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# Evaluation of the Efficacy and Safety of Topical Pregabalin Gel 8% versus Oral Pregabalin in Diabetic Neuropathic Pain: A Phase III, Multicentric, Placebo Controlled Study

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**Abstract:** ***Background**: Painful diabetic peripheral neuropathy (DPN) occurs in up to one-third of patients with diabetes mellitus. Oral pregabalin is approved as a first line drug to treat painful diabetic neuropathy. But, oral pregabalin in relieving neuropathic pain is associated with central nervous system adverse effects such as, dizziness, somnolence , and fatigue. These adverse effects often lead to discontinuation of treatment and poor patient adherence. Topical pregabalin 8% w/w was developed to overcome the limitations of oral pregabalin. **Aim**: To evaluate the efficacy and safety of 'Pregabalin Gel 8% w/w' in comparison with Pregabalin Capsule as a standard of care in patients with diabetic neuropathic pain. **Methodology**: This was a phase III randomized, double blinded, double dummy, parallel group, placebo controlled, two arm, multicenter clinical study. 220 patients with painful diabetic neuropathy. The patients were randomized into either of two treatment groups namely: Group A (Topical application of Pregabalin Gel 8 % w/w twice a day with Oral Placebo Capsule thrice a day; N=110) or Group 'B' ( oral Pregabalin Capsule as a standard of care thrice a day with Topical Placebo Gel twice a day ; N=110) for 63 days . The primary end point was ≥50 % change in Visual Analogue Scale (VAS). The secondary end points were ≥50 % change in Leeds Assessment of Neuropathic Symptoms; ≥50 % change in Patient Global Impression of Change (PGIC); ≥50 % change in Clinicians Global Impression of change (CGIC); ≥50 % change in DN4 Questionnaire; ≥50 % change in Quality-of-life Questionnaire; and ≥50 % change in Sleep Disturbance– Adults Scale.Safety assessments. **Results**: In group A, 91.7% had ≥ 50% change in Visual Analogue Scale after 63 Days of treatment with topical pregabalin. In group B, 93.5% had ≥ 50% change in Visual Analogue Scale after 63 Days of treatment with oral pregabalin The difference between the two treatment groups was not significant (p = 0.630). There was no difference in the secondary endpoints between the two treatment groups. There was no development of tolerance to the efficacy of pregabalin over 63 days. **Conclusion**: Topical pregabalin has analgesic efficacy comparable to oral pregabalin but it is better tolerated. Topical pregabalin was associated with significantly lesser somnolence and dizziness as compared to oral pregabalin.***

**Keywords:** Diabetic neuropathic pain, Pregabalin, Somnolence, Dizziness

## 1. Introduction

Painful diabetic peripheral neuropathy (DPN) is a highly prevalent and disabling condition, occurring in up to one-third of patients with diabetes mellitus [1]. DPN presents as distal symmetrical [2]. Painful diabetic neuropathy is associated with impaired sleep, disturbed concentration and impaired work performance, mood disorders such as anxiety or depression and impaired quality of life [3, 4].

Effective relief of the painful neuropathy is essential to improve the quality of life of these patients. The principles for the management of painful DPN include control of hyperglycemia in order to modulate the pathogenic processes that lead to DPN and pain management. The recommended first line drugs for treatment of diabetic neuropathic pain include Gabapentinoids such as pregabalin and gabapentin, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, alpha-lipoic acid, sodium channel blockers, and topical capsaicin. The U.S. Food and Drug Administration (FDA) has approved pregabalin, duloxetine, tapentadol, and the 8% capsaicin patch as drugs for the treatment of painful DPN [5,6]. Other drugs include topical lidocaine [7,8].

Pregabalin is a gabapentinoid approved as first line medication for the treatment of neuropathic pain including painful diabetic neuropathy and postherpetic neuralgia (PHN) [9]. Pregabalin is postulated to exert its analgesic action through antagonistic activity at the voltage gated Ca2+ channels where it binds to the alpha-2-delta subunit [10,11].
Several global guidelines have recommended pregabalin for the management of neuropathic pain. The Canadian pain society has recommended gabapentinoids for the management of neuropathic pain [12]. Pregabalin has been approved as 2nd line drug for management of neuropathic pain by the French Guidelines [13]. The European Federation of Neurological Societies guideline has recommended pregabalin as first-line treatment for neuropathic pain [14]. The American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine and the American Academy of Physical Medicine and Rehabilitation guidance recommend pregabalin as first-line treatment for neuropathic pain [15].

