Journal of Diabetes and Treatment
Sethi BK, et al. J Diabetes Treat 7: 10108.
www.doi.org/10.29011/2574-7568.0010108
www.gavinpublishers.com

OPEN ACCESS

GAVIN PUBLISHERS

Research Article

Assessment and Comparison of Safety and Efficacy between Topical Capsaicin (0.025%), Capsaicin (0.075%), and Oral Pregabalin in the Treatment of Diabetic Peripheral Neuropathy

Bipin Kumar Sethi[1], Nithin Reddy[1], Yashwanth Reddy[2], Faizuddin Ahmed[2*], Lakshmi Tejeshwini[2], Sainath Goud[2]

[1]Department of Endocrinology, Care Hospitals- Outpatient Centre, Hyderabad, India

[2]Department of Pharmacy Practice, Guru Nanak University, Hyderabad, India

[*]**Corresponding Author:** Faizuddin Ahmed, Department of Pharmacy Practice, Guru Nanak University, Hyderabad, India

Citation: Sethi BK, Reddy N, Reddy Y, Ahmed F, Tejeshwini L, et al. (2022) Assessment and Comparison of Safety and Efficacy between Topical Capsaicin (0.025%), Capsaicin (0.075%), and Oral Pregabalin in the Treatment of Diabetic Peripheral Neuropathy. J Diabetes Treat 7: 10108. DOI: 10.29011/2574-7568.010108

Received Date: 11 September, 2022; **Accepted Date:** 20 September, 2022; **Published Date:** 23 September 2022

Abstract

The International Diabetes Federation (IDF) predicts that 1 in 10 adults will suffer from Diabetes by 2030. While the primary focus of clinical professionals remains on the prevention and treatment of this metabolic disease, the chronic complications occurring with diabetes are often underestimated. One such complication is Neuropathy. Patients generally present with neuropathy of the peripheral nervous system but autonomic neuropathy is also well reported. There are limited safe treatment options available for peripheral neuropathy. According to the guidelines published by the American Diabetic Association (ADA) and the American Neurological Association (ANA), pregabalin should be considered the first line of treatment for treating Diabetic Neuropathy. With the growing use of pregabalin, there have been significantly increasing reports of adverse effects with its use; the most common being dizziness, drowsiness, and blurred vision. These adverse effects can negatively affect the patient's quality of life. Other treatment options including Gabapentin, Nortriptyline, Duloxetine, Venlafaxine, etc have a similar adverse event profile as pregabalin. Therefore, shifting the focus from the systemic route of treatment toward the topical can significantly help in treating the disease while improving the quality of life. One such topical therapy for the treatment of peripheral neuropathy is Topical Capsaicin. It is commonly available in different concentrations, much cheaper, and easy to use. This study aims to compare the safety and efficacy of oral pregabalin and the topical capsaicin ointments in two different concentrations in diabetic neuropathy patient's.

Keywords: Diabetes, Neuropathy, Pregabalin, Capsaicin, Burning feet

Abbreviations: ADA: American Diabetic Association; AIDS: Acquired Immunodeficiency Syndrome; ANA: American Neurological Association; ANOVA: Analysis of Variance; CGRP: Calcitonin Gene-related Peptide; CIDP: Chronic Inflammatory Demyelinating Polyneuropathy; CKD: Chronic Kidney Disease; DPN: Diabetic Peripheral Neuropathy; DSPN: Distal Symmetric Polyneuropathies; HIV: Human Immunovirus; IDF: International Diabetes Federation; IgA: Immunoglobulin A; IVIG: Intravenous Immunoglobulin; NCV: Nerve Conduction Velocity; NGF: Nerve Growth Factor; NMDA: N-methyl-D-aspartate; NPQ: Neuropathic Pain Questionnaire PSAT: Pain Scores After Treatment; PSBT: Pain Scores Before Treatment; QST: Quantitative Sensory Testing; SD: Standard Deviation; TRPV1: Transient Receptor Potential Vanilloid 1; USFDA: United States Food and Drug Administration.

Introduction

Diabetic Peripheral Neuropathy (DPN) is defined as the presence of signs and symptoms of peripheral nerve dysfunction occurring in people with diabetes, after excluding other causes [1]. It is the most frequent chronic complication associated with Diabetes [2]. It is a heterogeneous condition affecting different parts of the human nervous system and has different clinical presentations [3]. While many patients may present with symptoms of nerve dysfunction, about 50% may be asymptomatic [4]. Early recognition of diabetic neuropathies may help prevent further complications like a poorly healing injury to the insensate foot leading to amputations. Among different types of neuropathies, the most frequently studied are the "Distal Symmetric Polyneuropathies (DSPN)," and "Diabetic Autonomic Neuropathies" [4]. It has now been proven that patients with pre-diabetes can also develop neuropathy [5]. Due to the lack of understanding of the underlying pathophysiology leading to nerve dysfunction, there is a virtual absence of treatment strategies targeting nerve damage [4]. Hence prevention and palliative care of these chronic complications are one of the key components for sustained diabetic care.

The prevalence of symptomatic neuropathy may be as high as 21% [6], while neuropathic deficits are found on examination in up to 50% of all patients with diabetes [7]. Another study estimated that the incidence of DPN in the United States is 28% [8]. In a historical cohort study on 4,400 patients, approximately 50% of the patients developed one or the other types of peripheral neuropathies at the end of the 25th year of follow-up [9]. Depending on the population studied, the prevalence can again range between 6% to 51%. Many studies have also shown that patients with Type-II Diabetes are more prone to develop neuropathy than those with Type-I [10].

