestine into blood circulation is generally slow and saturable process, therefore, high thiamine levels in blood and tissues are needed. So, a variety of lipophilic thiamine derivatives have been developed. Benfotiamine is one of the lipid-soluble derivatives with much better bioavailability than the water-soluble form as; thiamine concentrations in blood and tissues produced by oral administration of Benfotiamine is 67% higher than that produced by thiamine nitrate [7], [9], [10].

Guilherme Vannucchi Portari et al. study showed that the free thiamine level was increased by four times in the thiamine group and by 100 times in the Benfotiamine group with  $p < 0.05$ . Also, it showed that the levels of all blood thiamine were much higher in the Benfotiamine group compared to all other groups [2].

This study showed that the mean blood levels of Vitamin B1 were markedly increased after 2.5 hours in group A & B who received oral Benfotiamine, while mildly increased in group C who received intramuscular thiamine) with statistically significant difference between the three treatment groups for patients with HBA1C less than 8 % ( $p$ -value = 0.041) and non-significance for patients with HBA1C above 8 %. ( $p$ -value = 0.312). This is similar to what was published about the pharmacokinetic study of Benfotiamine compared to thiamine hydrochloride, that after oral administration of Benfotiamine, the bioavailability of thiamine in plasma and thiamine diphosphate (TDP) in erythrocyte were  $1147.3 \pm 490.3\%$  and  $195.8 \pm 33.8\%$ , respectively. [8]

Group B had the lowest vitamin B1 level at baseline,  $66.37\mu\text{gm}$ , while group A had  $73.68\mu\text{gm}$  and group C had  $84.13\mu\text{gm}$  of vitamin B1. This might be a contributing factor in a high increase in the blood level of vitamin B1 in group B compared to the other two groups, as thiamine uptake increases with thiamine deficiency [7], in addition to the high administered dose in group B (2 tablets daily).

### The difference in the blood level of Vitamin B1 in the three treatment groups between baseline and after six days of treatment

As thiamine is a positively charged molecule, it needs a carrier to cross biological membranes, and its absorption is slower than substances with lipophilic properties. Benfotiamine (S-benzoyl thiamine, O-monophosphate) is first dephosphorylated in the intestinal villi by an extracellular alkaline phosphatase producing S-benzoyl thiamine that passes easily through the intestinal membranes and endothelial cells into the mesenteric circulation, to be metabolized by hepatocyte thioesterases into thiamine [2]. Also, Benfotiamine has a significantly higher bioavailability compared to other lipid-soluble preparations as; Fursultiamine and Tiaminedisulphide [10]

Our study showed higher thiamine blood concentrations and steady-state blood concentration after six days of administration of oral Benfotiamine compared to intramuscular administration of thiamine HCl. So, we can conclude that thiamine HCl needs continuous and more frequent intake to keep vitamin B1 levels stable and high.

### The median percent change of DNS decreased between baseline and after 14 days in the three treatment groups.

This study showed a reduction in the percent change of DNS in group A & B by 50% and group C by 60%, with a very highly statistically significant difference ( $p$ -value  $< 0.001$ ) in group A & B (oral Benfotiamine 300mg and 600mg respectively). Moreover, the overall sample showed a highly statistically significant difference in group C (injectable Thiamine 150 mg, one ampoule twice weekly).

BENDIP study showed that after two weeks of treatment, the improvement from baseline in NSS was more pronounced at the higher Benfotiamine dose and increased with treatment duration. [1]. Also, Gabor Winkler et al. study that studied the clinical efficacy of three different doses of Benfotiamine found that the most positive effect could be observed undoubtedly in the group treated with Benfotiamine vitamin in combination with B6 and B12 of high doses. [11]

Since there was no statistically significant difference in vitamin B1 blood level in each group between patients who received insulin or oral hypoglycemic at 2.5 hours (T2) or six days (T6) from baseline and there was no significance in percent drop in DNS in each group whether patients received insulin or oral hypoglycemic at two weeks from treatment, Benfotiamine is considered beneficial in controlled and uncontrolled patients with diabetes (HBA1C less or more than 8 %) and with oral hypoglycemic or insulin medication.

WHO published data that 94.7% of injections in Egypt are unnecessary and could be replaced by a suitable oral preparation [12]. Also, as per this study, the pharmacokinetic advantage of parenteral over oral drugs does not necessarily translate to better clinical outcomes. As, this study for oral vitamin B containing Benfotiamine showed a marked increase in vitamin B1 level after 2.5 hours and six days compared to an intramuscular injection containing thiamine and a decrease in DNS after 14 days in all treatment groups, oral vitamin B with Benfotiamine could replace parenteral vitamin B with thiamine. Also, Wendy Schijns et al. study showed that oral and IM intake of vitamin B12 increases blood vitamin B12 levels similarly. [13]

### Safety

There were no adverse or serious adverse events reported during the study, which confirmed the safety of oral Benfotiamine in the two different doses and intramuscular vitamin B. However, BENDIP study showed a few Benfotiamine-related mild adverse events as; slight gastrointestinal disorders and skin allergic reactions. [1].

## Conclusions

Oral Benfotiamine 300 mg is safe and more effective compared to intramuscular thiamine HCl in management of diabetic peripheral neuropathy, through increasing the blood level of vitamin B1 in controlled and uncontrolled diabetic patients with peripheral neuropathy and while using insulin or oral hypoglycemic medications.

## Limitations

As the study is pilot, the number of patients is small, and the duration of the study is short.

DNS is a subjective test for peripheral polyneuropathy.

## Recommendations

A long-term study (6 months) with objective tests for peripheral polyneuropathy (PN) is recommended to have better judgment of the effect of Benfotiamine 300 mg in the management of DPN with larger sample size.

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## Author Contributions

Authors participated in design of study protocol. Also, enrolled patients, collected data, carried out necessary assessments required for the study and filled in the CRFs of the patients. The corresponding author (Dr M. Hesham El Hefnawy) partially participated in CSR and manuscript writing.

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