But clinical trials have indicated that oral pregabalin in relieving neuropathic pain is associated with central nervous system adverse effects such as, dizziness, somnolence, and fatigue. These adverse effects often lead to discontinuation of treatment and poor patient adherence [16].

Topical formulations result in low systemic drug concentrations and achieve therapeutic drug concentrations locally. First-line use of topical agents may be of particular benefit in patients where the safety and tolerability of oral therapy is a concern [17]. Transdermal delivery of pregabalin could be an effective treatment option to minimize or avoid dose-limiting side effects [18].

**Objective**

The objective of this study was to evaluate the efficacy and safety of 'Pregabalin Gel 8% w/w' in comparison with Pregabalin Capsule as a standard of care in patients with diabetic neuropathic pain.

## 2. Methodology

This was a phase III randomized, double blinded, double dummy, parallel group, placebo controlled, two arm, multicenter clinical study. The study was conducted in accordance with the principles of Good Clinical practice (GCP) after regulatory approvals and ethics committee approvals. The study planned to enrol a total of 220 patients with painful diabetic neuropathy. The patients were randomized into either of two treatment groups namely: Group A (Topical application of Pregabalin Gel 8 % w/w twice a day with Oral Placebo Capsule thrice a day; N=110) *or* Group 'B' (oral Pregabalin Capsule as a standard of care thrice a day with Topical Placebo Gel twice a day; N=110) for 63 days. The inclusion criteria were patients of either gender between 18 to 75 years with a diagnosis of chronic diabetic neuropathic pain restricted only to feet area, patients reporting daily pain in lower extremity in one or both the legs, patients having pain score greater than or equal to 4 on Visual Analogue Scale (VAS) of 0-10 at the time of screening and on day of enrolment (after washout period of seven days), patients with a score of 12 or more on Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Scale Score, patients with HbA1c concentration < 12.2 % at screening. Patients excluded were patients with complications of diabetes such as retinopathy , nephropathy or requring dialysis ,patients with impaired liver function , impaired renal function or peripheral artery disease , uncontrolled angle-closure glaucoma, patients with any orthopaedic problem of the feet patients with Vitamin B12 level below 180 ng/L or uncontrolled hypothyroidism in spite of adequate treatment, patients taking drugs that can cause QT prolongation , patients with history of alcohol abuse , pregnant and lactating women, or patients who were receiving treatment with anti-depressants, antiepileptics or other drugs for treating diabetic neuropathic pain. Efficacy was assessed on proportion of participants achieving reduction of pain in below mentioned scales and improvement in quality-of-life questionnaire. The primary end point was ≥50 % change in Visual Analogue Scale (VAS). The secondary end points were ≥50 % change in Leeds Assessment of Neuropathic Symptoms;≥50 % change in Patient Global Impression of Change (PGIC) ;≥50 % change in Clinicians Global Impression of change (CGIC) ;≥50 % change in DN4 Questionnaire;≥50 % change in Quality-of-life Questionnaire; and ≥50 % change in Sleep Disturbance– Adults Scale.Safety assessments included recording of Adverse Reactions and changes in serum biochemistry at end of treatment as compared to baseline.

***Statistical analysis***

The reduction in pain scores and neuropathic symptoms at the end of 12 weeks from base line using VAS was analysed by using Wilcoxon Sign rank test for change and Analysis of variance with Kruskal Wallis test between the groups. Secondary efficacy variables Patient Global Impression of Change (PGIC), Clinicians Global Impression of change (CGIC), DN4 Questionnaire, Quality of life Questionnaire and Sleep Disturbance – Adults Scale were analyzed by using Wilcoxon sign rank test for within group and Kruskal Wallis analysis of variance for between groups. Mean changes in Laboratory data and vital signs were assessed by using student t-test for within groups and Students unpaired 't' test or one way analysis of variance for comparison between groups.

