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Original Research Article

ROLE OF KRILL OIL SUPPLEMENTATION IN DIABETIC NEUROPATHY PATIENTS – A RANDOMIZED CONTROL TRIAL

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Abstract
Diabetic peripheral neuropathy (DPN) is a common, symptomatic, long-term microvascular complication of diabetes mellitus. This study was undertaken to see the efficacy and safety of krill oil supplementation in diabetic neuropathy patients. This was a prospective observational study. The patients were categorized into two groups, Group I included those patients who were prescribed krill oil while group II patients received placebo irrespective of their antidiabetic treatment. Each patient was initially accessed and followed up at 24 weeks. Demographic details, presenting symptoms, history of diabetes, laboratory values pertaining to diabetes (Fasting blood sugar, Postprandial blood sugar, and HbA1c) were recorded. Nerve conduction velocity (NCV), Intensity of pain, using a visual analog scale (VAS), diabetic neuropathy symptom (DNS) score and diabetic neuropathy examination (DNE) score, were assessed at baseline and then at 24-week follow-up. Data of 72 patients were analyzed. There was a statistically significant improvement in NCV, VAS, DNS and DNE score of the patient's Results of this study suggest that treatment with krill oil gives an improvement in diabetic neuropathy. Although promising, further studies are needed to assess long-term treatment of krill oil in a large sample of the population.

Keywords: Diabetic peripheral neuropathy, Krill Oil, Diabetic Neuropathy.

Introduction

Diabetic peripheral neuropathy (DPN) is common, symptomatic, long-term complication of type 1 and 2 diabetes mellitus. It leads to a major physical disability, poor quality of life[1], high mortality[2], and an estimated total annual cost of $22 billion[3]. Mechanisms involved in nerve damage are persistent hyperglycemia, microvascular insufficiency, oxidative stress, defective neurotrophism, and autoimmune nerve destruction. Therefore, till date, no effective treatment exists for DN, other than the control of

hyperglycemia[4, 5]. Several drugs have been used with varying degree of success including antidepressants, anti-epileptics, α-lipoic acid, baclofen, levodopa, methcobalamin, and bupropion.

The Norwegian word "krill" translates into "young fry of fish" and has been adopted as the term used to describe marine crustaceans belonging to the order Euphausiacea. Krill is widely known as whale food but is also a source of food for seals, squid, fish, seabirds, and to a much lesser degree, humans.

Reports of health benefits have contributed to the rise in seafood consumption. The American Heart Association recommends eating fish at least twice a week as a part of their guidelines for reducing heart disease and microvascular complication in diabetes.

Krill oil is derived from crustacean species called krill. Krill looks more like a shrimp-like creature that is found in the Antarctic. They are long and reddish-pink and live deep in the ocean. They are full of healthy omega-3 fatty acids, phospholipids and extremely potent antioxidants krills are harvested only two months out of the year under responsible fishing regulations. These are flash-frozen to maintain the potency of their therapeutic oil.

Krill oil contains a healthy balance of omega-3 and omega-6 fatty acids. A healthy balance of these fatty acids helps to prevent blood clotting, lower blood pressure and relieve inflammation Phospholipids block out toxins and disease-forming free radicals. Krill oil provides us with an ample supply of vitamins A, E, and D, plus minerals such as potassium, sodium and zinc. And it also contains large amounts of the B-complex nutrient, chlorine. However, the most powerful antioxidant in krill oil is astaxanthin. It is responsible for fighting free radicals within the body and protecting the blood-brain barrier. There are tremendous opportunities for research regarding the potential health effects of krill in cardiovascular, neurological developmental, cancer, arthritis, and diabetes.

We conducted a randomized double-blind, placebo-controlled trial using oral krill oil 500 mg per day treatment over 24 weeks period to study its effect and found promising results. The aim of this study to study the effect of krill oil supplementation on diabetic neuropathy through nerve conduction velocity test. The main objectives of this study to evaluate the nerve conduction velocity in Type 2 DM patients with neuropathy. To compare the nerve conduction velocity in Type 2 DM patients with neuropathy after krill oil supplementation with nerve conduction velocity in Type 2 DM patients with neuropathy after giving a placebo.

