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TOLERABILITY AND EFFICACY OF FIXED DOSE COMBINATION OF NORTRIPTYLINE AND PREGABALIN IN MANAGING PERIPHERAL NEUROPATHY IN DIABETICS

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ABSTRACT

Background: Treating diabetic peripheral neuropathy (DPN) is a challenging condition with the non-availability of effective therapies for many subjects making pharmacotherapy development vital. Combined use of Nortriptyline and pregabalin can result in complementary and enhancing effects through various mechanisms reducing the disease symptoms. However, existing literature data supporting this combination are limited.

Aim: The present study was aimed at assessing the tolerability and safety of a fixed dose combination of Nortriptyline and pregabalin in managing peripheral neuropathy in diabetics.

Methods: The study assessed 112 type 2 diabetics with painful diabetic neuropathy for >1 month and NRS pain intensity of >50%. All subjects received a fixed dose combination of 10mg Nortriptyline and 75mg pregabalin once daily in the morning. Efficacy was assessed with mean pain score change on 11-point NRS at 3 visits from baseline (day 1) to 3rd visit (day 28). DSIRS (Daily Sleep Interference Rating Scale) and PGIC (Patient Global Impression of Change) scale were used to assess the efficacy. Safety was assessed with a causal relationship, severity, duration, and nature of all adverse events to study the drug at each visit.

Results: PGIC, DSIRS, and NRS at baseline were 4.02, 7.02, and 7.92 which reduced at 2 months and further at the 3rd visit to 1.37, 3.46, and 2.44 respectively. In 5.35% (n=6) subjects, adverse events were reported that were mild in severity and were resolved completely within 24 hours of giving the appropriate and symptomatic medications.

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Conclusion: The present study concludes that a fixed-dose combination of nortriptyline and pregabalin is a well-tolerated and efficacious modality for the therapeutic management of subjects with diabetic peripheral neuropathy.

Keywords: Diabetes mellitus, diabetic neuropathy, nortriptyline, pregabalin

Introduction

Diabetes mellitus is a metabolic and chronic condition with its primary characteristic symptom being hyperglycemia which leads to long-term dysfunction and damage in various organs and structures in the affected subjects including the blood vessels, heart, nerves, kidneys, and eyes. Among these organ and system effects, one condition is diabetic peripheral neuropathy which is elaborated as sensorimotor polyneuropathy which is length dependent and symmetrical which is attributed to microvascular and metabolic alterations secondary to prolonged hyperglycemia and also leads to cardiovascular comorbidities as suggested by Toronto Consensus Panel on Diabetic Neuropathy.[1]

Sensory symptoms in subjects with diabetic peripheral neuropathy usually manifest in the toes as initial symptoms and further progress to the upper limbs in a typical pattern of stocking and glove. Motor participation is not usually seen in the first phase of diabetic peripheral neuropathy subjects.[2] Subjects usually present with different sensory symptoms such as electric shocks, burning, pin and needles sensation, tingling, Novocain-like insensitivity, loss of pain sensation, hyperalgesia suggesting an increased sensitivity to painful stimulus, and/or allodynia depicting painful sensation to innocuous stimulus.[3]

Developing a more effective therapy to treat diabetic peripheral neuropathy is vital since it is quite difficult to manage diabetic peripheral neuropathy as many subjects affected with this do not have a reach to the appropriate management therapies. Also, there is a lack of information on the combination and pharmaceutical therapies that can help in reversing and stopping the alterations caused by diabetic peripheral neuropathy and can help in partially relieving the pain associated with diabetic peripheral neuropathy. Hence, it can be considered that the therapeutic management of diabetic peripheral neuropathy has various requirements that are still not well-understood and achieved.[4,5]

