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Original Article

Comparison of Efficacy of Topical Glycerin Trinitrates with Capsaicin in Painful Diabetic Neuropathy

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Objective: To compare the efficacy of topical glycerin trinitrates with capsaicin in painful diabetic peripheral neuropathy.

Material & Methods: This quasi experimental study was conducted in Diabetes Management Centre Medical Unit-IV Services Hospital, Lahore over a period of six months from 01-06-2008 to 30-11-2008. Sixty-two patients of diabetes mellitus having symptoms of neuropathy were included in this study and were divided into two groups of thirty one patients each. In group A topical capsaicin cream was applied twice a day for thirty minutes for the period of seven days at the strength of 0.075% w/w. In group B glycerin trinitrate cream was applied twice a day for thirty minutes for the period of seven days at the strength of 2% w/w. After seven days of treatment, intensity of numbness and paraesthesia and tissue perfusion were again assessed using visual analogue scale and periscan respectively. Periscan and visual analogue chart assessment were repeated after the seven days wash out period and patients were crossed over to the other treatment group. Numbness and paraesthesia were reassessed at the end of last treatment on visual analogue chart and periscan were repeated as well for tissue perfusion.

Results: The age of the patients in group A was 49.90±8.06 years and in group B was 49.58±6.62 years. In group A, the efficacy of GTN in peripheral neuropathy was 38.7% as compared to capsacin which was only 19.3%. Similar results were seen in group B, in which efficacy of GTN in peripheral neuropathy was 51.6% as compared to capsaicin that was 29%.The overall results when combined in both the groups showed a response to capsaicin in 15 (24.2%) patients only versus 28 (45.2%) to GTN. This difference was statistically significant (p=0.02356).

Conclusion: There is a significant difference in efficacy of topical glycerin trinitrates and capsaicin in the management of diabetic peripheral neuropathy. GTN cream, a well-tolerated drug, provides significant improvement in painful diabetic neuropathy.

Keywords: Diabetes mellitus, Diabetic peripheral neuropathy, Topical glycerin trinitrates, Capsaicin.

Introduction

Diabetes mellitus is a syndrome with disordered metabolism and inappropriate hyperglycemia due to either a deficiency of insulin secretion or combination of insulin resistance and inadequate secretion to compensate.[1] The natural history of type 2 diabetes mellitus (DM) in the elderly has not been previously described in a national longitudinal sample.[2] Diabetes is a leading cause of morbidity & mortality worldwide, and is sixth leading cause of death in United States.[3]

Diabetes Mellitus affects more than 120 million people worldwide and it is estimated that it will affect 220 million by the year 2020. It is usually irreversible and its late complications result in reduction of life expectancy and major increase in health costs. The complications include macro vascular and micro vascular damage.

The vast majority of diabetic patients are classified into one of two broad categories: type 1 in which there is an absolute deficiency of insulin, and type 2 diabetes, which is characterized by the presence of insulin resistance with an inadequate compensatory increase in insulin secretion. In addition to the main two types it can also develop during pregnancy and secondary to pancreatic disorders, endocrinopathies and drugs etc.[4]

Long standing hyperglycemia promotes the reaction of glucose with components of the arterial wall to form advanced glycation end products. AGEs [Advanced glycation end products] play a key role in RAoSMC [Rat aortic smooth muscle cell] proliferation via MAP kinase dependent pathways. Activation of vascular smooth muscle cell (VSMC) proliferation by MAP kinase system and increased formation of ROS may be the possible mechanisms of AGEs induced diabetic vasculopathy.[5] These products cross-link with collagen, thereby increasing arterial stiffness which in the presence of increased levels of low-density lipoprotein (LDL) and

cholesterol promotes atherogenesis. In this way high blood glucose levels lead to endothelial damage - manifesting as micro vascular or macro vascular damage. High glucose causes an uncoupling of VEGF [vascular endothelial growth factor] with NO [nitric oxide], which enhances endothelial cell proliferation.[6]

The most important prognostic factors are poor glycemic control, long duration of diabetes, increasing age, and higher body mass index. The diabetic patient is susceptible to series of complications that cause morbidity and premature mortality.[7]

In diabetes mellitus, involvement of peripheral nervous system may lead to numbness or paraesthesia in a glove and stocking pattern of distribution.[8] Despite the introduction of treatment strategies, diabetes remains a major cause of new-onset blindness, end-stage renal disease, and leg amputation, all of which contribute to the excess morbidity and mortality in people with diabetes.[9]

Neuropathies are among the commonest of long-term diabetes complications, and the management of chronic sensorimotor distal symmetric poly-neuropathy presents a significant therapeutic challenge.[10,11]