Materials and Methods

This study was carried out in PG Department of Medicine Sarojini Naidu Medical College, Agra in on diabetics attending indoor and outdoor clinics. The study was conducted over a period of 18 months from March 2011.

Study Design

The study design was a randomized double-blinded controlled trial.

Baseline NCV was performed.

Patients were divided into two groups; Group A received krill oil supplementation and Group B received placebo.

Krill oil supplementation was given in a dose of 500 mg daily oral for 24 weeks. After 24 weeks NCV was repeated.

NCV of supplemented group and placebo-receiving group was compared.

Inclusion Criteria

A case of diabetes mellitus (known case or recently detected) with sign or symptoms suggestive of diabetic neuropathy.

Exclusion Criteria

Patient having any other diseases known to cause peripheral neuropathy like a chronic renal failure, liver failure, hypothyroidism, leprosy, porphyria etc.

Myopathy. Presence of foot ulcers. Patient on drugs known to cause peripheral neuropathy like isoniazid and phenytoin. Overt diabetic retinopathy/blindness from any cause.

After dropouts both the study group and control group were having 36 patients each and hence data of total 72 patients were analyzed. Out of these 72 cases, 38 were taking oral hypoglycemic drugs, 10 were on insulin and 24 were taking both and these were randomly distributed in both groups. Krill oil was given to study group.

Results and Discussion

Burning, aching pain or tenderness and pricking sensation were found in a maximum number of patients as shown in Table 1 and Bar diagram 1 below.

Loss of vibration sense, loss of deep sensation followed by loss or diminished reflexes are the most common findings seen in patients with Diabetes mellitus in both study group and control group as shown in Table 2 and Bar diagram 2 below:

The symptoms of hypothermia, paresthesia, cramp, and pain show statistically significant improvement in the study group. In the control group, there was no significant change as shown in Table 3 and Bar diagram 3 below

There is a statistically significant improvement in vibration sense loss, position sense loss, diminished or lost reflexes in the study group as shown in Table 4 and Bar diagram 4.

Table 5 and Bar diagram 5 shows that the mean NCV of right and left CPN after 24 weeks follow up, increased from 40.00± 2.39 and 40.21±1.80 to 49.75±2.15 and 49.92±1.90 in the study group. There was no statistically significant improvement in the control group.

Table 6 and Bar diagram 6 shows that the mean NCV of right and left median nerve after 24 weeks follow up increased from 42.40±2.18 and 41.27±1.35 to 51.16± 2.14 and 50.83±1.36 in the study group which was statistically significant.

There was a statistically significant improvement in VAS in the study group as shown in Table 7 and bar diagram 7.

In a recent review article (Hussein G et al., 2006) health benefits attributed to astaxanthin including reduced risk of cataracts, diabetes, heart disease, neural deterioration, and certain cancers; however, most of these studies were conducted using vitro or animal models. Despite the promising results for astaxanthin derived from krill.

Vitamin B-12 in krill (16-g/100g) is substantially higher than in shrimp (1.16-g/100g) or fish (4.17 to 4.45-g/100g) and exceeds the RDA of 2.4-g/d for adults. The assessment of the nutritive value of krill-based on vitamin content indicates that it has considerable appeal for human consumption because it provides a good source of vitamin B-12, E, and astaxanthin, as well as other potential antioxidant compounds.

The krill oil antioxidant values were obtained by evaluating leading national brand products in order to measure their antioxidant potency using the ORAC method (Flanigan J et al, 1996). ORAC stands for Oxygen Radical Absorbance

Capacity. Indirect ORAC comparisons- milligram for milligram- The value of krill oil was found to be 48 times that of fish oil.

Krill oil seems to be safe for most adults when used appropriately for a short duration of time (up to three months). Research on krill oil has not adequately evaluated its safety or possible side effects. However, it is likely that krill oil can cause some side effects similar to fish oil such as bad breath, heartburn, fishy taste, upset stomach, nausea, and loose stools.