The underlying pathophysiological mechanisms involved in causing DPN are not fully elucidated, but there is a consensus that the toxic effects of hyperglycemia are a primary factor for the progression of this chronic complication of diabetes [11,12]. These mechanisms include Polyol pathway hyperactivity, Nitrosative and oxidative stress, Microvascular changes in nerve fibers, Ion channel misregulation, Microglial activation, Central nervous system sensitization and Brain plasticity involving uncontrollable glutamate release and NMDA receptor dysregulation.

Clinical presentation depends on the type of nerve fibers are primarily impaired during the neuropathic conditions, i.e. Aα fibers (Large and deep-seated) and C Fibers (Short and superficial) [13]. Large fiber impairment is associated with deep-seated pain and leads to symptoms like pricking, numbness, tingling, and ataxia [14]. There is a loss of position senses and impaired vibration perception [15]. Large fiber impairment is also associated with reflex diminution, increased risk of falling and fractures and impedes normal life [13]. There is also an impaired perception of heat, electric shocks, allodynia, and burning sensation [17]. But normal strength and reflexes are preserved [19]. Small fiber neuropathy is electro-physiologically silent [16], but can be correlated with the emerging autonomic dysfunction in the patient [17]; which can have significant morbidity [18].

The diagnosis and differential diagnosis of Diabetic neuropathy relies heavily on the patient's clinical history [20]. The American Academy of Neurology has recommended that the patient's neuropathic condition should be classified based on any one of the following parameters i.e. Symptoms in the patient, neurological examination, Nerve Conduction Velocity (NCV) study, assessment of autonomic function and, Quantitative Sensory Testing (QST) [21]. Noninvasive testing devices like Semmes-Weinstein monofilament, Rydel-Seifer tuning fork, and tactile circumferential discriminator are also used to test patient's perception and sensitivity to vibration respectively. The American Academy of Neurology has also concluded that skin biopsy can be performed on patients for diagnosis of Diabetic Polyneuropathy, specifically, the small-fibre sensory neuropathy [21].

Nonpharmacological management of the condition generally employs intensive glycemic control. The UK Prospective Diabetic study disclosed that better glycemic control is associated with improvement in vibration perception [22]. Pharmacological treatment strategies include the use of Aldose reductase inhibitors like Zenarestat and Tolrestat, α-Lipoic Acid, and Benfotiamine. Small scale studies involving the use of L-Methylfolate, Pyridoxal 50-phosphate, and Methylcobalamin in the treatment of neuropathy have yielded positive results. Administering IVIG is a choice of treatment in patients with Peripheral Diabetic neuropathy associated with antineuronal autoimmunity, CIDP or autonomic neuropathy [23,24]. It is generally considered safe except that it can cause anaphylactoid reactions in patients with IgA deficiency. Pain control is established using tricyclic antidepressants, gabapentin, tramadol, carbamazepine, capsaicin, selective serotonin reuptake inhibitors, Duloxetine and Mexiletine [25]. The USFDA has approved only two drugs for pain management in Diabetic Peripheral Neuropathy i.e.; Pregabalin and Duloxetine.

Capsaicin in the treatment of Diabetic Peripheral Neuropathy

It is a chemical compound found naturally in various types of chili peppers and is responsible for scorching and burning sensation when brought into contact with any part of the body [26]. Capsaicin and capsaicin like molecules are collectively known as capsaicinoids [27]. Different species of peppers contain different concentrations of capsaicin; ranging from 2.5 mg/g in red pepper to 60 mg/g in oleoresin red pepper [28].

Mechanism of Action: Capsaicin is a selective and highly potent agonist of the TRPV1 receptor. This receptor, when stimulated, brings about an integrated response to a stimulus like changes in temperature, pH [29], and production of endogenous lipids namely phosphatidylinositol-4,5-bisphosphate (PIP2) [30], and Diacylglycerols (DAG's) [31].

Also, the TRPV1 receptor is directly mediated by lipid endovanilloids like Anandamide, N-arachidonoyl dopamine, and lipoxygenase products of arachidonic acid such as Leukotriene B4, 12-(S) and 15-(S)- hydroperoxy eicosatetranoic acid [32]. Temperatures higher than 43°C [33], pH <6 or >8 can activate the receptor. However, the combination of both stimuli can activate it at much lower temperature and not so abnormal pH [29]. When stimulated, TRPV1 activates transiently and depolarization is mediated by the influx of Na^{+} and Ca^{+2} ions. This depolarization leads to the propagation of nerve impulse through C and Aα fibers, into the spinal cord and brain which then leads to sensations like burning, itching, stinging and numbness [29]. In contrast, exogenous agonists of the TRPV1 receptors have the potential to fully activate it and can generate a persistent biochemical response [34]. The TRPV1 receptor is unusually, highly permeable to Ca^{+2} ions (generally, calcium to sodium permeability ratio of 8:1) which further increases with prolonged capsaicin exposure (25:1) [35]. Furthermore, there is also an intracellular release of Ca^{+2} ions from the endoplasmic reticulum as TRPV1 receptors are also present on the cell organelles [36].