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Presently, a GABAergic drug named Pregabalin is the primary drug used as a first-line drug to manage painful diabetic peripheral neuropathy subjects. Along with providing the needed pain relief, it is also helpful in managing the comorbidities associated with diabetic peripheral neuropathy such as sleep disturbances and anxiety, and is a well-tolerated drug. Another drug, nortriptyline, which is a TCA (tricyclic antidepressant) and is a primary active metabolite of amitriptyline with modest antimuscarinic effects, and is shown to be a useful agent in the treatment of diabetic peripheral neuropathy by inhibition of reuptake of serotonin and norepinephrine.[6]

Combined use of nortriptyline and pregabalin as a therapeutic modality can help in increasing and complementing the drug effects via different mechanisms which can help in reducing the various disease symptoms. However, the existing literature data is scarce with very few studies characterizing the safety and efficacy of using the combination of nortriptyline and pregabalin in managing the Indian subjects with diabetic peripheral neuropathy.[7] Hence, the present study aimed to assess the tolerability and safety of a fixed dose combination of Nortriptyline and pregabalin in managing peripheral neuropathy in diabetics.

Materials and Methods

The present clinical observation study was aimed at assessing the tolerability and safety of a fixed-dose combination of Nortriptyline and pregabalin in managing peripheral neuropathy in diabetics. The study was done at Department of Neurology, Super Specialty Hospital and Government Medical College, Nagpur, Maharashtra after the clearance was given by the concerned Institutional Ethical committee. The study population was from the Department of Neurology of the Institute. Informed consent was taken from all the study participants in verbal and written form after explaining the study design to all the study subjects in detail.

The inclusion criteria for the study were subjects that visited the Institute with type 2 diabetes mellitus and had evidence of painful diabetic neuropathy for more than the last 1 month and on NRS (numeric rating scale), had mean pain intensity of more than 50%. The exclusion criteria for the study were subjects that did not give consent for study participation, lactating females, pregnant females, other causes of painful conditions and neuropathy, allergic to nortriptyline or pregabalin, contraindication to take nortriptyline or pregabalin, and/or intolerance to nortriptyline or pregabalin.

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The study included 110 type 2 diabetic subjects with diabetic peripheral neuropathy from both genders. All the subjects were given a fixed dose combination of 10 mg nortriptyline and 75 mg Pregabalin once daily in the morning after they were finally included in the study and fitting in the inclusion criteria for the study.

To assess the efficacy of the fixed drug combination in the study subjects, the change in the mean pain score was assessed using an 11-point NRS (numeric rating scale) which was assessed on visit 1 or baseline at day1, visit 2 at day 14, and visit 3 at day 28. The numeric rating scale comprised of ratings from 0 to 10 where 0 described no pain and 10 represented the worst possible pain. A rating between 1-3, 4-6, and 7-10 respectively represented the mild pain, moderate pain, and severe pain on NRS or numeric rating scale.

To further assess the efficacy of the fixed drug combination in the study subjects, DSIRS (daily sleep interference rating scale) and PGIC (patient global impression of change) scales were used. To assess the safety, causal relationship, severity, duration, and nature of all the adverse effects of the study drug were evaluated and recorded at all the recall visits for all the study subjects.

The data gathered were analyzed statistically using SPSS (Statistical Package for Social Sciences) version 21.0 (IBM Corp., Armonk, NY, USA) and ANOVA (analysis of variance) test to assess the descriptive variables. The data were expressed as mean and standard deviation and frequency and percentage. The significance level was considered at $p<0.05$.

Results

The present clinical observation study was aimed at assessing the tolerability and safety of a fixed-dose combination of Nortriptyline and pregabalin in managing peripheral neuropathy in diabetics. The study assessed 112 subjects that were recruited from all the subjects with type 2 diabetes mellitus visiting the institute with diabetic peripheral neuropathy. On day 1 or baseline visit, all the subjects were assessed for pain on NRS (numeric rating scale), blood pressure, weight, and height as vital signs, and were also assessed for physical examination. Among these screened 112 subjects, 105 were finally included that met the final inclusion criteria, and 7 subjects were excluded as they did not fulfill the inclusion criteria. During follow-up, 3 subjects were further excluded as they did not come for follow-up. The study finally assessed 102 subjects who turned up for all the follow-up visits. However, the subjects assessed for safety

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were 105 as they came for at least one follow-up visit and were administered with a minimum of one dose of fixed drug combination.