Observations:

Table.1 Duration of Diabetes Mellitus and Symptoms of Sensory and Motor Neuropathy (DNS-Diabetic Neuropathy Symptom Score) at Initial Assessment

Symptoms / **Duration of Diabetes (years)**	**Number of patients**							
	Study group(n=36)				**Control group(n=36)**			
	0-5	**6-10**	**11-15**	**16-20**	**0-5**	**6-10**	**11-15**	**16-20**
Prickling sensations	2 (5.56)	8 (22.22)	14 (38.89)	4 (11.11)	3 (8.33)	2 (5.56)	12 (33.33)	4 (11.11)
Numbness	2 (5.56)	7 (19.44)	14 (38.89)	4 (11.11)	1 (2.78)	3 (8.33)	12 (33.33)	4 (11.11)
Burning, aching pain or tenderness	4 (11.11)	7 (19.44)	14 (38.89)	6 (16.67)	2 (5.56)	4 (11.11)	12 (33.33)	6 (16.67)
Unsteadiness in walking	1 (2.78)	2 (5.56)	8 (22.22)	6 (16.67)	1 (2.78)	2 (5.56)	8 (22.22)	6 (16.67)

(Figures in parentheses indicate percentage)

Table.2 Duration of Diabetes Mellitus and Signs of Sensory and Motor Neuropathy (DNE-Diabetic Neuropathy Examination Score) at Initial Assessment

Symptoms / Duration of Diabetes (years)	Number of patients															
	Study group(n=36)								Control group(n=36)							
	0-5		6-10		11-15		16-20		0-5		6-10		11-15		16-20	
	No.	%	No.	%	No	%	No	%	No	%	No	%	No	%	No.	%
Muscle strength	0	0.0	2	5.6	5	13.9	4	11.1	0	0.0	1	4.8	5	13.9	5	13.9
Index finger: Sensitivity to Pinpricks	1	2.8	8	22.2	14	38.9	5	13.9	1	2.8	4	11.1	12	33.3	4	11.1
Big toe: Sensitivity to pinpricks, Sensitivity to touch, Vibration perception, sensitivity to joints.	2	5.6	8	22.2	14	38.9	6	16.7	2	5.6	4	11.1	12	33.3	4	11.1
Reflexes lost or diminished	2	5.6	4	11.1	12	33.3	6	16.7	2	5.6	4	11.1	12	33.3	4	11.1

Table.3 Symptoms of Sensory & Motor Neuropathy (DNS) After Krill Oil Administration in Study Group as Compared to Control Group

Symptoms	**Study group(n=36)**					**Control group(n=36)**				
	Initial		**follow up**		**% change**	**Initial**		**follow up**		**% change**
	No.	%	No.	%		No.	%	No.	%	
Prickling sensations	28	77.78	10	27.78	64.29	21	58.33	23	63.89	-9.52
Numbness	27	75.00	11	30.56	59.26	20	55.56	22	61.11	-10.00
Burning aching pain or tenderness	31	86.11	15	41.67	51.60	24	66.66	23	63.89	4.1
Unsteadiness in walking	17	47.22	9	25.00	47.05	17	47.22	17	47.22	0
	p value=0.012975*					p value=0.418031 NS				

*The groups are significantly different.

NS- The groups are not significantly different Single Factor ANOVA is used

Table.4 Signs of Sensory and Motor Neuropathy(DNE) After Krill Oil Administration in Study Group as Compared to Control Group

Symptoms	**Study group(n=36)**					**Control group(n=36)**				
	Initial		**follow up**		**% change**	**initial**		**follow up**		**% change**
	No.	%	No.	%		No.	%	No.	%	
Muscle strength	11	30.56	6	16.67	45.45	11	30.56	11	30.56	0.00
Index finger: Sensitivity to pinpricks	28	77.78	12	33.33	57.14	21	58.33	23	63.89	-9.52
Big toe: Sensitivity to pinpricks, Sensitivity to touch, Vibration perception, Sensitivity to joint position	30	83.33	12	33.33	60.00	22	61.11	23	63.89	-4.55
reflexes lost or diminished	24	66.67	10	27.78	58.33	22	61.11	23	63.89	-4.55
	p value=0.025748*					p value=0.811881^{NS}				