In addition, there is intracellular calcium-dependent calcium release [37]; which along with the above mentioned mechanisms, establish a powerful response; overburdening the local calcium sequestering mechanisms. Hence, this surcharge of Ca^{+2} results in the activation of calcium-dependent proteases [38]. These proteases act on microtubules and nerve fibers leading to their depolymerization [39]. Chloride ions are accumulated in the cells due to the abundant Ca^{+2} influxes, resulting in osmotic swelling. In addition, high concentrations of capsaicin can also inhibit mitochondrial respiration by directly competing with ubiquinone in electron chain transport; occurring at the terminals of pain receptors [40]. There is already an accumulation of mitochondria at nociceptors in response to Nerve Growth Factor (NGF) [41].

All these effects i.e. intracellular calcium accumulation, activation of proteases, depolymerization of cytoskeletal structures and inhibition of mitochondrial respiration at nociceptive terminals lead to impaired pain receptor activity for prolonged periods [42]. Subsequently, "Defunctionalization," [42,43] of nociceptors takes place with clinical characteristics of curtailed response to painful stimuli [44] which in turn is due to reduced receptor response, intracellular signaling pathways and downregulated ion channels. This phenomenon is responsible for prolonged analgesia associated with capsaicin use. It is important to understand that defunctionalization is not the same as nerve terminal degeneration. In simple terms, capsaicin results in loss of electrical activity in the nerve via downregulation of ion channel and depolarization block without axonal collapse. In contrast, nerve terminal degeneration is associated with the loss of axonal integrity [45].

Pregabalin in the treatment of Diabetic Peripheral Neuropathy

It is primarily, an anti-epileptic medication that has now been proven to be effective in the treatment of neuropathic pain associated with post-herpetic neuralgia, and diabetic neuropathy due to its neuro-modulating activity [46]. Several double-blind, controlled trials are in support of the above indications.

Mechanism of Action

The predominant mechanism through which pregabalin acts is the presynaptic inhibition of the α2β subunit of voltage-gated calcium channel which subsequently results in decreased neurotransmitter release. The specific neurotransmitters whose release is inhibited include Substance P, Glutamate and Calcitonin-gene related peptide (CGRP) [47,48]. Substance P plays a critical role in the pathophysiology of diabetic neuropathy. But now, it has also been known that there is a steady stimulation of glutamate receptors in the spinal cord of neuropathic patients [49]. Enhanced glutamate levels in the spinal cord, and consequently in the primary afferent nerves, is responsible for pain transmission and ectopic discharges from the site of nerve injury [50]. Similarly, CGRP is also known to play a role in pain generation and transmission in conditions like migraine and peripheral neuropathy [51].

Adverse effects with oral pregabalin and topical capsaicin

The majorit of clinical studies involving the use of pregabalin for the treatment of various types of neuropathic pain states have shown that dizziness, somnolence, headache, dry mouth, peripheral edema, weight gain, blurred vision, motor incoordination and ataxia are the most common side effects (occurred in 1-10% patients) even at lower doses. The intensity of these side effects is generally increased with an increased in dose and at highest prescribed dose (600 mg/day), the incidences of side effects increased with higher frequency of dizziness (70%), blurred vision (63%) and headache (31%) [9]. Hence, there is a dire need to shift our focus from systemic drug treatment of DPN, to other newer approaches like topical drug application. There have been very limited studies before which compared the efficacy of Topical Capsaicin against Oral Pregabalin in the treatment of Diabetic Peripheral Neuropathy. Certain topical formulations have also been approved for the treatment of painful DPN like Topical Capsaicin (0.025% w/w) and Capsaicin (0.075% w/w) [52]. A rare double blind controlled study compared Topical Capsaicin (0.075% w/w) with Oral Amitriptyline and it was found to be equally effective in the symptomatic treatment of DPN [53].

Materials and Methods

Study Design and Subjects

This prospective, open-label randomized controlled study was carried out in the endocrinology department of a tertiary care hospital from July 2019 to February 2020, with the approval of Institutional Ethics Committee. The study included 45 diabetic patients presenting with symptoms of diabetic peripheral neuropathy. These 45 patients were randomized into 3 groups of 15 each. Group 1 was given low concentration capsaicin (0.025% w/w) BD, group 2 was given high concentration capsaicin (0.075% w/w) BD, and group 3 was given Pregabalin 75mg BD for the pharmacological management of Diabetic Peripheral Neuropathy.

During the study period, the data which were collected are: Pain scores using The Neuropathic Pain Questionnaire (NPQ). The questionnaire had a subjective question, for which, Wong-Baker's Faces Pain Scale was used to minimize scoring bias. The subjects were assigned either of the three treatment options. After the follow-up period i.e. 8 weeks, pain scores were again assessed using the same questionnaire, and any adverse effects with the drug were taken down for statistical analysis. Reduction in the mean pain scores was taken as a measure of efficacy. The study duration was 6 months. Data were collected in the standardized data collection forms designed specifically for the study. The essential parameters necessary for fulfilling the primary and secondary objectives of the study were only recorded.

Inclusion and Exclusion Criteria

All the patients enrolled in the study were examined by the consultant endocrinologist and there records were reviewed.

Inclusion Criteria

Subjects will be included in the study based on the following criteria:

- Male or Female aged 18-70- must be ambulatory and must be consenting to participate in the study.
- The subjects should be suffering with Diabetes Mellitus and should also experience the symptoms of Diabetic Peripheral Neuropathy (DPN) in the peripheries (hands and legs).
- They should have at least one of the symptoms of DPN like Burning and pricking sensation in Hands and Feet (Palms and soles), Tingling and Numbness of the peripheries and reduced ability to feel pain, vibrations or temperature changes.