The mean pain score in the study subjects assessed on a numeric rating scale at baseline or first visit was 7.92±0.64. A reduction in the mean pain score at NRS was recorded at 2nd visit to 4.93±0.76. A further decrease in the mean pain score was seen at 3rd visit 2.44±0.78. At baseline or 1st visit, the mean score for DSIRS (Daily sleep interference rating scale) was 7.02±1.03 which decreased to 3.94±1.13 at the 2nd visit and further decreased to 3.46±1.24 at the third visit. The mean score for PGIC (patient global impression of change) at baseline or visit 1 was 4.02±0.00. The mean score for PGIC (patient global impression of change) at 2nd visit was decreased to 1.61±0.63 and a further reduction in mean PGIC scores was seen at 3rd visit to 1.37±0.56. These differences were found to be statistically significant with $p<0.001$ (Table 1).

The study results showed that changes in the mean pain scores assessed at NRS (numeric rating scale) from visit 2 to visit 1 (baseline) were -2.97±0.97. The change in the mean pain score from visit 3 to visit 2 on NRS was -2.47±1.12. The change in the mean pain score from visit 3 to visit 1 (baseline) on NRS was found to be -5.46±1.00. The change in the mean pain scores using DSIRS was -3.01±1.56 from visit 2 to baseline (visit 1). The alteration in the mean pain scores using DSIRS from visit 3 to visit 2 was -0.46±0.48, and the change in mean pain scores from visit 3 to baseline was -3.50±1.66. The alteration in the mean pain scores from visit 2 to baseline using the PGIC was -2.35±0.59. The change from visit 3 to visit 2 was -0.22±0.43. The mean change in pain scores on PGIC from visit 3 to visit 1 (baseline) was -2.59±0.56. No pain worsening was seen on PGIC in any subject at the 2nd or 3rd visit. The change in the mean pain scores was found to be highly significant statistically with $p<0.001$ as shown in Table 2.

Adverse events to the fixed drug combination were reported in 5.35% (n=6) subjects. All the reported 6 adverse events were mild and were not related to the study design. All the adverse events reported were resolved completely following the administration of over-the-counter drugs, symptomatic treatment, and appropriate medications. The most common adverse event reported in 1.90% (n=2) subjects was body pain. Drowsiness and headache were seen in 3.89% (n=4) of study subjects. Fever, hyperacidity, and fever with pain were reported by one subject each. All the reported adverse effects were mild in severity and were resolved completely within 24 hours after giving appropriate and symptomatic medication for the side effects.

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Discussion

The present study assessed 112 subjects that were recruited from all the subjects with type 2 diabetes mellitus visiting the institute with diabetic peripheral neuropathy. On day 1 or baseline visit, all the subjects were assessed for pain on NRS (numeric rating scale), blood pressure, weight, and height as vital signs, and were also assessed for physical examination. Among these screened 112 subjects, 105 were finally included that met the final inclusion criteria, and 7 subjects were excluded as they did not fulfill the inclusion criteria. During follow-up, 3 subjects were further excluded as they did not come for follow-up. The study finally assessed 102 subjects who turned up for all the follow-up visits. However, the subjects assessed for safety were 105 as they came for at least one follow-up visit and were administered with a minimum of one dose of fixed drug combination. These data were comparable to Mahmood R et al[8] in 2017 and Asrar MM et al[9] in 2021 where authors followed a similar study design and assessed subjects with demographic data comparable to the present study.