**The groups are significantly different.*

NS- The groups are not significantly different

Table. 5 Effect of Krill Oil Supplementation on Nerve Conduction Velocity in Right and Left Common Peroneal Nerve (CPN) in Diabetes Mellitus Patients

		Study group(n=36)				**Control group(n=36)**			
		Initial	follow up	t-value	p value	initial	follow up	t-value	p value
Right C.P.N.	Mean	40.00	49.75	-18.1974	<0.0001	40.51	40.61	-0.1946	0.8463
	SD	2.39	2.15			2.21	2.15		
Left C.P.N.	Mean	40.21	49.92	-22.26	<0.0001	40.39	40.74	-0.8965	0.3731
	SD	1.80	1.90			1.72	1.59		

Table.6 Effect of Krill oil Supplementation on Nerve Conduction Velocity in Right and Left Median Nerve in Diabetes Mellitus Patients

		Study group(n=36)				**Control group(n=36)**			
		initial	follow up	t- value	p value	initial	follow up	t- value	p value
Right Median Nerve	Mean	42.40	51.16	-17.2055	<0.0001	42.31	41.99	0.6833	0.4967
	SD	2.18	2.14			2.07	1.90		
Left Median Nerve	Mean	41.27	50.83	-29.9331	<0.0001	41.58	41.89	-0.7991	0.427
	SD	1.35	1.36			1.70	1.59		

Table.7 VAS (Visual Analogue Scale) at Initial Assessment and After Follow up in Study Group and Control Group

Specifications	**study group(n=36)**		**control group(n=36)**	
	Initial	**follow-up**	**No.**	**%**
Mean	5.64	2.50	5.69	5.44
SD	1.74	1.00	1.79	1.50
t-value	9.3877		0.6423	
p-value	<0.0001		0.5228	

