Research Article

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THE USE OF TOPICAL *CITRULLUS COLOCYNTHIS* IN TREATMENT OF PAINFUL DIABETIC NEUROPATHY: A PILOT INTERVENTIONAL STUDY

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ABSTRACT

Topical *Citrullus colocynthis* formulations are used as botanical treatment for painful diabetic neuropathy in Asian countries. This pilot study aimed to evaluate the safety and efficacy of topical formulation of *Citrullus colocynthis* fruit extract in treatment of painful diabetic neuropathy. The study was designed as a prospective interventional case series. Eight adults with clinical diagnosis of painful diabetic neuropathy confirmed by electrodiagnosis received oil-based topical formulation of *Citrullus colocynthis* fruit extract twice daily for three months. The patients were evaluated before and after the intervention in terms of Neuropathic Pain Scale, Electrodiagnostic findings and reported adverse reactions after three months. Mean neuropathic pain scores reduced significantly three months after the intervention. Significant small size improvements were documented in some of electrodiagnostic findings. No local or systemic adverse effects were reported. More studies with randomized placebo-controlled design are recommended for meticulous evaluation of the effects of topical *Citrullus colocynthis* in treatment of painful diabetic neuropathy.

Keywords: Diabetes, Painful Diabetic Neuropathy, *Citrullus colocynthis*, Complementary and Alternative Medicine, Herbal Medicine, Traditional Persian Medicine

INTRODUCTION

Diabetes Mellitus is one of the most prevalent and serious metabolic diseases in the world which is predicted to increase dramatically. It is estimated that 347 million people worldwide are afflicted with diabetes with a prevalence of 6.4 %[1] which has an increasing pattern[2]. The prevalence of Diabetes Mellitus among various countries ranges from 1 % - 30 %, and it is higher in the developed countries compared with the developing countries[3]. Diabetes is frequently associated with long-term complications with macrovascular and microvascular origin. Diabetic neuropathy is one of the most common complications of diabetes mellitus. It is the most common neuropathy[4]; it is estimated that about 50 percent of patients with diabetes mellitus will eventually develop some form of neuropathy. A community-based study of 15,692 patients with Diabetes Mellitus showed that 49 % of them had clinical neuropathy, and of these 21 % showed painful symptoms[5]. Painful diabetic neuropathy can have a serious impact on the patients' quality of life. This burden is a result of moderate to high intensity pain, sleep disturbance, polypharmacy, health resources use, activity limitation, and severe depression in some cases[6]. Oxidative stress plays an important role in pathogenesis of diabetic neuropathy[7]. In addition, hyperglycemia causes oxidative stress in the peripheral nervous system that can lead to the development of diabetic neuropathy. Optimal glucose control is the most important preventive option for diabetic neuropathy[8]. However, the role of glycemic control in the diabetic neuropathy is thought to be insufficient and uncertain[9]. The most therapeutic efforts on painful diabetic neuropathy focused on pain control. The pharmacological treatments for painful diabetic neuropathy includes a number of antidepressants (e.g. amitriptyline, duloxetine and venlafaxine), as well as anticonvulsants (e.g. pregabalin and sodium valproate). Topical agents such as capsaicin cream, lidocaines patch and isosorbide dinitrate topical spray has also been tried, showing some uncertain benefits[10]. Previous studies mainly focused on pain control rather than natural course of the painful diabetic neuropathy. Aldose reductase inhibitors are investigated as secondary preventive measures for delaying this course. Even though promising effects have been shown in some studies, larger recent evaluations showed a lack of significant benefits[11]. *Citrullus colocynthis*, commonly known as the colocynth, bitter apple, bitter cucumber, dessert gourd, egusi, or vine of Sodom is a dessert vine plant that has been traditionally used for various medicinal purposes in Persian, Indian and in Chinese traditional medicine[12]. In previous studies, *Citrullus colocynthis* has shown anti oxidative, anti-inflammatory, antiulcerogenic and anesthetic properties[13]. Its simultaneous antioxidative and anesthetic effects make it a potential herbal agent for treatment of painful diabetic neuropathy. This pilot study's purpose was to evaluate the

effect of topical formulation from *Citrullus colocynthis* for treatment of painful diabetic neuropathy.

