ORIGINAL ARTICLE

Assessment of the Role of Eruca Sativa Oil (Taramira Oil) in the Treatment of Painful Diabetic Peripheral Neuropathy and its Comparison with Conventional Treatment

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ABSTRACT

Background: This interventional study was conducted in Islam Central Hospital and Munawar surgical hospital Sialkot.

Aim: To assess the role of Taramira Oil (as a counter-irritant) in the treatment of painful diabetic peripheral neuropathy.

Methods: A total of Ninety (90) patients comparable in respect of age, sex, weight, height and duration of diabetes were selected. All of the subjects complained of symmetrical burning pain in feet with the absence of any other obvious cause of peripheral neuropathy. They were divided in three groups (each with 30 patients). One group received Imipramine (Tofranil), 2nd was given Carbamazepine (Tegretol) and the 3rd group applied Taramira Oil on the affected surfaces. Those patients who required antidepressants and /or anti convulsants due to other problems were excluded. Also patients who had diabetic foot ulcer were not recruited. Patients were followed up for six weeks and their pain intensity was recorded periodically on a visual analogue scale ranging from 0-10.

Results: According to results, the patients in each group showed a trend towards gradual decrease in pain intensity grade over six weeks. However the relationship of mean pain intensity grades among the three study groups was not found to be statistically significant at each visit i.e., p value at 0 week=0.127, at 2 weeks= 0.3, at 4 weeks=0.558 and at 6 weeks=0.732. The relationship between age, sex and duration of diabetes of the three groups was also assessed and was also found to be non-significant statistically.

Conclusion Taramira Oil was found to be equally efficacious to Carbamazepine and Imipramine in relieving the pain of peripheral diabetic neuropathy.

Keywords: Painful diabetic peripheral neuropathy, Carbamazepine, Imipramine, Counter-irritation

INTRODUCTION

Diabetic sensory polyneuropathy is the most common form of diabetic neuropathy and its prevalence and severity appear to parallel the glycemic control and duration of diabetes[1]. It affects more than 50% of patients who have had diabetes for 25 years or more[2]. It is rarely found within the first five years after insulin dependent diabetes mellitus (IDDM) has been diagnosed but is usually found soon after a diagnosis of non-insulin dependent diabetes mellitus (NIDDM), often following many years of asymptomatic hyperglycemia[3].

Peripheral neuropathy is typically the earliest to be detected among the diabetic complications and usually has a gradual onset and a progressive course[4]. The feet and lower part of the legs are often affected first because the distal portions of the longer nerves are damaged before the proximal ones. Sensory symptoms are usually symmetrical and pain in the feet may take the form of paresthesia, hyperesthesia or burning sensations[5]. It is estimated that about 7.5% of diabetics experience pain from diabetic neuropathy[6]. Chronic painful symptoms can last for many years[7] and may severely impair the quality of life interfering with sleep, work and activities of daily living[8].

As the neuropathy progresses, the feet become numb and patients are unable to feel foot trauma[9]. Motor fibre involvement results in muscle weakness and atrophy, which can lead to such foot deformities as Charcot's joint, creating increased pressure and callus formation. Repeated and unrecognized trauma to the insensate extremity leads to ulceration, infection and risk of lower extremity amputation[10].

The painful peripheral diabetic neuopathy remains a perplexing problem for the patient and clinician[11]. Despite the great number of studies on the elucidation of the pathophysiology involved[12,13] and the various recommendations for treatment[14], none has proved to be consistently effective. Although several possible etiologies have been proposed, we still do not truly understand the mechanisms underlying diabetic neuropathy[15]. The major mechanisms include increased activity of polyol pathway, abnormalities in vasoactive substances, non-enzymatic glycation, increased presence of free radicals and perturbed neurotrophism[16].

MATERIAL AND METHODS

This interventional study was carried out in Islam central hospital and Munawar Surgical hospital sialkot.

This study was completed in six months from January 2012 to June 2012. Islam Central Hospital and Munawar Surgical Hospital are two major hospitals of sialkot where patients are referred from the periphery.