## 3. Results

One hundred and ten patients were enrolled in each treatment arm. The mean age of the patients in Group A was 52.93±9.70 years as compared to 54.22±10.20 years in group B (oral pregabalin). A male predominance was observed in both the treatment groups (64.2% vs 61.7 in group A and B respectively). The mean BMI was comparable between the two treatment groups (25.60 ± 2.72 $kg/m^2$ vs 25.45 ±2.62 $kg/m^2$). Hypertension was the most common comorbid disease observed in both the treatment groups (28.4% vs 25.2% in group A and B respectively). Patients in both the treatment groups were treated with both old and new oral hypoglycemic drugs for management of diabetes mellitus. At baseline 45.9% of the cases among Group A were on Metformin which was comparable to 43.9% of the cases among Group B and the difference was not significant.

A progressive decrease in VAS scores was observed in both the treatment groups at all time points as compared to baseline. (Table 1) There was no significant difference in VAS scores between the two treatment groups. (Figure 1) Topical Pregabalin had comparable analgesic effect as oral Pregabalin. After 63 Days of treatment, mean VAS score was 1.93 in Group A and 1.77 in Group B, mean VAS score showed a significant fall of 70.4% among Group A and 72.9% among Group B from baseline. There was no significant difference between two treatment groups in terms of ≥50% change in Visual Analogue Scale ($\chi 2$ = 0.232, p = 0.630). 91.7% of cases among Group A had ≥50% change in Visual Analogue Scale which was comparable to 93.5% of cases among Group B and the difference was not significant. Topical Pregabalin had comparable analgesic efficacy as oral Pregabalin. There was no significant difference between two treatment groups in terms of number of patients who required dose escalation after 8 Days of treatment ($\chi 2$ = 1.529, p = 0.216). This indicated that pain relief progressively increased over 2 months with topical Pregabalin without

the need for adding oral Pregabalin in a significant number of patients underscoring the efficacy of topical pregabalin and no development of tolerance to the analgesic effect of Pregabalin over long term use.

**Table 1:** Comparison of changes in VAS scores between the two treatment groups

| Duration (Days) | Mean VAS score ($\overline{X}$ ± SD) | | P value |
|---|---|---|---|
| | Group A (N = 109) | Group B (N = 107) | |
| Baseline | 6.53 ± 1.13 | 6.50 ± 1.21 | 0.984 (NS) |
| D8 | 4.55 ± 1.20 | 4.50 ± 1.29 | - |
| D36 | 3.10 ± 1.10 | 2.94 ± 1.20 | - |
| D63 | 1.93 ± 1.07 | 1.77 ± 1.25 | - |
| Mean diff (Baseline – D8) (p value) | *-1.98 ± 0.93 (0.001) | *-2.01 ± 0.91 (0.001) | 0.802 (NS) |
| Mean diff (Baseline – D36) (p value) | *-3.44 ± 1.04 (0.001) | *-3.56 ± 1.11 (0.001) | 0.406 (NS) |
| Mean diff (Baseline – D63) (p value) | *-4.60 ± 1.21 (0.001) | *-4.74 ± 1.32 (0.001) | 0.548 (NS) |

By Wilcoxon Sign Rank Test *Significant NS = Not Significant
By Mann Whitney U Test (Betn Groups)