Exclusion Criteria

Subjects will be excluded from the study based on the following criteria:

- Patients below 18 or above 70 years of age, or patients who are immobile or those who aren't consenting to be a part of this study.
- Patients who are suffering with neuropathy from diseases other than diabetes mellitus; like Uremic neuropathy- common in CKD patients, Small fiber neuropathy (occurs in endocrine disorders like Hypothyroidism), Alcohol abuse, HIV/AIDS, Amyloid polyneuropathy, Heavy metal poisoning, Vasculitis, Sarcoidosis, Guillian-Barr Syndrome, Hot flushes during menopausal period, and Postherpetic Neuralgia.
- Patients who are suffering from skin rashes, erythema and other skin conditions like psoriasis, scleroderma, Steven-Johnson's syndrome, Toxic epidermal necrolysis etc., which can affect the absorption of the drug.
- Patients who are suffering from chronic and debilitating bone and joint disorders like Rheumatoid and osteoarthritis and also those involved in an accident resulting in moderate to severe bone injuries.
- Patients who have a history of taking the following medications for longer durations like Amiodarone, Cancer chemotherapeutic agents like Platinum derived compounds, Vinca alkaloids, and Paclitaxel, Antibiotics like Chloroquine, Dapsone, Isoniazid, and Nitrofurantoin [54], Anti-epileptics like Carbamazepine, Phenytoin and Phenobarbital [55], and Anti-alcohol drugs like Disulfiram. These drugs are known to cause peripheral neuropathies Figure 1.

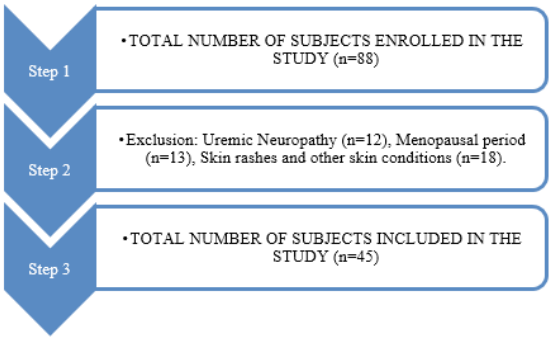

Figure 1: Subjects enrolled in the study.

Statistical Analysis

Data was analyzed using SPSS version 25.0. Normal data distribution was confirmed using Kolmogorov-Smirnoff/ Shapiro-Wilk test. Descriptive statistics were also analyzed and continuous variables presented as mean ±SD. Paired T-tests were performed individually to the three datasets to check for significance before and after therapy. ANOVA was then applied to statistically analyze

different treatment arms for hypothesis testing. The P value of <0.05 was considered statistically significant.

Results

Baseline characteristics of the study population were comparable for age, gender and diabetic medication. The normal distribution of data for individual treatment arms was confirmed using Kolmogorov-Smirnoff and Shapiro-Wilk tests. In all the three treatment groups, the P value was found to be insignificant when compared to the predetermined limit (0.05). Hence, null hypothesis was accepted i.e. the data obtained from the study population was normally distributed.

The difference in the means of pain scores before and after therapy was higher in the pregabalin group i.e. 13.266; followed by the Capsaicin (0.075% w/w) group which had a mean difference of 11.333. The lowest difference in means was for Capsaicin (0.025% w/w) group i.e. 4.866.

The P-values for all the treatment groups; after applying tests for normality; was calculated to be >0.05. Hence the null hypothesis was accepted, i.e. the data was normally distributed. The Skewness was <1 for all the three groups, indicating minimum deviation from population symmetry. Kurtosis was positive indicating standard normal distribution. Paired Student T tests were done for each treatment arm and evaluated for significance in pain scores before and after therapy. It was done to calculate the level of efficacy with different treatment options. The P value for the Capsaicin (0.025% w/w), Capsaicin (0.075% w/w) and Oral Pregabalin groups were found to be 0.003, 0.002 and <0.0001 respectively. The P values obtained were highly significant, specifically for the pregabalin group where there was a significant difference in the average mean of PSBT and PSAT [Figure 2-4]

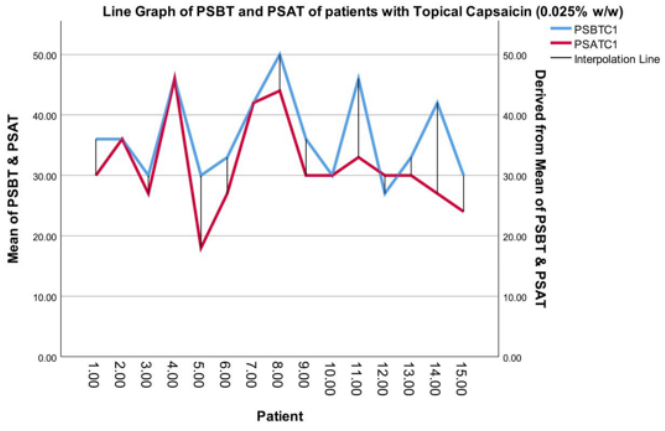

Figure 2: Line graph representing pain scores of patients before and after using Topical Capsaicin 0.025% w/w.