Male and female patients were recruited in the study without any specific socio-economic background and rural-urban differentiation, visiting Medical Outdoor for the treatment of Diabetes Mellitus and the management of its complications. All of these patients were having clinical features of painful diabetic peripheral neuropathy.

Inclusion Criteria

- Both male and female patients were selected
- Patients were of ages between 30 and 60 years.
- Patients were comparable in the aspects of age, weight, height duration of diabetes and glycemic control.
- All patients were having symmetrical burning or crawling pains in feet.
- Patients had patent peripheral pulses on clinical examination.

Exclusion Criteria

- Patients with any neurological deficit that would compromise assessment of sensory system.
- Patients who had foot ulcer, whether neuropathic or ischaemic
- Patients requiring anticonvulsants and/or antidepressants due to other problems were excluded from study.
- Patients with complications requiring surgery were excluded.
- Patients with concomitant contributing disease were excluded from study e.g. septicemia, vasculitis, immune deficiency states, malignancy, uncontrolled hypertension, uncompensated heart failure etc.
- Patients with advanced nephropathy or who had suffered cerebrovascular accident were not recruited.
- Patients known to be sensitive to any of the drugs used in study.
- Newly diagnosed diabetics were excluded as they may develop transient paresthesias due to hyperglycemic neuropathy.
- Patients in whom cause of neuropathy, other than diabetes was obvious.

Ninety patients were selected with age more than 30 years and less than 60 years and fulfilling the criteria laid down for selection as judged by history, detailed clinical examination and necessary investigations. These were divided in three groups **A**, **B** and **C** (each with 30 patients) comparable for age, sex, weight and height. **Group A** was given Imipramine (Tofranil) starting in a dose of 25 mg at night and gradually increasing to 75 mg at night (Increasing 25 mg every 5 days). **Group B** received Carbamazepine (Tegretol) in a dose that was gradually built up to 200 mg thrice daily. **Group C** applied Taramira oil locally on soles of feet and distal half of legs at night. There was a run-in period of 2 weeks during which patients were educated about diabetes, their diabetes was controlled, treatment protocol was explained and necessary investigations done.Patients were seen at 0 week, 2 weeks, 4 weeks and 6 weeks and on every visit they recorded their response on a visual analogue scale of pain intensity, having grades of pain from 0-10

Statistical analysis: The results regarding the effects of Imipramine, Carbamazepine and Taramira Oil in painful diabetic peripheral neuropathy were analyzed by comparing the variables using statistical package for social sciences (SPSS). ANOVA test was applied to see the significance of relationship between pain intensities of the three treatment groups at 0, 2, 4 and 6 weeks. Chi-square test was applied to see the significance of relationship of ages of patients and duration of diabetes among three treatment groups. Chi-square test was also applied to assess the relationship of anti-diabetic treatment and sex of patients in the three treatment groups. p-value of <0.05 was taken as significant.

Limitations of study

1. This study was performed on a small scale. A similar study performed upon a large no. of patients will provide stronger evidence in favour of Taramira Oil.
2. In our study, the diagnosis of peripheral neuropathy was made by history and physical examination but not with the electrophysiological tests like nerve conduction studies.
3. No similar study using Taramira Oil was conducted in the past or recently, so we do not have data for comparison.
4. Pain is a subjective feeling and its threshold may vary from person to person which can make the recording of visual analogue scale of pain intensity as non-comparable in different patients.
1. Although Taramira Oil is freely available in the subcontinent but it may not be as easily available in other parts of the world.

RESULTS

Table 3 shows that between 1-6 years of diabetes duration, there were 3 patients in Taramira group, 6 in Carbamazepine group and 6 in Imipramine group.

Between 7-12 years of age, there were 23 patients in Taramira group, 20 in Carbamazepine group and 15 in Imipramine group. Of diabetes duration >12 years there were 4 patients in Taramira group, 4 in Carbamazepine group and 9 in Imipramine group. Mean duration of diabetes in Taramira group was 9.83 years (SD=2.57), in Carbamazepine group was 9.17 (SD=2.98) and in Imipramine group was 10.17 (SD=4.50). This difference was found to be non-significant statistically (**p**=0.212).