Figure 1: Duration and symptoms of diabetes mellitus

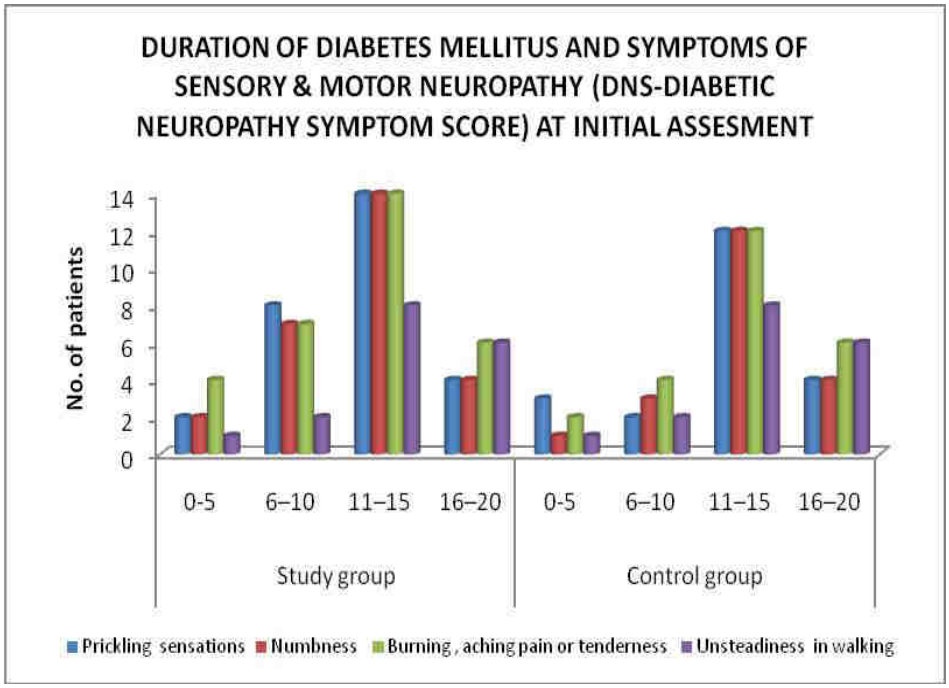


Figure 2: Duration of diabetes and sign and sensory mortar neuropathy

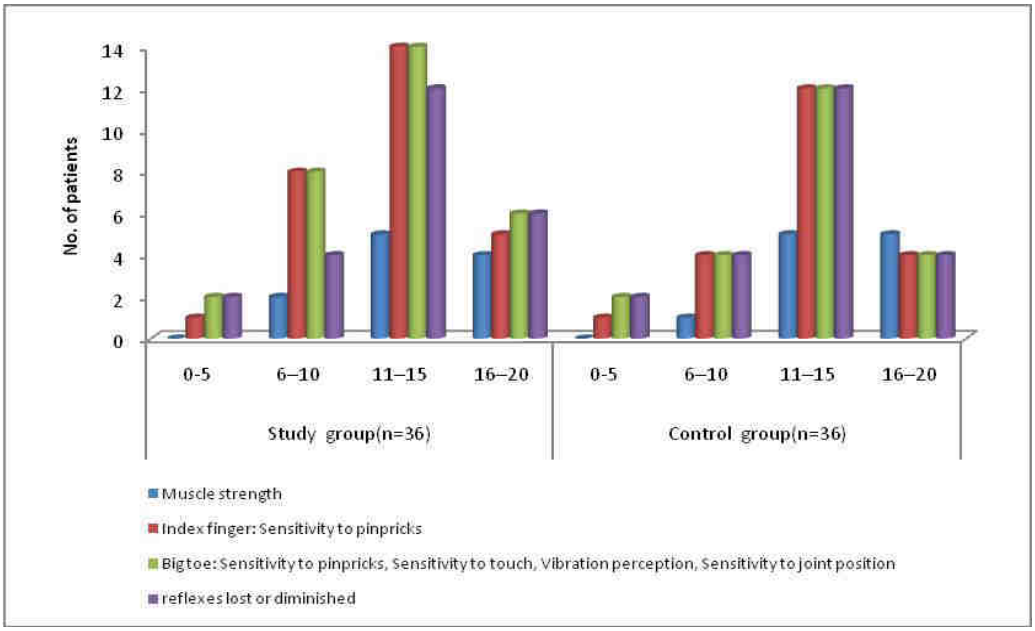


Figure 3: Symptoms of Sensory & Motor Neuropathy (DNS) After Krill Oil Administration

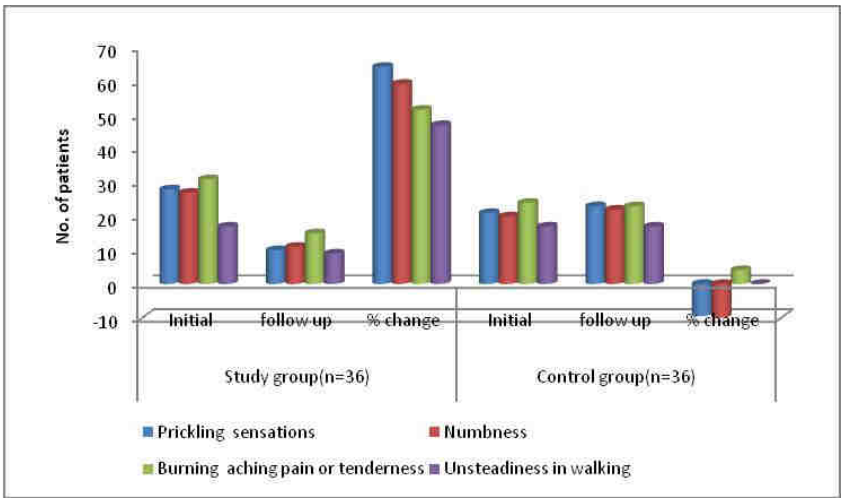


Figure 4: Signs of Sensory and Motor Neuropathy (DNE) After Krill Oil Administration