Diabetic peripheral neuropathy (DPN) may manifest with several diverse clinical presentations, including troublesome, neuropathic pain and, at the other end of the spectrum, the insensitive foot at risk of ulceration. Whereas the former gives rise to many unfamiliar and uncomfortable painful and paresthetic symptoms that impact quality of life,[12] foot ulceration may lead to amputation, which has major social and economic implications for the health care system.[13]

There are currently two main approaches to DPN therapy. First, there are those treatments that alleviate the persistent painful symptoms in the lower limbs. These include the tricyclic antidepressants, anticonvulsants, opioids, and opioid-like agents; the efficacy of these is supported by multiple randomized controlled trials (RCTs) and, in some cases (e.g., the tricyclic drugs), meta-analyses.[14]

The second group of therapies consists of those that primarily target the putative pathogenetic mechanisms. Included in this group are a number of mainly experimental treatments, such as the antioxidant-lipoic acid[15] which, although not available in the U.S., is approved in a number of countries, and the aldose-reductase inhibitor epalrestat, which is only available in Japan.[16]

Diabetic peripheral neuropathy is estimated to be present in 50% of people living with diabetes mellitus. Comorbidities of diabetes mellitus, such as macro vascular and micro vascular changes, also interact with DPN and affect its course. In patients with DM, DPN is the leading cause of foot ulcers, which in turn are a major cause of amputation in the United States. Although most patients with DPN do not have pain, approximately 11% of patients with DPN have chronic, painful symptoms that diminish quality of life, disrupt sleep, and can lead to depression. Despite the number of patients affected by DPN pain, little consensus exists about the pathophysiology, best diagnostic tools, and primary treatment choices.[17]

Diabetic peripheral neuropathic pain (DPNP) affects approximately 11% of patients with diabetic peripheral neuropathy (DPN). Its pathogenesis remains unknown, and none of the various treatments used can be considered a cure. It shares certain similarities in clinical signs and response to treatment with other forms of neuropathic pain but is also distinct in its apparent association with glucose-related metabolic changes. Most patients with DPN do not experience pain, and in fact many have a lack of sensation. The reason why some patients with DPN develop DPNP is unknown.[18]

This study was designed to find out the efficacy of two treatment options in all diabetic patients with painful peripheral neuropathy.

Material and Methods

Setting: The study was conducted in Diabetes Management Center (a specialized center serving more than hundred patients of diabetes mellitus per day), Services Hospital, Lahore.

Study Design: Quasi experimental study.

Sample Size: Sixty two patients of diabetes mellitus having symptoms of neuropathy were included in this study.

Study Duration: Six months from 01-06-2008 to 30-11-2008.

Sampling Technique: Non probability convenience sampling

Inclusion Criteria

1. Known patients of diabetes mellitus.
2. Age 18-60 years of either sex.
3. Patients with chronic bilateral symmetrical painful peripheral neuropathy.

Exclusion Criteria

1. Allergic to capsaicin or glycerin trinitrates.
2. Creatinine more than 1.5mg%.
3. Taking systemic nitrates.

4. Foot ulcer whether neuropathic or ischemic.
5. Any neurological deficit that will compromise assessment of sensory system.
6. Taking anticonvulsants and/or antidepressants.
7. Color blindness.

Data Collection Procedure

After taking the informed consent and fulfilling the inclusion and exclusion criteria patients were inducted in the study. By using allocation table, random allocation was done into two groups of thirty one patients each. In beginning a 2 week run in period was given to every patient for diabetes control through life style advice and hypoglycemic agents including insulin. After maximum stabilization of diabetes mellitus, intensity of numbness and parasthesia were quantified by using visual analogue chart. Perfusion of hands was also measured using a periscan image. Then following procedure was followed:

Group A: Topical capsaicin cream was applied on the hands twice a day for thirty minutes for the period of seven days at the strength of 0.075% w/w. It is a counter irritant. It costs Rs.64 per 25 grams.

Group B: Glycerin trinitrate cream was applied on the hands twice a day for thirty minutes for the period of seven days at the strength of 2% w/w. It is a vasodilator. It cost Rs. 140 per 100 grams. It was a dispensable item.

After seven days of treatment, intensity of numbness and paraesthesia and tissue perfusion were again assessed using visual analogue scale and periscan respectively. Patients then went through a seven days wash out period during which they did not receive any specific treatment for their numbness and paraesthesia.

Periscan and visual analogue chart assessment were repeated after the seven days wash out period and patients were crossed over to the other treatment group. Numbness and paraesthesia were reassessed at the end of last treatment on visual analogue chart and periscan were repeated as well for tissue perfusion.

Statistical Analysis Procedure

Data was analyzed using SPSS version 10. The quantitative variables like age and periscan were presented as mean and standard deviation. The qualitative variables like sex, pre-evaluation symptoms, paraesthesia and neuralgic pain were presented as frequency and percentages. Variables of paraesthesia and neuralgic pain were analyzed qualitatively as compared to their intensity on visual analogue chart by applying Chi Square test. Similarly these variables were also analyzed quantitatively with comparison to the readings of tissue perfusion on periscan by applying student 't' test. P value <0.05 was considered significant.