Table 4 shows comparison of anti-diabetic treatments in the three groups. It explains that: In Taramira group 12 patients were taking insulin while 18 were on oral hypoglycemics. In Carbamazepine group 8 patients were taking insulin and 22 were on oral hypoglycemics. In Imipramine group 7 patients were taking insulin and 23 were on oral hypoglycemics.

Table 5 shows that at the start of study at 0 week: In Taramira group, 11 patients were in the range of 1-5 of pain intensity scale while 19 were in the range 6-10. Similarly in Carbamazepine group 7 patients were in the range 1-5 and 23 were in the range 6-10. In Imipramine group 14 were in the range 1-5 and 16 were in between 6-10. Mean pain intensity of Taramira group was 6.83 (SD=2.21), of Carbamazepine group was 7.30 (SD=2.05) and of Imipramine group was 6.13 (SD=2.36). ANOVA test was applied and it was found that this difference was statistically non-significant (**p**=0.127, **F**=2.113, **df**=2)

Table 6 shows that at the end of study at 6 weeks: In Taramira group, 25 patients were in the range of 0-5 of pain intensity scale while 5 were in the range 6-10. Similarly in Carbamazepine group 26 patients were in the range 0-5 and 4 were in the range 6-10. In Imipramine group 26 were in the range 0-5 and 4 were in between 6-10. Mean pain intensity of Taramira group was 3.17 (SD=2.79), of Carbamazepine group was 2.83 (SD=2.20) and of Imipramine group was 2.67 (SD=2.45). ANOVA test was applied and it was found that this difference was statistically non-significant (**p**=0.732, **F**=0.313, **df**=2). However small difference that is evident from the means and 95% confidence interval (CI) of three groups shows that Imipramine is more effective than Carbamazepine and Carbamazepine more than Taramira Oil.

Table 7 shows that: ANOVA test was applied on the mean pain intensities of the three groups at 0 week (at the start of study). The relationship was found to be non-significant (p=0.127). ANOVA test was applied on the mean pain intensities of the three groups at 2 weeks. The relationship was found to be non-significant (p=0.3). ANOVA test was applied on the mean pain intensities of the three groups at 4 weeks. The relationship was found to be non-significant (p=0.558). ANOVA test was applied on the mean pain intensities of the three groups at 6 weeks. The relationship was not found to be significant (p=0.732)

Table 1: Relationship of age in three treatment groups

Age	**Taramira Oil**	**Carbama zepine**	**Imipramine**	**Total**
30-39	5(16.7%)	3(10%)	6(20%)	14(15.6%)
40-49	7(23.3%)	13(43.3%)	8(26.7%)	28(31.1%)
50 & above	18(60%)	14(46.7%)	16(53.3%)	48(53.3%)
Mean age	50.33	47.40	49.60	49.11
Std. dev.	8.33	7.52	8.72	8.21

Pearson Chi-Square value= 3.714 Degree of freedom (df)= 4 p-value= 0.446 (not significant)

Table 2: Comparison of sex in different groups

Gender	**Taramira Oil**	**Carbama zepine**	**Imipramine**	**Total**
Male	14(46.7%)	16(53.3%)	15(50%)	45(50%)
Female	16(53.3%)	14(46.7%)	15(50%)	45(50%)

Pearson Chi-Square value= 0.267, Degree of freedom (df)= 2, p-value= 0.875 (not significant)

Table 3: Relationship of duration of diabetes among three groups

Duration of diab. in years	**Taramira Oil**	**Carbama zepine**	**Imipramine**	**Total**
1-6	3(10%)	6(20%)	6(20%)	15(16.7%)
7-12	23(76.7%)	20(66.7%)	15(50%)	58(64.4%)
13 & aove	4(13.3%)	4(13.3%)	9(30%)	17(18.9%)
Mean duration	9.83	9.17	10.17	9.72
Std. dev.	2.57	2.98	4.50	3.44