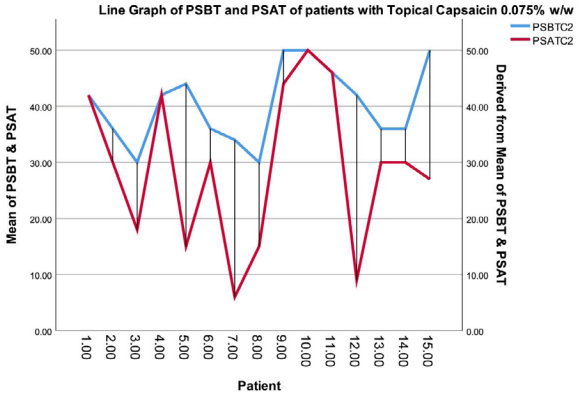

Figure 3: Line graph representing pain scores of patients before and after using Topical Capsaicin 0.075% w/w.

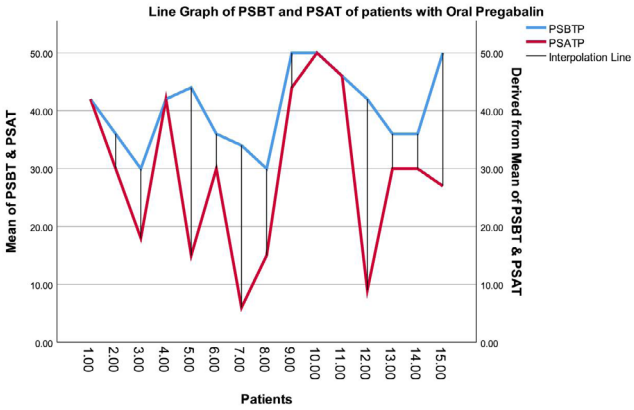

Figure 4: Line graph representing pain scores of patients before and after using Oral Pregabalin 75mg BD.

ANOVA was performed to compare efficacy between different treatment options. When the topical capsaicin (0.025% w/w) group was compared to oral pregabalin group, the P value was found to be 0.017, which indicates significance. Hence the alternate hypothesis, i.e., in this case; "There is a significant difference between the two treatment options and Pregabalin is superior to capsaicin (0.025% w/w)," was accepted. Similarly, when oral pregabalin group was compared to topical capsaicin (0.075% w/w), the P-value was found to be 0.638 i.e. there wasn't any significant difference in efficacy with both treatment options. Moreover, difference in the means of pain scores after therapy (PSAT) between the Pregabalin and capsaicin (0.075% w/w) group was minimum i.e. -1.533. Hence, it was concluded from the statistical results that high concentration topical capsaicin (0.075% w/w) was "non-inferior" to oral pregabalin in the treatment of Diabetic Peripheral Neuropathy.

Out of 15 patients in the oral pregabalin group, 5 of them reported a single and 2 of them reported two adverse effects each relating to neurocognitive deficits like somnolence, dizziness and excessive daytime sleepiness. Two patients from high concentration capsaicin (0.075% w/w) group reported a single adverse effects relating to skin irritations. Low concentration capsaicin (0.025% w/w) group didn't report any adverse effects during the course of therapy. ANOVA was performed to determine if there is any statistical significance in the occurrence of adverse effects in these groups. The p= 0.003 was calculated, concluding that there was a significant difference between the groups, and pregabalin had a higher frequency of adverse effects compared to capsaicin Tables 1-3.

Characteristics	Total (n=45)
Age (years)	45.4±6.3
Sex	
Male (%)	37.20%
Female (%)	62.8%
Mean Duration of Diabetes (Months)	9.2±4.8

Table 1: Baseline Characteristics of the study population.

Descriptive Statistics:	Value:
Capsaicin (0.025% w/w) group:	
Pain Score Before Therapy:	
Mean:	36.4667
	(Std. error= 1.83580)
Median:	36.0000
Standard Deviation:	7.11002
Pain Score After Therapy:	
Mean:	31.60000
	(Std. error= 1.96348)
Median:	30.0000
Standard Deviation:	7.60451
Capsaicin (0.075% w/w) group:	
Pain Score Before Therapy:	
Mean:	40.2667
	(Std. error= 1.77675)
Median:	42.0000
Standard Deviation:	6.88131
Pain Score After Therapy:	
Mean:	28.93333
	(Std. error= 3.61408)
Median:	30.0000
Standard Deviation:	13.99728
Oral Pregabalin group:	
Pain Score Before Therapy:	
Mean:	40.6667
	(Std. error= 2.12394)
Median:	39.0000
Standard Deviation:	8.22598
Pain Score After Therapy:	
Mean:	27.4000
	(Std. error= 1.36905)
Median:	27.0000
Standard Deviation:	5.30229

Table 2: Descriptive Statistics of pain scores from three treatment arms.

ANOVA	P-Value
1) Topical Capsaicin (0.025% w/w) vs Oral Pregabalin	0.017
2) Topical Capsaicin (0.075% w/w) vs Oral Pregabalin	0.638

Table 3: Statistical comparison of both topical capsaicin groups with oral pregabalin using ANOVA.

Discussion

Diabetic Peripheral neuropathy is one of the most common microvascular complications of Diabetes, occurring over time and is severely debilitating. They predispose the patients to foot ulcers, and loss of sense perception in muscles. The severity of Diabetic Neuropathy is regulated partly by the glycemic condition of the patient i.e. more is the patient hyperglycemic, severe is his condition. The mainstay for treatment is controlling the blood glucose levels which in turn prevent progression of nerve damage. The most irritating symptom of neuropathy is pain. Pain management in patients with diabetic neuropathy has been a challenge due to eminent progression of nerve damage.