Results

In the pre-evaluation symptoms, in group A 30 (96.8%) patients had symptom of paraesthesia and 29 (93.5%) patients had neuralgic pain. In group B, 29 (93.5%) patients had paraesthesia and 28 (90.3%) patients had neuralgic pain **(Table 1).**

Table1: Distribution of patients by pre-evaluation symptoms

Symptoms	Group A (n=31)		Group B (n=31)	
	No.	Percentage.	No.	Percentage
Paraesthesia	30	96.8	29	93.5
Neuralgic Pain	29	93.5	28	90.3

In group A, on baseline 4 (12.9%) patients had normal, 9 (29%) patients had moderate and 18 (58.1%) patients had severe paraestheisa. In group B, on baseline 3 (9.7%) patients had moderate and 28 (90.3%) patients had severe paraestheisa (Table 2).

Table-2: Distribution of patients by baseline paraesthesia.

Paraesthesia	Group A (n=31)		Group B (n=31)	
	No.	Percentage.	No.	Percentage
Mild	4	12.9	0	0
Moderate	9	29.0	3	9.7
Severe	18	58.1	28	90.3

In group A, on baseline 5 (16.1%) patients had normal, 10 (32.3%) patients had moderate and 16 (51.6%) patients had severe neuralgic pain. In group B, on baseline 9 (29%) patients had moderate and 22 (71%) patients had severe neuralgic pain **(Table 3).**

In group A, after 28 days 20 (64.5%) patients had normal, 8 (25.8%) patients had moderate and 3 (9.7%) patients had severe paraesthesia. In group B,

Table-3: Distribution of patients by baseline neuralgic pain.

Neuralgic Pain	Group A (n=31)		Group B (n=31)	
	No.	Percentage	No.	Percentage
Mild	5	16.1	0	0
Moderate	10	32.3	9	29.0
Severe	16	51.6	22	71.0

after 28 days 19 (61.3%) patients had normal, 6 (19.3%) patients had moderate and 6 (19.3%) patients had severe paraesthesia **(Table 4).**

Table-4: Distribution of patients by paraesthesia after 28 days

Paraesthesia	Group A (n=31)		Group B (n=31)	
	No.	Percentage.	No.	Percentage
Mild	20	64.5	19	61.3
Moderate	08	25.8	06	19.3
Severe	03	9.7	06	19.3

In group A, after 28 days 21 (67.7%) patients had normal, 7 (22.6%) patients had moderate and 3 (9.7%) patients had severe neuralgic pain. In group B, after 28 days 17 (54.8%) patients had mild, 11 (35.5%) patients had moderate and 3 (9.7%) patients had severe neuralgic pain **(Table 5)**.

Table-5: Distribution of patients by neuralgic pain after 28 days.

Neuralgic Pain	Group A (n=31)		Group B (n=31)	
	No.	Percentage.	No.	Percentage
Mild	21	67.7	17	54.8
Moderate	07	22.6	11	35.5
Severe	03	9.7	03	9.7

According to our results, in group A, the efficacy of GTN in peripheral neuropathy was 22.6% as compared to capsaicin which was only 19.3%. Similar results were seen in group B, in which efficacy of GTN in peripheral neuropathy was 51.6% as compared to capsaicin that was 29%**.** The overall results when combined in both the groups showed a response to capsaicin in 15 (24.2%) patients only versus 28 (45.2%) to GTN. This difference was statistically significant (p=0.02356) **(Table 6).**

Table-6: Efficacy of topical glycerin trinitrates and capsaicin in diabetic peripheral neuropathy.

Drugs	Pain relieved		Not relieved		
	No.	%	No.	%	Total
Capsaicin	15	24.2	47	75.8	62
GTN	28	45.2	34	54.8	62
Total	43		81		124
X^2 Yates Corrected = 5.127, p = 0.02356					

Discussion

In diabetes mellitus, involvement of peripheral nervous system may lead to numbness or paraesthesia in a glove and stocking pattern of distribution.[8] Despite the introduction of treatment strategies, diabetes remains a major cause of new-onset blindness, end-stage renal disease, and lower leg amputation, all of which contribute to the excess morbidity and mortality in people with diabetes.[9]

Neuropathies are among the commonest of long term diabetes complications, and the management of chronic sensorimotor distal symmetric poly neuropathy presents a significant therapeutic challenge.[10,11]

DPN may manifest with several diverse clinical presentations, including troublesome neuropathic pain and at the other end of the spectrum, the insensitive foot at risk of ulceration. Whereas the former gives rise to many unfamiliar and uncomfortable painful and paraesthetic symptoms that impact quality of life,[12] foot ulceration, which may lead to amputation, has major social and economic implications for the health care system.[13]