MATERIALS AND METHODS

Study Design and Patient Selection

This study was designed as a prospective interventional case series. Eight patients attending the Diabetes Clinic of the Shiraz University of Medical Sciences between October and December 2013, with a clinical diagnosis of painful diabetic neuropathy of the lower extremities for a period of three months or more were included in our study. The clinical diagnosis was confirmed by means of an electrodiagnostic study. Other inclusion criteria included controlled diabetes (70 < FBS < 130 and 2 hppG < 180) and age of more than 18 years. Exclusion criteria in this study were patients with other diseases causing lower extremity pain, such as peripheral vascular disease and radiculopathy, history of allergic dermatitis, diabetic foot ulcers, and current use of other treatments for painful diabetic neuropathy.

Intervention

The Topical formulation from *Citrullus colocynthis* was made according to the traditional product instruction. No change was made in production method because it was important to evaluate the efficacy of the same product available in local market as used by patients. *C. colocynthis* dry fruit was bought from Tehran local market and its identity was verified by Dr. Zarshenas, Ph.D. The bought *C. colocynthis* was collected from Southern Iran. Voucher sample (voucher specimen No. PM 776) has been kept at the herbarium Shiraz University of Medical Sciences. An aqueous extract of dry *Citrullus colocynthis* fruit was boiled in sesame oil with gentle heat for one hour. After evaporation of water phase, the remained *Citrullus colocynthis* extract in sesame oil was filtered and kept in glass bottles. All patients received 2cc of this oil-based topical formulation of the *Citrullus colocynthis* fruit extract twice daily for three months. The topical formulation was applied on the plantar and dorsal surface of both feet.

Outcomes

The patients were evaluated before and after the intervention in terms of (1) Neuropathic pain scale (eleven point numeric rating-scale after one and three months), (2) Electrodiagnostic criteria of lower extremities including:

- NCV of common peroneal nerve (CPN)
- NCV of tibial nerve
- Distal latency of superficial peroneal nerve (SPN)
- Distal latency of sural nerve
- Sensory amplitude of SPN
- Sensory amplitude of sural nerve
- Motor amplitude of CPN
- Motor amplitude of tibial nerve

All electrodiagnostic studies were done by one operator (Dr Kaynoush Homayouni, physiatrist) with the same device ("MEDLEC SYNERGY VIASIS" electromyography device) between 6-8 pm in 23-25 ^{0}C room temperature maintained by air conditioner. The patients were also informed to report any observed adverse reaction from the oil. According to the study design (one arm interventional case series), no randomization, allocation and blinding were made. Wilcoxon Signed Ranks test was used for statistical comparison of the means before and after the intervention. A *p*-value of less than 0.05 was considered significant.

Ethical Approval

This study was approved by the Ethics Committee of the Shiraz University of Medical Sciences (SUMS) (SUMS Ethics code: CT-9377-7007). Protocols were in accordance with the Declaration of Helsinki.

RESULTS

All the patients received defined intervention for a three month period and were analyzed for outcomes, with no loss of follow up. The enrolled patients had a mean age of 54.75 ± 5.51 years (four male and four female). The mean durations of Diabetes Mellitus and symptoms of painful diabetic neuropathy were 12.25 ± 4.89 and 2.06 ± 1.07 years, respectively. Among the different types of unpleasant sensations reported due to painful diabetic neuropathy, a burning foot sensation was the most prevalent symptom. Detailed information on patients' basic characteristics is summarized in Table 1. Mean neuropathic pain scores reduced significantly one month (P = 0.017) and three months (P = 0.018) after the intervention. (Figure 1) Significant improvements were documented in nerve conduction velocity and motor amplitude of common peroneal and tibial nerves. In addition, the distal latency of sural nerve was significantly improved after three months. Conversely, no significant changes were observed in distal latency of superficial peroneal nerve and sensory amplitude of sural nerve (Table 2). No local or systemic adverse effects were reported. However, three patients complained of the greasy sensation due to oil based formulation.