Different drugs from various classes have been tested for symptomatic relief for the patients. Current guidelines from the American Diabetes Association and American Academy and Neurology recommend the use of Pregabalin as the first line treatment for Diabetic Neuropathy. Several randomized controlled trials have confirmed its greater efficacy over other commonly used anti-neuropathic drugs like Gabapentin, Mexiletine, Duloxetine, etc. The main drawback of the pregabalin therapy is its associated adverse effects. Many patients have somnolence, dizziness and excessive sleepiness while taking pregabalin. Work related injuries and deaths have also been associated with pregabalin

use. This is primarily due to the inability to handle and operate heavy machinery while on pregabalin. These adverse effects were common among all anti-neuropathic drugs as they are primarily neuroleptics in nature.

Hence, there is a dire need to shift the focus from oral therapy to topical therapies for the treatment of diabetic neuropathy. Several topical therapies have been approved and some are experimented for the treatment of Diabetic Peripheral Neuropathy. Among them, Topical Lidocaine gel 5% patch has been commonly used and it was considered "non-inferior," to other oral therapies. Similarly, capsaicin 8% patch has been approved for the symptomatic relief of neuropathy. Topical Amitriptyline (4%)/Ketamine (2%) gel has also been approved in some countries for use in DPN. Other experimental topical therapies include topical clonidine and topical phenytoin.

This study was conducted prospectively where patients were prescribed with oral pregabalin and topical capsaicin ointments (two different concentrations) for neuropathic pain. They were evaluated for safety and efficacy. 45 patients were evaluated in the span of 6 months, where 15 of them were prescribed with pregabalin, the other 15 with topical capsaicin (0.075% w/w) and another 15 were prescribed with topical capsaicin (0.025% w/w). As routine, the pain scores of neuropathic patients are taken down at the time of presentation and then prescribed with a medication. At follow-up i.e. 8 weeks, the patients are again asked to answer the same questions.

Data was collected directly from patient interviews and it was statistically analyzed using SPSS. The normal distribution of data was checked using the Kolmogorov-Smirnoff and Shapiro-Wilk tests. P values for all the three groups were greater than 0.05, which translates as statistically insignificant, resulting in acceptance of null hypothesis. After confirming their normality, parametric tests were rigorously applied. Firstly, Paired Sample T test was performed for individual treatment groups to know if there was any statistical difference between the pain scores before and after therapy. The P values for all the three groups was statistically significant (P for Pregabalin <0.0001, Capsaicin (0.075% w/w) = 0.002 and for Capsaicin (0.025% w/w) = 0.001). Hence it was concluded from the above results that all the three treatment options were effective in relieving pain in neuropathic patients; pregabalin being superior to both topical capsaicin groups.

The statistical significance of efficacy between the treatment groups was analyzed using Two-way ANOVA. When Pregabalin was compared with Capsaicin (0.025% w/w), p= 0.017 was calculated, which was statistically significant. This led to the acceptance of the alternate hypothesis i.e.; there was a statically significant difference between these two groups and pregabalin was superior to Capsaicin (0.025% w/w) [PSAT mean difference between Pregabalin and Capsaicin (0.025% w/w) = -4.2]. Similarly, when pregabalin was compared with Capsaicin (0.075% w/w), p= 0.638 was calculated, which is statistically insignificant. Hence, in this case, the null hypothesis was accepted and concluded that there was no significant difference between the two treatment groups. High concentration capsaicin (0.075% w/w) was found to be "non-inferior" to oral pregabalin in the treatment of Diabetic Peripheral Neuropathy.

Similarly, the frequencies of adverse events were higher with the pregabalin group than the capsaicin groups (p= 0.003). Hence, it could be concluded from this study that high concentration capsaicin is non-inferior to oral pregabalin in the treatment of Diabetic Peripheral Neuropathy. Other similar studies have also indicated that high concentration capsaicin could be effectively used in patients presenting with Diabetic Peripheral Neuropathy. The high discontinuation rates in pregabalin group was primarily due to the conventional adverse events associated with it; which were all absent with capsaicin use.

Limitations

1. This study did not take into consideration, the diabetic medication prescribed to the subjects for glycemic control. Medications with greater HBA1c reduction potential such as Sulfonyl-urea's and Insulin may have also affected the individual's neuropathic condition positively.

2. This study does not take into consideration, the conditions like Insulin Neuritis and Acute painful diabetic neuropathy- an uncommon form of Small fiber Neuropathy which subsides with glycemic control.

3. This study employs the use of a questionnaire for assessing the presenting condition and improvement of the subjects. Questionnaires sometimes yield subjective information with may lead to personal bias.

Conclusion

It is concluded from the above study that high concentration capsaicin ointments (0.075% w/w) is found to be non-inferior to oral pregabalin in the treatment of Diabetic Peripheral Neuropathy. There were not many benefits with low concentration capsaicin (0.025% w/w). Also, the incidences of adverse effects were much higher in the pregabalin group than high concentration capsaicin (0.075% w/w).

References

1. Boulton AJ, Gries FA, Jervell JA (1998) Guidelines for the diagnosis and outpatient management of diabetic peripheral neuropathy. Diabet Med J Br Diabet Assoc 15: 508-514.