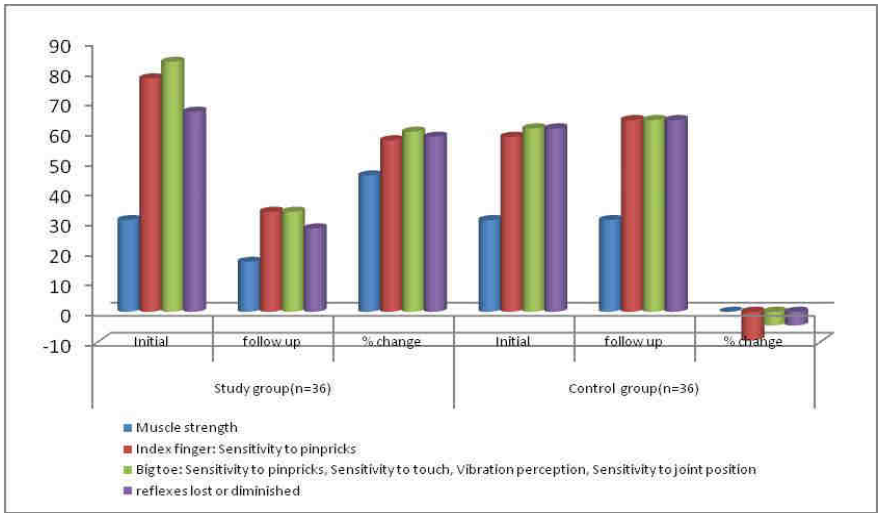


Figure 5: Effect of Krill Oil Supplementation on Nerve Conduction Velocity in Right and Left Common Peroneal Nerve

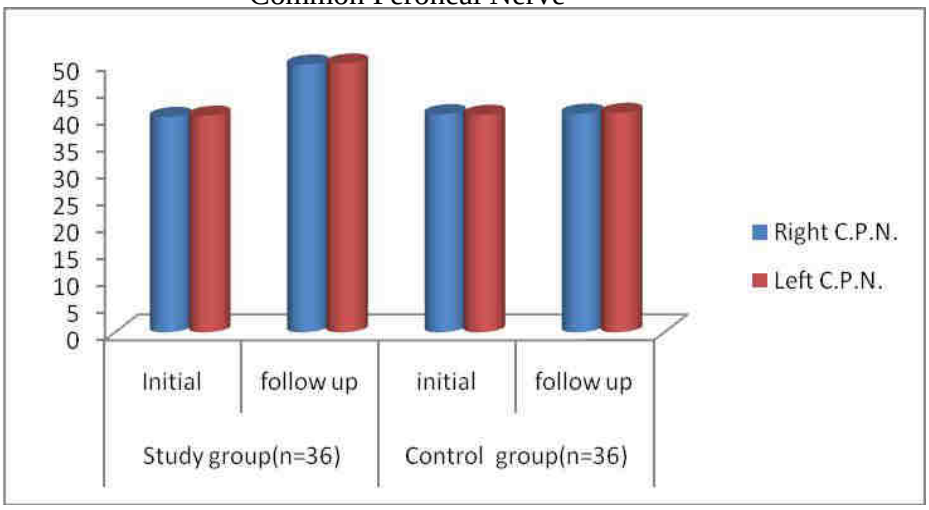


Figure 6: Effect of Krill oil Supplementation on Nerve Conduction Velocity in Right and Left Median Nerve in Diabetes Mellitus Patients