The study results showed that the mean pain score in the study subjects assessed on a numeric rating scale at baseline or first visit was 7.92±0.64. A reduction in the mean pain score at NRS was recorded at 2nd visit to 4.93±0.76. A further decrease in the mean pain score was seen at 3rd visit 2.44±0.78. At baseline or 1st visit, the mean score for DSIRS (Daily sleep interference rating scale) was 7.02±1.03 which decreased to 3.94±1.13 at 2nd visit and further decreased to 3.46±1.24 at the third visit. The mean score for PGIC (patient global impression of change) at baseline or visit 1 was 4.02±0.00. The mean score for PGIC (patient global impression of change) at 2nd visit was decreased to 1.61±0.63 and a further reduction in mean PGIC scores was seen at 3rd visit to 1.37±0.56. These differences were found to be statistically significant with $p<0.001$. These results were consistent with the previous studies of Azmi S et al[10] in 2019 and Tolle T et al[11] in 2008 where authors reported a similar decrease in diabetic peripheral neuropathy pain after pregabalin and nortriptyline intake as seen in the results of the present study.

It was also seen that changes in the mean pain scores assessed at NRS (numeric rating scale) from visit 2 to visit 1 (baseline) were -2.97±0.97. The change in the mean pain score from visit 3 to visit 2 on NRS was -2.47±1.12. The change in the mean pain score from visit 3 to visit 1 (baseline) on NRS was found to be -5.46±1.00. The change in the mean pain scores using DSIRS

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was -3.01±1.56 from visit 2 to baseline (visit 1). The alteration in the mean pain scores using DSIRS from visit 3 to visit 2 was -0.46±0.48, and the change in mean pain scores from visit 3 to baseline was -3.50±1.66. The alteration in the mean pain scores from visit 2 to baseline using the PGIC was -2.35±0.59. The change from visit 3 to visit 2 was -0.22±0.43. The mean change in pain scores on PGIC from visit 3 to visit 1 (baseline) was -2.59±0.56. No pain worsening was seen on PGIC in any subject at the 2nd or 3rd visit. The change in the mean pain scores was found to be highly significant statistically with $p<0.001$. These results were in agreement with Lesser H et al[12] in 2004 and Bansal D et al[13] in 2009 where authors suggested similar changes in the pain intensity at different visits as seen in the present study results.

In the present study, adverse events to the fixed drug combination were reported in 5.35% (n=6) subjects. All the reported 6 adverse events were mild and were not related to the study design. All the adverse events reported were resolved completely following the administration of over-the-counter drugs, symptomatic treatment, and appropriate medications. The most common adverse event reported in 1.90% (n=2) subjects was body pain. Drowsiness and headache were seen in 3.89% (n=4) of study subjects. Fever, hyperacidity, and fever with pain were reported by one subject each. All the reported adverse effects were mild in severity and were resolved completely within 24 hours after giving appropriate and symptomatic medication for the side effects. These findings correlated with the studies of Khajuria K et al[14] in 2021 and Veves A et al[15] in 2008 where similar adverse effects to the present study were reported by the authors in their respective studies.

Conclusions

Considering its limitations, the present study concludes that a fixed dose combination of nortriptyline and pregabalin is a well-tolerated and efficacious modality for therapeutic management of subjects with diabetic peripheral neuropathy. However, further longitudinal studies are warranted to reach a definitive conclusion.

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S. No	Scale	Visit 1	Visit 2	Visit 3	p-value
1.	**NRS**	7.92±0.64	4.93±0.76	2.44±0.78	**<0.001**
2.	**DSIRS**	7.02±1.03	3.94±1.13	3.46±1.24	
3.	**PGIC**	4.02±0.00	1.61±0.63	1.37±0.56	

Table 1: Decrease in pain at different visits in study subjects with different scales

S. No	Parameters for efficacy	Change from visit 2 to visit 1	Change from visit 3 to visit 2	Change from visit 3 to visit 1	p-value
1.	**NRS**	-2.97±0.97	-2.47±1.12	-5.46±1.00	<0.001
2.	**DSIRS**	-3.01±1.56	-0.46±0.48	-3.50±1.66	
3.	**PGIC**	-2.35±0.59	-0.22±0.43	-2.59±0.56	

Table 2: Changes in the parameters of efficacy in study subjects at different visits