2. Dianna Quan, Romesh Khardori (2021) Diabetic Neuropathy: Practice Essentials, Background, Anatomy. Medscape.

3. Sima AAF (2008) The heterogeneity of diabetic neuropathy. Front Biosci J Virtual Libr 13: 4809-4816.

4. Pop-Busui R, Boulton AJM, Feldman EL, et al. (2017) Diabetic Neuropathy: A Position Statement by the American Diabetes Association. Diabetes Care 40: 136-154.

5. Stino AM, Smith AG (2017) Peripheral neuropathy in prediabetes and the metabolic syndrome. J Diabetes Investig 8: 646-655.

6. Abbott CA, Carrington AL, Ashe H, et al. (2002) The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. Diabet Med J Br Diabet Assoc 19: 377-384.

7. Young MJ, Boulton AJ, MacLeod AF, Williams DR, Sonksen PH (1993) A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population 36:150-4.

8. Gregg EW, Gu Q, Williams D, et al. (2007) Prevalence of lower extremity diseases associated with normal glucose levels, impaired fasting glucose, and diabetes among U.S. adults aged 40 or older. Diabetes Res Clin Pract 77: 485-488.

9. Pirart J (1977) Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973 (3rd and last part) (author's transl)]. Diabete Metab 3: 245-256.

10. Hicks CW, Selvin E (2019) Epidemiology of Peripheral Neuropathy and Lower Extremity Disease in Diabetes. Curr Diab Rep 19: 86.

11. Dobretsov M, Hastings SL, Romanovsky D, Stimers JR, Zhang J-M (2003) Mechanical hyperalgesia in rat models of systemic and local hyperglycemia. Brain Res 960: 174-183.

12. Oyibo SO, Prasad YDM, Jackson NJ, Jude EB, Boulton AJM (2002) The relationship between blood glucose excursions and painful diabetic peripheral neuropathy: a pilot study. Diabet Med J Br Diabet Assoc 19: 870-873.

13. Williams R (2016) Williams Textbook of Endocrinology. 13th edition. (Melmed S, Polonsky KS, Larsen PR, Kronenberg H, eds.). Philadelphia, PA: Elsevier.

14. Vinik A, Casellini C, Nevoret M-L (2000) Diabetic Neuropathies. In: Feingold KR, Anawalt B, Boyce A, et al., eds. Endotext. South Dartmouth (MA): MDText.com, Inc.

15. Bansal V, Kalita J, Misra UK (2006) Diabetic neuropathy. Postgrad Med J 82: 95-100.

16. Oaklander AL (2016) Immunotherapy Prospects for Painful Small-fiber Sensory Neuropathies and Ganglionopathies. Neurotherapeutics 13: 108-117.

17. Hovaguimian A, Gibbons CH (2011) Diagnosis and Treatment of Pain in Small Fiber Neuropathy. Curr Pain Headache Rep 15: 193-200.

18. Samuelsson K, Kostulas K, Vrethem M, Rolfs A, Press R (2014) Idiopathic Small Fiber Neuropathy: Phenotype, Etiologies, and the Search for Fabry Disease. J Clin Neurol Seoul Korea 10: 108-118.

19. Russell JW, Smith AG, Singleton JR (2007) 78 - Impaired Glucose Regulation and Neuropathy. In: Gilman S, ed. Neurobiology of Disease. Burlington: Academic Press: 849-858.

20. Dyck PJ (1988) Detection, characterization, and staging of polyneuropathy: Assessed in diabetics. Muscle Nerve 11: 21-32.

21. Boulton AJM, Vinik AI, Arezzo JC, et al. Diabetic Neuropathies: A statement by the American Diabetes Association. Diabetes Care. 2005;28(4):956-962.

22. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) - The Lancet.

23. Sander HW, Chokroverty S. Diabetic amyotrophy: current concepts. Semin Neurol. 1996;16(2):173-178.

24. Chan YC, Lo YL, Chan ES. Immunotherapy for diabetic amyotrophy. Cochrane Database Syst Rev. 2017;2017(7).

25. Javed S, Petropoulos IN, Alam U, Malik RA. Treatment of painful diabetic neuropathy. Ther Adv Chronic Dis.:14.

26. McCleane G. Chapter 68 - TOPICAL ANALGESIC AGENTS. In: Smith HS, ed. Current Therapy in Pain. Philadelphia: W.B. Saunders; 2009:501-507.

27. Giacalone M, Forfori F, Giunta F. Chapter 20 - Chili Pepper Compounds in the Management of Neuropathic Pain. In: Watson RR, Preedy VR, eds. Bioactive Nutraceuticals and Dietary Supplements in Neurological and Brain Disease. San Diego: Academic Press; 2015:187-195.

28. Parrish M. Liquid chromatographic method for determining capsaicinoids in capsicums and their extractives: collaborative study. In: ; 1996.

29. Anand P, Bley K. Topical capsaicin for pain management: therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. Br J Anaesth. 2011;107(4):490-502.

30. O'Neill J, Brock C, Olesen AE, Andresen T, Nilsson M, Dickenson AH. Unravelling the Mystery of Capsaicin: A Tool to Understand and Treat Pain. Dolphin AC, ed. Pharmacol Rev. 2012;64(4):939-971.

31. Sungjae Yoo, Ji Yeon Lim. Sensory TRP Channel Interactions with Endogenous Lipids and Their Biological Outcomes. April 2014:4708-4744.