There are currently two main approaches to DPN therapy. First, there are those treatments that alleviate the persistent painful symptoms in the upper and lower limbs. These include the tricyclic antidepressants, anticonvulsants, opioids, and opioid-like agents; the efficacy of these is supported by multiple randomized controlled trials (RCTs) and, in some cases (e.g., the tricyclic drugs), meta-analyses.[14]

The second group of therapies consists of those that primarily target the putative pathogenetic mechanisms. Included in this group are a number of mainly experimental treatments, such as the antioxidant-lipoic acid,[15] which although not available in the U.S., is approved in a number of countries, and the aldose reductase inhibitor epalrestat, which is only available in Japan.[16]

In our study the mean age of the patients in group A was 49.90±8.06 years and mean age in group B was 49.58±6.62 years. As compared with the study of Fedele et al the mean age of the patients was 56 years, which is comparable with our study. In our study, in group A there were 45.2% male and 54.8% female patients, while in group B, there were 35.5% male and 64.5% female patients. As compared with the study of Fedele et al[20] there were 51.2% male and

48.8% female patients which is comparable in our study. Topical and physical treatment, capsaicin, is found in red pepper, depletes tissue of substance P and reduces chemically induced pain. Although several controlled studies combined in meta-analyses seem to provide some evidence of efficacy in diabetic neuropathic pain, it may be best reserved for those with localized discomfort rather than those with widespread generalized neuropathic pain.[19] In our study, in group A, the efficacy of capsaicin in diabetic peripheral neuropathy was found in 19.3% patients and 38.7% patients in GTN. While in group B, the efficacy of capsaicin in diabetic peripheral neuropathy was found in 29% patients as compared to 51.6% patients in GTN. The overall results when combined in both the groups showed a response to capsaicin in 15 (24.2%) patients only versus 28 (45.2%) to GTN. This difference was statistically significant (p=0.02356).

Four trials looked at capsaicin 0.075% cream, four times daily for 4 to 8 weeks. Two of four trials showed significant benefit with capsaicin. When data were pooled for diabetic neuropathy, capsaicin had a number-needed-to-treat of 4.2 (2.9 to 7.5). An 8-week, study was conducted to determine the effectiveness of topical capsaicin 0.075% cream in relieving pain associated with diabetic neuropathy. Patients were selected who experienced moderate to very severe pain, which interfered with sleep or activities on a daily basis, and who were unresponsive or intolerant to conventional therapy. The results after 8 weeks showed a statistically significant difference in favor of the capsaicin-treated patients, with 90% of these patients improved. The results of this study indicate that topical capsaicin 0.075% cream is safe and effective in managing painful diabetic neuropathy.[21] Topical glycerin trinitrates (GTN) are nitric oxide (NO) donors and when applied locally, cause vasodilatation of vasa nervosa hence improve the circulation of nerves.[22,23] The resultant improved circulation in vasa nervosa should improve neuropathic pain. This glycerin trinitrates topical cream has been considered to improve symptoms of chronic painful diabetic neuropathy in recent trials.[23] However topical glycerin trinitrates have not been widely tested yet regarding their efficacy in relieving diabetic neuropathic pain.

Various drugs are effective in the management of painful diabetic neuropathy, but none is completely satisfactory. In this study, partial efficacy of both GTN and capsaicin was witnessed. The effect of GTN on neuralgic pain relief was statistically more prominent as compared to capsaicin (p= 0.02356).Both groups A and B experienced significant improvement in pain score in their drug phase of trial, when compared to placebo phase of other group (p<0.001). After crossing over the treatment arm, patients of group B observed significant improvement in all pain scores compared to group A (p<0.001). The numbers needed to treat (NNT) calculated on VAS as pain parameters came out to be 4. The drug was well tolerated by all the patients except palpitation and headache for some days in five patients. GTN spray, a well-tolerated drug, provides significant improvement in painful diabetic neuropathy.

Conclusion

There is a significant difference in efficacy of topical glycerin trinitrates and capsaicin in the management of diabetic peripheral neuropathy. GTN cream is a well-tolerated drug which provides significant improvement in painful diabetic neuropathy. These data provide a basis for future trials for longer duration in a larger group of patients.

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Answer Picture Quiz

1. This lesion is classical spider angioma. One can easily appreciate the central body and radiating 'legs' consisting of dilated and tortuous vessels. Typically the lesion will blanch on pressure.
2. The commonest cause is chronic liver disease which is very common in our country due to extremely prevalent chronic hepatitis C. Less commonly it may be seen in alcohol related or other varieties of CLD. Rarely the lesion may be due to hormone therapy or idiopathic.
3. The pathogenesis is not fully understood, however it is believed to be due to imbalance between male and female hormones which occurs commonly in CLD.