ORIGINAL ARTICLE

COMPARISON OF TOPICAL CAPSAICIN AND TOPICAL TURPENTINE OIL FOR TREATMENT OF PAINFUL DIABETIC NEUROPATHY

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Background: Diabetes Mellitus is a pandemic of the modern era owing to our rapidly deteriorating lifestyle. Painful diabetic neuropathy is one of the costliest and disabling complications of diabetes mellitus. No single treatment exists to prevent or reverse neuropathic changes or to provide total pain relief. Topical Capsaicin and Turpentine Oil are found to be effective in treatment of painful diabetic neuropathy. **Methods:** Patients of either gender with ages between 18 and 70 years having painful diabetic neuropathy already taking one oral drug for painful neuropathy and treatment for diabetes mellitus and an HbA1C less than 8.5% were included while Pregnant or lactating mothers, patients with chronic liver disease and patients with renal insufficiency (creatinine >3.0 mg/dl) and peripheral arterial disease were excluded from study. Patients were randomly divided into two groups (A & B) using computer generated random number table. Group A was given topical application of capsaicin while Group B was given topical application of commercially available turpentine oil over painful site on feet. **Results:** 300 patients were equally divided in two groups. The patients in group A had a Visual Analog Pain Score of 7.91±5.10 at baseline and 5.10±1.343 after 3 months of treatment (*p*-value 0.0001). The patients in group B had a Visual Analog Pain Score of 7.83±1.012 at baseline and 5.20±1.187 after 3 months of treatment (*p*-value 0.0001). Chi Square test was applied to compare efficacy of both groups. It was noted that 71 (53%) had efficacy in group A and 63 (47%) had efficacy in the group B but the difference was not statistically significant. (*p*-value=0.399). **Conclusion:** It has been concluded that turpentine oil is effective in managing diabetic neuropathic pain similar to capsaicin cream.

Keywords: Diabetes Mellitus; Painful diabetic neuropathy; Capsaicin; Turpentine oil

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INTRODUCTION

Diabetes Mellitus is a pandemic of the modern era owing to our rapidly deteriorating lifestyle.[1] The incidence of diabetes mellitus is continuously rising and it has reached 422 million worldwide in 2014. The worldwide prevalence of diabetes has reached up to 8.5% in 2014.[2] Diabetes Mellitus leads to a number of complications encompassing macrovascular complications (Myocardial infarction, stroke and peripheral vascular disease) and microvascular complications (Nephropathy, retinopathy and neuropathy).[3] All these complications give rise to considerable impairment in quality of life of diabetic patients.[4]

Painful diabetic neuropathy is one of the costliest and disabling complications of diabetes mellitus. Poor glycaemic control is leading to a rising incidence of painful diabetic neuropathy.[5]Almost one third of diabetic population suffers from painful diabetic neuropathy.[6] A UK study reported prevalence of painful diabetic neuropathy around 21%.[6] However, it is different in different countries depending upon the strictness of glycaemic control.

Painful diabetic neuropathy usually exhibits as a glove and stocking distribution of symptoms with escalation at night time. Its spectrum ranges from pins and needles sensations to burning, stabbing or electric like shock sensation which can be intermittent or unremitting. Allodynia is a painful sensation in response to non-obnoxious stimuli which shows hypersensitivity response of nociceptive receptors. Stimuli as mild as touch of clothing can give rise to excruciating pain. The pain is usually worse at night and disturbs sleep, causing disruption of activities during the day thereby impacting their employment and social life. In extreme cases, there can be loss of appetite resulting in anorexia known as "diabetic neuropathic cachexia."[7]

No single treatment exists to prevent or reverse neuropathic changes or to provide total pain relief. Treatment of PDN is based on three major approaches: intensive glycaemic control and risk factor management, treatments based on pathogenetic mechanisms, and symptomatic pain management. Clinical guidelines recommend pain relief in PDN through the use of antidepressants such as amitriptyline and duloxetine, the γ-aminobutyric acid analogues gabapentin and pregabalin, opioids and topical agents such as capsaicin.[8]

Capsaicin is an alkaloid derived from red chilli peppers and topical application has been found to be effective in PDN. Capsaicin is a highly

selective and potent exogenous agonist for the TRPV1 receptor whose persistent activation results in intracellular calcium sequestration resulting in depletion of neurotransmitters of nociceptor cell membranes. It also inhibits cellular mitochondrial respiration and depletes substance P which is an important mediator of pain across pain carrying small C fibers.[9] Capsaicin has been used as topical analgesic for neuropathic pain for a very long time.