32. Alawi K, Keeble J (2010) The paradoxical role of the transient receptor potential vanilloid 1 receptor in inflammation. Pharmacology & therapeutics.

33. Makoto Tominaga. The Role of TRP Channels in Thermosensation - TRP Ion Channel Function in Sensory Transduction and Cellular Signaling Cascades - NCBI Bookshelf.

34. Mingyue Zhang, David Ruwe, et al. Effects of TRPV1 Activation by Capsaicin and Endogenous N-Arachidonoyl Taurine on Synaptic Transmission in the Prefrontal Cortex. Neuroscience.

35. Chung MK, Güler AD, Caterina MJ (2008) TRPV1 shows dynamic ionic selectivity during agonist stimulation. Nat Neurosci 11: 555-564.

36. Gallego-Sandín S, Rodríguez-García A, Alonso MT, García-Sancho J (2009) The Endoplasmic Reticulum of Dorsal Root Ganglion Neurons Contains Functional TRPV1 Channels. J Biol Chem 284: 32591-32601.

37. Huang W, Wang H, Galligan JJ, Wang DH (2008) Transient receptor potential vanilloid subtype 1 channel mediated neuropeptide secretion and depressor effects: role of endoplasmic reticulum associated Ca2+ release receptors in rat dorsal root ganglion neurons: J Hypertens 26: 1966-1975.

38. Chard PS, Bleakman D, Savidge JR, Miller RJ (1995) Capsaicin-induced neurotoxicity in cultured dorsal root ganglion neurons: Involvement of calcium-activated proteases. Neuroscience 65: 1099-1108.

39. Han P, McDonald HA, Bianchi BR, et al. (2007) Capsaicin causes protein synthesis inhibition and microtubule disassembly through TRPV1 activities both on the plasma membrane and intracellular membranes. Biochem Pharmacol 73: 1635-1645.

40. Shimomura Y, Kawada T, Suzuki M (1989) Capsaicin and its analogs inhibit the activity of NADH-coenzyme Q oxidoreductase of the mitochondrial respiratory chain. Arch Biochem Biophys 270: 573-577.

41. Chada SR, Hollenbeck PJ (2004) Nerve Growth Factor Signaling Regulates Motility and Docking of Axonal Mitochondria. Curr Biol 14: 1272-1276.

42. Bley KR (2010) TRPV1 Agonist Approaches for Pain Management. In: Gomtsyan A, Faltynek CR, eds. Vanilloid Receptor TRPV1 in Drug Discovery: Targeting Pain and Other Pathological Disorders. New York: Wiley: 325–47.

43. Holzer P (2008) The pharmacological challenge to tame the transient receptor potential vanilloid-1 (TRPV1) nocisensor. Br J Pharmacol 155: 1145-1162.

44. Szallasi A, Blumberg PM (19999) Vanilloid (Capsaicin) Receptors and Mechanisms. Pharmacol Rev 51: 159-212.

45. Kawakami T, Hikawa N, Kusakabe T, et al. (1993) Mechanism of inhibitory action of capsaicin on particulate axoplasmic transport in sensory neurons in culture. J Neurobiol 24: 545-551.

46. Derry S, Bell RF, Straube S, Wiffen PJ, Aldington D, Moore RA (2019) Pregabalin for neuropathic pain in adults. Cochrane Database Syst Rev.

47. Fehrenbacher JC, Taylor CP, Vasko MR (2003) Pregabalin and gabapentin reduce release of substance P and CGRP from rat spinal tissues only after inflammation or activation of protein kinase C. Pain 105: 133-141.

48. Sills GJ (2006) The mechanisms of action of gabapentin and pregabalin. Curr Opin Pharmacol 6: 108-113.

49. Chen S-R, Samoriski G, Pan HL (2009) Antinociceptive effects of chronic administration of uncompetitive NMDA receptor antagonists in a rat model of diabetic neuropathic pain. Neuropharmacology 57: 121-126.

50. Burchiel KJ, Russell LC, Lee RP, Sima AF (1985) Spontaneous activity of primary afferent neurons in diabetic BB/Wistar rats: A possible mechanism of chronic diabetic neuropathic pain. Diabetes 34: 1210-1213.

51. Iyengar S, Ossipov MH, Johnson KW (2017) The role of calcitonin gene–related peptide in peripheral and central pain mechanisms including migraine: PAIN 158: 543-559.

52. XI-Ding Yang, Ping-Fei Fang, Da-Xiong Xiang, Yong-Yu Yang (2019) Topical treatments for Diabetic Neuropathic Pain (Review). Experimental and Therapeutic Medicine 17: 1963- 1976.

53. Biesbroeck R, Bril V, Hollander P, Kabadi U, Schwartz S, et al. (1995) A double□blind comparison of topical capsaicin and oral amitriptyline in painful diabetic neuropathy. Adv Ther 12: 111□120.

54. Mark R. Jones, Ivan Urits, John Wolf, Devin Corrigan (2019) Drug Induced Peripheral Neuropathy, A Narrative Review.Current Clinical Pharmacology 14: 1-11.

55. SD Shorvon, EH Reynolds (1982) Anticonvulsant peripheral Neuropathy: A Clinical and electrophysiological study of patients on single drug treatment with Phenytoin, carbamazepine or Barbiturates. Journal of Neurology, Neurosurgery and Psychiatry 45: 620-626.