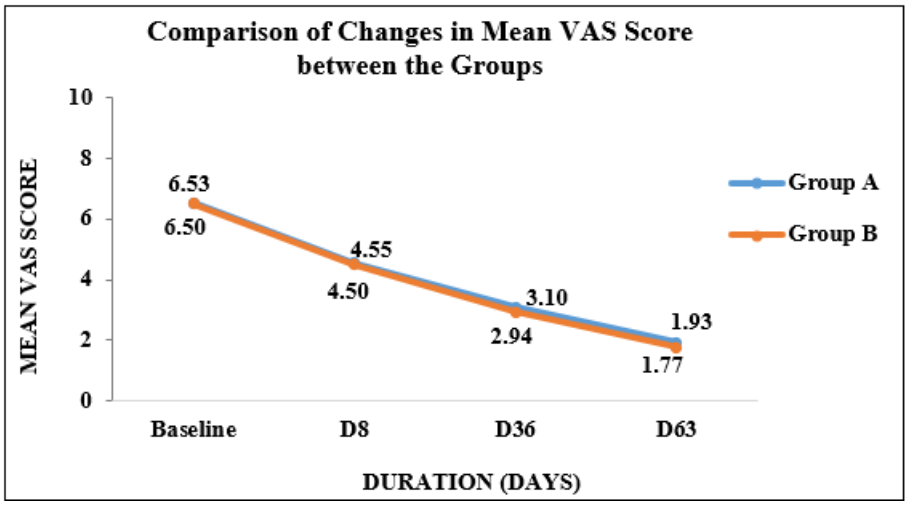


**Figure 1:** Comparison of changes in mean VAS score between the treatment groups

There was no significant difference between two treatment groups in terms of ≥50% change in Leeds Assessment of Neuropathic Symptoms ($\chi 2 = 0.183$, $p = 0.175$). 43.1% of the participants in group A had ≥ 50% change in Leeds Assessment of Neuropathic Symptoms. 52.3% of the participants in group B had ≥ 50% change in Leeds Assessment of Neuropathic Symptoms. (Table 2).

**Table 2:** Comparison of patients with **≥50 %** and < 50 change in Leeds assessment of neuropathic symptoms between the two treatment groups

| Percentage (%) | Group A (N = 109) | | Group B (N = 107) | | P value |
|---|---|---|---|---|---|
| | No | % | No | % | |
| ≥ 50 | 47 | 43.1 | 56 | 52.3 | $\chi 2 = 0.183$ |
| <50 | 62 | 56.9 | 51 | 47.7 | 0.175 (NS) |

By Chi Square Test NS = Not Significant

There was no significant difference between two treatment groups in terms of change in DN4 questionnaire between the groups (Table 3)

**Table 3:** Comparison of patients with ≥50% and < 50% change in DN4 questionnaire between the groups

| Percentage (%) | Group A (N = 109) | | Group B (N = 107) | | P value |
|---|---|---|---|---|---|
| | No | % | No | % | |
| ≥ 50 | 73 | 67.0 | 77 | 72.0 | $\chi 2 = 0.634$ |
| < 50 | 36 | 33.0 | 30 | 28.0 | 0.426 (NS) |

By Chi Square Test NS = Not Significant

There was no significant difference between two treatment groups in terms of change in quality of life domains (Table 4) and change in sleep disturbamce adults scale between the groups (Table 5). There was no significant difference between the two treatment groups in physicians global impression of treatment and patient's global impression of treatment ($p = 0.156$).

**Table 4:** Comparison of Patients with ≥50 % and < 50% Change in Quality-of-Life Questionnaire between the Groups

No significant difference between the two treatment groups in quality of life

| Percentage (%) | Group A (N = 109) | | Group B (N = 107) | | P value |
|---|---|---|---|---|---|
| | No | % | No | % | |
| ≥ 50 | 13 | 11.9 | 19 | 17.8 | $\chi 2$=1.454 |
| < 50 | 96 | 88.1 | 88 | 82.2 | 0.227 (NS) |

By Chi Square Test NS = Not Significant

**Table 5:** Comparison of Patients with ≥50% and <50% Change in Sleep Disturbance-Adult Scale between the Groups

| Percentage (%) | Group A (N = 109) | | Group B (N = 107) | | P value |
|---|---|---|---|---|---|
| | No. | % | No. | % | |
| ≥ 50 | 16 | 14.7 | 29 | 27.1 | $\chi 2$ = 5.053 |
| < 50 | 93 | 85.3 | 78 | 72.9 | *0.024 |

By Chi Square Test *Significant

**Comparison of adverse events between treatment groups**

A significantly greater number of patients in the oral pregabalin treatment group had somnolence (9.1%) as compared to patients treated with topical pregabalin (2.7%). Patients who experienced somnolence in the topical pregabalin group had been treated with oral pregabalin as rescue medication. Dizziness was reported by 2.7% patients in the oral pregabalin group while there were no reports of dizziness in the topical pregabalin group. (Table 6)