Turpentine Oil has been observed to be used as safe topical analgesic for relief of neuropathic pain. It has been approved by FDA as an over the counter medicine for topical application as a skin protectant drug.[10] It causes side effects only when used orally or inhaled preparation.[11] A study by Russian scientist found turpentine oil to be effective in treatment of distal diabetic polyneuropathies.[12] Turpentine, whose major constituents are the terpines pinene and camphene are derives from pine trees and is among the essential oils used as soothing agents.[13] Scanty data is available regarding its role in treatment of painful diabetic neuropathy. No data is present regarding its mechanism of action. There are no studies in which a comparison has been made between capsaicin and turpentine oil for painful diabetic neuropathy treatment. Physicians need a better medicine addition in their arsenal to combat painful diabetic neuropathy and this study has been done to evaluate and compare the efficacy of these two safe and cost effective topical medications.

MATERIAL AND METHODS

It was a randomized Controlled Trial done at Department of Endocrinology and Metabolism, Services Hospital, Lahore for duration of 6 Months (from February to July 2016). Total 300 patients were enrolled in study. Sampling Technique was non-probability consecutive sampling. Patients of both genders with ages between 18 and 70 years having painful diabetic neuropathy already taking one oral drug for painful diabetic neuropathy with stable doses for last 3 months in addition to treatment of diabetes mellitus (Either oral medications, Insulin or combination of oral medication and insulin) and an HbA1C less than 8.5% were included in study.

Pregnant or lactating mothers, patients with chronic liver disease, patients having peripheral vascular disease and patients with renal insufficiency (creatinine >3.0 mg/dl) were excluded from study. Informed consent was taken from each participant of the study. Patients were randomly divided into two groups (A & B) using computer generated random number table. Treatment for diabetes mellitus was tailored to keep blood sugar levels within target. Group A was given topical application of capsaicin (Capcidol ® Cream containing natural capsicum Extract 0.075% w/w). Group B was given topical application of commercially available turpentine oil over painful site on feet. Patients were advised to apply both topical applications at painful site and don't wash it for 30 minutes after application. A baseline visual analogue pain score was established at the start of treatment. Patients were called for follow up at 1st, 2nd and 3rdmonths after starting treatment and asked for pain relief using a visual analogue scale as shown in figure-1.

Diabetes Mellitus was defined as fasting blood sugar more than 126 mg/dl or 2 hours postprandial blood sugar more than 200 mg/dl as measured on two separate occasions and patients taking treatment for diabetes.

Primary outcome measure was significant reduction in pain on visual analogue scale. A 3-point reduction in pain on visual analogue scale for pain was considered significant as shown in figure-1.

Data was collected through self-conducted interviews using a standardized Performa by investigators. Information comprised age, gender, address, contact number, HbA1C at start of treatment, visual analogue pain score at baseline, 1st, 2nd and 3rd month after starting treatment. All the collected information was transferred to SPSS version 20 and analysed. Mean and standard deviation were calculated for all quantitative variables like age, HbA1C at baseline, visual analogue pain score at baseline, 1st, 2nd and 3rd month after starting treatment. Frequency and percentages were calculated for all qualitative variables like gender. Efficacy was compared in both groups using chi square test. The *p*-value of <0.05 was taken as significant. Independent sample t test was applied to see efficacy of treatment in group A and group B. *p* value of <0.05 was taken as significant.

RESULTS

Overall 521 patients were screened and 300 patients were enrolled in the study after screening for inclusion criteria. 150 patients were put in group A (receiving Capsaicin) and 150 patients were put in group B (receiving Turpentine oil). Demographic and baseline clinical characteristics were generally similar across treatment groups. (Table-1)

The patients in group A had a Visual Analog Pain Score of 7.91±5.10 at baseline and 5.10±1.343 after 3 months of treatment (*p*-Value 0.0001). The patients in group B had a Visual Analog Pain Score of 7.83±1.012 at baseline and 5.20±1.187 after 3 months of treatment (*p*-Value 0.0001). Chi Square test was applied to compare efficacy of both groups. It was noted that 71 (53%) had efficacy in group A and 63 (47%) had efficacy in the group B but the difference was not statistically significant. (*p*-value=0.399).

Table-1: Demographics of the Study Population

	Group A	Group B
Age	49.65±11.821	47.21±11.135
Gender		
Male	91 (60.7%)	79 (52.66%)
Female	59 (39.4%)	71 (47.33%)
Mean Level of HbA1C	7.93±0.325	8.12±0.215
Body Mass Index	29.47±4.342	30.32±3.996
Duration of Diabetes	12.68±4.248	13.97±4.362
Type of therapy		
Insulin	17 (11.33%)	15 (10%)
Oral Hypoglycaemic	78 (52%)	92 (61.33%)
Combination therapy	55 (36.66%)	43 (28.66%)
Type of Diabetes Mellitus		
Type 1 Diabetes Mellitus	17 (11.3%)	15 (10%)
Type 2 Diabetes Mellitus	132 (88.7%)	135 (90%)
Duration of painful diabetic neuropathy	6.99±3.842	7.21±3.542