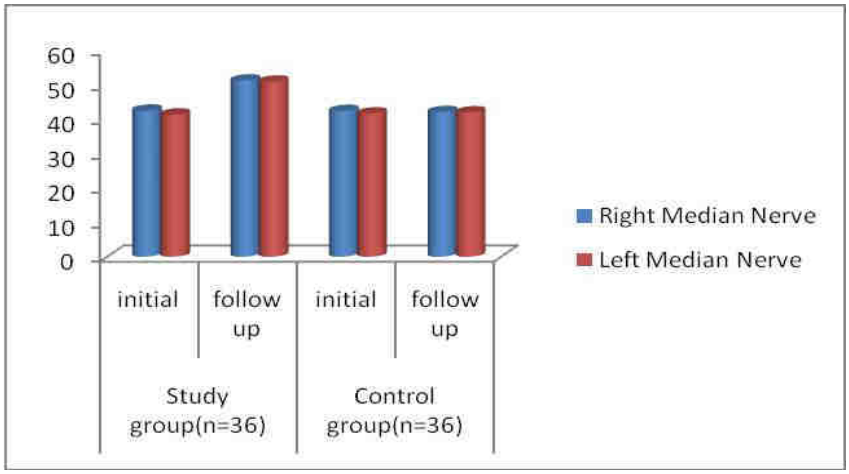
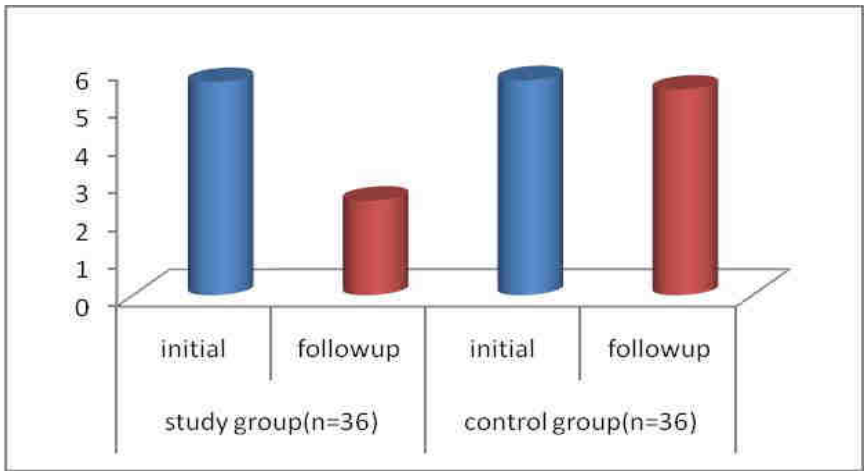


Figure 7: VAS (Visual Analogue Scale) at Initial Assessment and After Follow up in Study Group and Control Group



In our study, among 72 Diagnosed type 2 diabetic neuropathy patients, nerve conduction velocity was measured before and after treatment at 0 and 24 weeks. Total 72 cases of diabetic neuropathic patients were subdivided into two groups. Group I consists of the patients of diabetic neuropathy receiving Krill oil and group II consists of the patient of diabetic neuropathy which was receiving placebo. Both groups were receiving their antidiabetic treatment as well. Patients were distributed according to different age starting from 40 years and according to sex. In both groups, a maximum number of patients were having age from 61-70 years.

From the study, it was observed that diabetic neuropathy occurred maximally in the patients who had diabetes of about 11-15 years (36.11%) or more.

In the peripheral neuropathy, maximum number of patients had loss of vibration sense (72.22%), followed by muscle cramp and pain (72.20%),

hypoesthesia (68.05%), paresthesia (68.00%), loss of position sense (54.66%), diminished reflexes (63.88%) and muscle weakness (30.05%) (Table 1 and 2).

On analysis in the study group, there was 64.29% improvement in pricking sensation,

59.26% improvement in numbness, 51.60% improvement in burning aching pain or tenderness, 47.05% improvement in unsteadiness in walking, 45.45% improvement in muscle strength, 57.14% improvement in sensitivity to pinprick sensation in index finger, 60%improvement insensitivity to pinprick, touch, vibration, joint position sense, 58.33% improvement in reflexes (table 3 and 4). The nerve conduction velocity was improved in right and left CPN and Median nerve. In the study group, these parameters were improved and improvement was statistically significant (p value<0.05) (table 5 and 6). VAS mean value was significantly lowered in the study group (table -7). Blood sugar level (fasting and postprandial) was improved in both group but serum cholesterol, SGOT, SGPT, serum creatinine level did not show any significant improvement

Conclusion

Krill oil has a beneficial effect in peripheral neuropathy, in the form of relief of subjective symptoms and signs and it has got the significant effect in the form of improvement in nerve conduction velocity. Although promising, further studies are needed to assess long-term treatment of Krill oil given orally in an outpatient setting to assess its potential as a viable treatment option for patients with DSPN and its safety and toxicity profile.

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