DISCUSSION

This pilot study showed the possible significant effects of topical formulation from *Citrullus colocynthis* fruit extract on decreasing the pain in patients with painful diabetic neuropathy. Some potential effects were also observed in electrodiagnostic findings of these patients. Analgesic and antioxidative properties of *Citrullus colocynthis* can partially describe the observed findings[13]. Multiple animal and human studies have investigated the antidiabetic properties of *Citrullus colocynthis* with beneficial effects[14-16], but no report is found on its direct effect on diabetic neuropathy. More mechanistic studies should be performed to clarify the exact pathophysiological pathway for the observed effects in this pilot study. There are also multiple preclinical and clinical reports on other herbal formulations used in painful diabetic neuropathy[17-19].

Table 1: Basic characteristics of patients with painful diabetic neuropathy (N = 8)

Patient number	Age (years)	Sex	BMI	Duration of diabetes (years)	Duration of PDN symptoms (years)	Other diabetic vascular complications	Risk factors	Type of current diabetes medication	Type of unpleasant sensation
1	51	♂	25.7	15	3	-	H/L	Met, Sul, Thi	P, B, D
2	55	♂	26.4	12	1	-	H/L	Met, Sul, Thi	B, D
3	46	♂	26.1	12	3	M/A	H/L	Met, Sul	B, S
4	59	♀	25.9	9	4	-	Sm	Met, Sul	P, N, S
5	60	♀	26.2	20	1	-	H/L	Met, Thi	P, B, N, D
6	52	♀	25.6	13	2	-	HTN, H/L	Met, Sul	P, B, N, D
7	51	♀	32.5	2	1	-	HTN, Sm	Ins	B, T, S
8	64	♂	28.7	15	1.5	-	H/L	Ins, Met, AGI	N, S

♂: Male, ♀: Female, M/A: Micro-Albuminuria, H/L: Hyper-Lipidemia, Sm: Smokig, HTN: Hypertension, Met: Metformin, Sul: Sulfonylurea, Thi: Thiazolidinediones,AGI: Alpha-glucosidase inhibitor, Ins: Insulin, P: Pain, B: Burning, T: Tingling, N: Numbness, S: Superficial, D: Deep

Table 2: Electro diagnostic findings of patients with painful diabetic neuropathy before and after treatment with topical *C. colocynthis* (N = 8)

Electro diagnostic study	Mean ± SD (Before)	Mean ± SD (After)	P value
NCV- Common Proneal Nerve (m/sec)	44.87 ± 4.38	46.37 ± 4.35	**0.041**
NCV- Tibial Nerve (m/sec)	41.75 ± 3.37	45.35 ± 5.63	**0.018**
Distal latency- Superficial Proneal Nerve (millisecond)	2.80 ± 0.33	2.80 ± 0.33	0.140
Distal Latency- Sural Nerve (millisecond)	3.25 ± 0.39	3.00 ± 0.43	**0.017**
Sensory Amplitude- Sural Nerve (microvolt)	12.12 ± 6.53	13.00 ± 5.99	0.109
Motor Amplitude- Common Proneal Nerve (microvolt)	1.55 ± 1.08	1.91 ± 1.16	**0.018**
Motor Amplitude- Tibial Nerve (microvolt)	2.17 ± 1.03	2.78 ± 0.80	**0.016**