**Table 6:** Comparison of adverse events between treatment groups

| Events | Group A (N = 110) | | Group B (N = 110) | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Somnolence | 03 | 2.7 | *10 | 9.1 |
| Vomiting | - | - | 01 | 0.9 |
| Dizziness | - | - | 03 | 2.7 |

## 4. Discussion

Topical pregabalin is postulated to act with a distinctly different mechanism of action as compared to oral pregabalin which acts by specific binding to the α2–δ subunit of voltage-gated calcium channel. Topical pregabalin is postulated to act by increasing the local release of nitric oxide. Nitric oxide (NO) derived from neuronal nitric-oxide synthase (nNOS) and inducible nitric-oxide synthase (iNOS) plays a key role in various pain and inflammatory states. Pregabalin may increase the release of nitric oxide, and can consequently increase the release of endogenous opioids to attenuate neuropathic pain [19].

During preclinical testing, Pregabalin Gel 8% w/w did not show any local reaction like signs of erythema and edema and did not produce any systemic toxicity or adverse effects up when applied topically for 28 consecutive days.

The current study demonstrated the efficacy of topical pregabalin was comparable to that of oral pregabalin in relieving diabetic neuropathic pain. The VAS score at baseline progressively decreased from 6.53 in the topical pregabalin group to 4.55 on Day 8, 3.10 on Day 36 and 1.93 on day in the topical pregabalin group. This progressive reduction in scores over the 63 days period of the study in the topical pregabalin group was comparable to that seen in the oral pregabalin treated patients. In group A, 94.5% of the participants in group A had ≥ 30% change in Visual Analogue Scale after 36 Days of treatment while **91.7%** had ≥ 50% change in Visual Analogue Scale after 63 Days of treatment with topical pregabalin. In group B, 94.4% of the participants in group B had ≥ 30% change in Visual Analogue Scale after 36 Days of treatment while 93.5% had ≥ 50% change in Visual Analogue Scale after 63 Days of treatment with oral pregabalin The difference between the two treatment groups was not significant ( p = 0.630)

The >50% reduction in scores in the Leeds Assessment of neuropathic symptoms was comparable between the two treatment groups 56.9% in group A and 52.3% in group B. There was no significant difference in the different domains of the quality-of-life questionnaire, Patient Global Impression of Change (PGIC) and ≥50 % change in Clinicians Global Impression of change (CGIC) in the topical pregabalin and oral pregabalin treatment groups. There was no significant difference between the two treatment groups in good sleep quality (p = 0.974). Only a small proportion of patients treated with topical pregabalin required rescue analgesia indicating the efficacy of topical pregabalin. The consistent reduction in pain all through the 63 day study indicated that there was no development of tolerance to the analgesic effects of topical pregabalin.

Topical pregabalin was well tolerated. There were no reports of local adverse effects such as burning, pruritus or allergic rashes in the topical pregabalin group. Systemic adverse effects such as dizziness (2.7%) and somnolence (9.1%) were significantly more in the oral pregabalin group. Patients in the topical pregabalin group reported somnolence only when oral pregabalin was added as a rescue analgesic in a small proportion of patients (2.7%). All hematology parameters and serum biochemistry parameters were comparable at end of treatment and the difference was not significant.

## 5. Conclusion

Management of diabetic neuropathic pain is often challenging and may require a multimodal approach. Oral pregabalin has been demonstrated to relieve neuropathic pain in several clinical trials. But, oral pregabalin is associated with adverse effects such as dizziness and somnolence which interfere with daily activities. The topical formulation of pregabalin is expected to be better tolerated as it would undergo minimal systemic absorption after application. The current study findings have proved that topical pregabalin has analgesic efficacy comparable to oral pregabalin but it is better tolerated. Topical pregabalin was associated with significantly lesser somnolence as compared to oral pregabalin. Topical pregabalin effectively balanced analgesic efficacy with safety and had an improved tolerability profile as compared to oral pregabalin over 63 days. Topical pregabalin can be expected to improve patient

adherence to treatment and thus would lead to improved pain relief and improved quality of life of the patients with diabetic neuropathic pain. No tolerance develops to the analgesic effects of topical pregabalin. Topical pregabalin retains its analgesic efficacy over long term use. Topical pregabalin will be a useful addition to the therapeutic armamentarium of diabetic neuropathic pain.

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