Table-2: Comparison of efficacy in the both groups

		Groups		Total
		A	B	
Efficacy	Yes	71 (53%)	63 (47%)	134 (100%)
	No	70 (48%)	76 (52%)	146 (100%)
Total		141 (50.3%)	139 (49.7%)	280 (100%)
Chi Square value		0.710		
***p*-value**		0.399		

Table-3: Paired and independent sample *t*-test for efficacy in both groups

Visual Analog Pain Score	Group A n=150	Group B n=150	Independent sample *t* test
At Baseline	7.91±5.10	7.83±1.012	0.608
After 3 months of treatment	5.10±1.343	5.20±1.187	0.501
Reduction in Visual Analog Pain Score	2.81±1.021	0.496±0.190	
Paired sample *t*-test (*p* value)	0.0001	0.0001	

DISCUSSION

Painful diabetic neuropathy is a disabling condition affecting 21% of all patients with diabetes mellitus.[6] There is a broad range of drugs available for treatment of painful diabetic neuropathy like Pregabalin, Gabapentin, Tricyclic antidepressants, SSRIs, Conventional antiepileptic drugs and Topical applications. It is agreed upon that there is no single most effective therapy for its treatment and there is often need for combination therapy as monotherapy often proves ineffective.[9] There is a great scarcity of comparative studies for the drugs used in treatment of painful diabetic neuropathy.[14] There is no study available comparing the efficacy of topical applications capsaicin and turpentine oil.

This was a small-scale study including only 300 patients of painful diabetic neuropathy conducted at a specialized diabetic centre. The study concluded that capsaicin and turpentine both are very effective in alleviating the symptoms of painful diabetic neuropathy significantly when given adjuvant to pregabalin and there was no significant difference between the efficacy of two topical applications on comparison.

Capsaicin has long been studied in treatment of painful diabetic neuropathy. In one study conducted by Tandan R *et al*., showed that mean reduction in visual pain score with capsaicin treatment was 44.6%. A burning sensation at the application site was noted by some subjects but both its magnitude and duration decreased with time. In the present study, it was demonstrated that significant reduction in visual analogue pain score occurred in 51% of subjects which is very similar to the results of Tandan R *et al*.[15]

Capsaicin study group conducted a study evaluating the efficacy of capsaicin in treatment of painful diabetic neuropathy and found out that capsaicin proved to be effective in alleviating pain symptoms of painful diabetic neuropathy with a reduction of 69.5% in visual analogue pain score at the end of 8 weeks treatment with capsaicin. Capsaicin was applied 4 times daily for a period of 8 weeks. It was significantly effective than the vehicle cream used in parallel. The results are similar to our study which demonstrated a similar efficacy of 51% with capsaicin in treatment of painful diabetic neuropathy along with pregabalin.[16]

A study conducted by Kiani J *et al*., compared the topical applications of amitriptyline 2% and capsaicin 0.75% and found out that 50% pain reduction taken as significant was achieved in 22 (43.1%) and 19 (37.3%) of patients with amitriptyline and capsaicin, respectively (p=0.545). the results of capsaicin arm were similar to our results of 51% efficacy in capsaicin arm.[17]

Turpentine oil is a commercially available essential oil. Its constituents are terpines pinene and camphene which have been used for treatment of several pain conditions. While and yellow turpentine baths used by Russian scientists in diabetic patients produced positive effects on neuropathic pain and several other parameters. Though no other study has been conducted demonstrating its efficacy in painful diabetic neuropathy.[13]

A study by Russian scientists studied the positive effects of turpentine oil on functional state of the neuro-muscular apparatus in patients with distal diabetic polyneuropathies.[12]

Turpentine oil is a commercially available product which is very common and cost effective. It will prove to be a very important treatment modality in medicine arsenal of local physicians dealing with painful diabetic neuropathy which has always proven to be a resistant problem to various treatments. Given the chronicity and irreversibility of the condition, it is very difficult for poor

population of Pakistanis to take these costly treatments for longer duration of time.

Keeping in view, the small sample size of the study and the scarcity of data on the subject especially with turpentine oil, large scale randomized controlled studies are needed to convincingly establish the efficacy of these applications and to compare the efficacy of these medications.

CONCLUSION

This study demonstrates that turpentine oil is effective in managing diabetic neuropathic pain similar to capsaicin cream. Treatment with capsaicin and turpentine oil is safe and free of side effects associated with systemic therapies. Further studies are required to confirm the efficacy of topical application of capsaicin and turpentine oil as a treatment of Painful diabetic neuropathy.

AUTHORS' CONTRIBUTION

UM: Principal Investigator. ZA: Statistical analysis and data collection. Z: Statistical Analysis

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