Pearson Chi-Square value= 5.831, Degree of freedom (df)= 4, p-value= 0.212 (not significant)

Table 4: Anti-diabetic treatment in different groups

Treatment	**Taramira Oil**	**Carbama zepine**	**Imipra-mine**	**Total**
Insulin	12(40%)	8(26.7%)	7(23.3%)	27(30%)
OHGs	18(60%)	22(73.3%)	23(76.7%)	63(70%)

Pearson Chi-Square value= 2.22, Degree of freedom (df)= 2, p-value= 0.329 (not significant)

Table 5: Comparison of pain intensity among three groups at 0 week

Pain scale	Taramira Oil	Carbama zepine	Imipra-mine	Total
1-5	11(36.7%)	7(23.3%)	14(46.7%)	32(35.6%)
6-10	19(63.3%)	23(76.7%)	16(53.3%)	58(64.4%)
Mean scale	6.83	7.30	6.13	6.76
Std. dev.	2.21	2.05	2.36	2.24

Pearson Chi-Square value= 3.58, Degree of freedom (df)= 2, p-value= 0.127 (not significant)

Table 6: Comparison of pain intensity among three groups at 6 weeks

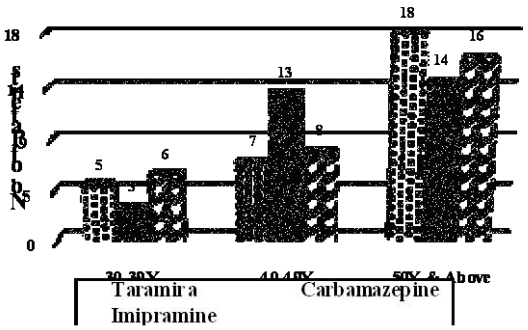
Pain scale	Taramira Oil	Carbama zepine	Imipra-mine	Total
0-5	25(83.3%)	26(86.7%)	26(86.7%)	77(85.6%)
6-10	5(16.7%)	4(13.3%)	4(13.3%)	13(14.4%)
Mean scale	3.17	2.83	2.67	2.89
Std. dev.	2.79	2.20	2.45	2.47
Std. error	0.51	0.40	0.45	0.45
95% CI	2.15-4.19	2.03-3.63	1.77-3.57	---

(CI= confidence interval), Pearson Chi-Square value= 0.180, Degree of freedom (df)= 2
p-value= 0.732 (not significant)

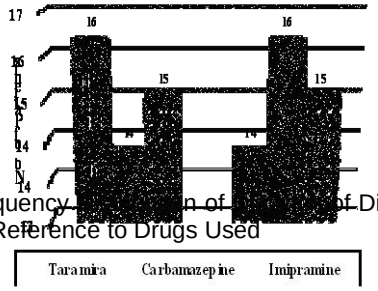
Table 7: Comparison of changes in pain intensity throughout the study among three drug groups

Weeks	Mean Pain Intensity Grade			Anova
	Taramira Oil	Carbamaze-pine	Imipramine	
0	6.83	7.30	6.13	F statistics =2.113 df =2 p =0.127
2	4.47	4.53	3.67	F statistics =1.220 df =2 p =0.3
4	3.40	3.37	2.80	F statistics =0.588 df =2 p =0.558
6	3.17	2.83	2.67	F statistics =0.313 df =2 p = 0.732

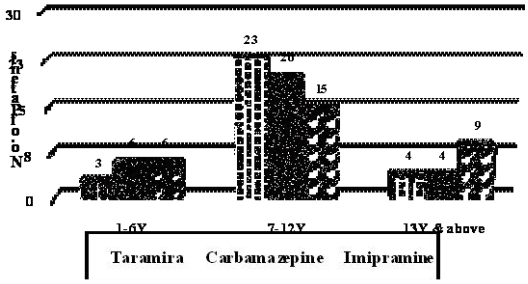
Graph I. Frequency Distribution of Ages of the Patients with Reference to Drugs Used