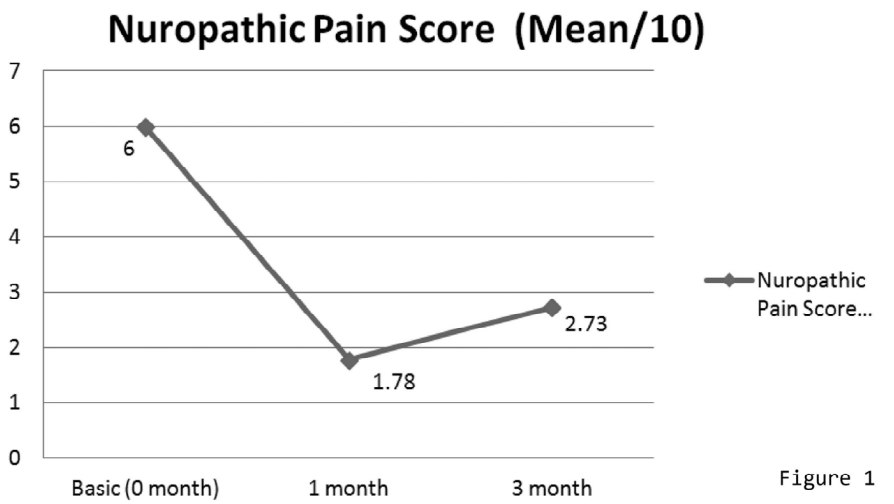

Figure 1: Mean neuropathic pain score of patients with painful diabetic neuropathy before and after treatment with topical *C. colocynthis* (N = 8)

Most of the reports have focused on Chinese herbs. The top most frequently used herbs were ordinally milk vetch root (*Radix astragali* seu Hedysari), sub erect spatholobus stem (*Caulis spatholobi*), peony root (*Radix paeoniae* Rubra), sichuan lovage rhizome (*Rhizoma ligustici* Chuanxiong), danshen root (*Radix salviae* Miltiorrhizae), leech (Hirudo), unprocessed rehmannia root (*Radix rehmanniae* Recens), cassia twig (*Ramulus cinnamomi*), earthworm (Lumbricus), Chinese angelica (*Radix angelicae* Sinensis), and figwort root (*Radix scrophulariae*), which were used more than 3 times in clinical studies[20]. Topical herbal formulations were also used for pain control in other neuropathies[21].

Considering the side effects of oral medications, topical formulation for pain control has many advantages in treatment of painful diabetic neuropathy. Tricyclic antidepressants and anticonvulsants are traditionally used as oral agents for pain control in painful diabetic neuropathy[22]. Several side effects are reported for these classes of medications in painful diabetic neuropathy[9].

Somnolence and dizziness are reported as the most common side effects of gabapentin and pregabalin, in addition to liver injury, is a less common complication that can lead to discontinuation of the prescribed medication[23]. Drowsiness is also a common side effect of TCAs[22]. Different topical formulations for pain control in painful diabetic neuropathy were investigated previously. Capsaicin cream as the most studied herbal topical agent for painful diabetic neuropathy has shown clinical benefit in pain control and patients' quality of life[24]. Neuronal apoptosis caused by capsaicin neurotoxicity is presumed as its mechanism for relieving the neuropathic pain[25]. Initial exacerbation of symptoms is another problem with Capsaicin[25]. No similar side effects were observed in our study. One of the most important limitations of this study was the lack of control group. The design of this study did not permit us to omit the placebo effect, which is important in subjective findings such as neuropathic pain. However, electrodiagnostic findings are less likely to be affected by placebo. Small sample size was another problem that limits generalizability of the study. However, pilot evaluation of herbal products with restricted sample size is mandatory in human studies for safety confirmation. The lack of histopathology evaluation of the patients, before and after the intervention, was due to the ethical limitations of performing nerve biopsies; this was an important defect in describing the mechanistic chain of pain control and electrodiagnostic changes in the painful diabetic neuropathy patients. The duration of the study was also short for long term evaluation of the therapeutic effects especially on nerve repair. The observed decreasing effect of the *Citrullus colocynthis* topical formulation in pain control between one and three months may be due to down regulation of receptors in its unknown therapeutic pathway. Considering the electro diagnostic findings before and after the intervention as objective outcome, more to the point and subjective evaluation of patients' pain relief was the significance of our study. This pilot interventional study showed that application of topical formulation from *Citrullus colocynthis* fruit extract could decrease the pain in patients with painful diabetic neuropathy. Some possible improvement in the electrodiagnostic findings with small size effect was also observed; this needs to be further investigated. Further studies are required with a randomized, placebo-controlled design with larger samples, for a thorough evaluation of the effects of topical formulation from *Citrullus colocynthis* in treatment of painful diabetic neuropathy.

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