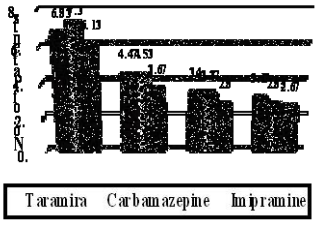
Graph II. Frequency Distribution of Gender of Patients with Reference to Drugs Used



Graph III. Frequency Distribution of Duration of Diabetes of Patients with Reference to Drugs Used



Graph IV. Frequency Distribution of Patients with Mean Grades of Neuropathic Pain Index and Drug Used



DISCUSSION

Varying estimates of the prevalence and incidence of clinically significant neuropathy in diabetic patients exist, ranging upto 60%. Subnormal electrophysiological testing can be shown in almost 100% of diabetics, although in many of these patients the neuropathy is subclinical. The most prevalent form of diabetic neuropathy is predominantly sensory neuropathy. Symptoms may be mild or absent and the presence of neuropathy is detected by clinical examination. When symptoms are present they are usually characterized by the insidious onset of paresthesias. Pain may also be present and can be disabling. The onset is usually subacute involving the distal aspects of lower extremities. The pain is variously described by the patients as sharp, stinging, tearing, stabbing, shooting, burning, crushing, deep aching or gnawing. Although not invariably, pains typically intensify at night, with resultant insomnia. There may be hyperesthesia of the skin such that contact with clothes or bed sheets is intolerable. These painful symptoms can last for many years and severely impair the quality of life of affected patients.

Patients and practitioners alike often view this challenging disorder as incurable. A broad spectrum of therapeutic alternatives and physiologic approaches to this complex clinical problem are available. Yet there is no universally accepted method of treating it. Careful assessment and rational approach based on the nature and location of pain will lead to success. Commonly used systemic drugs in this regard include tricyclic antidepressants, anticonvulsants, aldose reductase inhibitors and counter-irritants. These all have been used with variable efficacy.

The results of this study support our hypothesis and reveal that Taramira Oil, acting as a counter-irritant, is very effective in relieving the symptoms of painful diabetic peripheral neuropathy. This study also helps us in re-evaluating the effects of systemic drugs in neuropathic pain.

This is an original study and no similar study has been conducted in the past. However we know that different counter-irritants have been used for the treatment of neuropathic pain of diabetes, especially capsaicin that has been used for centuries to remedy pain. The striking feature of our study is that no significant statistical difference was found in the efficacy of systemic drugs and Taramira Oil in relieving the painful symptoms of diabetic peripheral neuropathy thus indicating that Taramira Oil can be used as an alternative treatment option having advantages of cost effectiveness and free of systemic adverse effects.

In our study we compared the effects of Imipramine, Carbamazepine and Taramira Oil by recording the visual analogue scale of pain intensity on every visit. The mean pain intensity scale at the start of the study did not show any significant difference among three groups (p= 0.127). Similarly no significant statistical difference was found in the mean pain intensity scale of three groups at each follow up visit uptill the end of study (at 6 weeks p=0.732). This shows at least equal, if not greater, efficacy of Taramira Oil in relieving the pain of diabetic peripheral neuropathy.

In our study relationship between age, gender, duration of diabetes and anti-diabetic treatment of three groups was also assessed and each was found to be statistically non-significant.

CONCLUSION

1. Locally applied counter-irritant Taramira Oil is equally effective to systemic drugs imipramine and carbamazepine in the treatment of painful diabetic peripheral neuropathy without producing any significant undesirable local effects.
2. Orally used imipramine and carbamazepine are a good treatment option in painful diabetic peripheral neuropathy, although they may produce a number of systemic side effects and are also not cost-effective.

RECOMMENDATIONS

It is recommended that a study should be carried out to compare the beneficial effects of Tara Mira Oil and already proved efficacious drug Capsaicin in the treatment of painful diabetic peripheral neuropathy to choose one most beneficial, safe and cost-effective approach to treat this troublesome complication of diabetes mellitus.

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