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RESEARCH ARTICLE
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"A COMPARATIVE STUDY OF EFFICACY AND SAFETY OF PREGABALIN WITH METHYLCOBALAMIN VERSUS DULOXETINE WITH METHYLCOBALAMIN IN DIABETIC PERIPHERAL NEUROPATHY PATIENTS WITH TYPE 2 DIABETES MELLITUS"

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ABSTRACT

BACKGROUND: Diabetic peripheral neuropathy (DPN) is the most common microvascular complication in type I and type II diabetes mellitus, an average 30% of patients with clinical manifestation as a painful neuropathy. Symptomatic treatment with an anticonvulsant and SNRI (Serotonin Nor-Adrenaline Receptor reuptake inhibitor) like Pregabalin (PGB) and Duloxetine (DLX with Methylcobalamin (MCB)) improve neuropathic pain and sleep.

METHODS: 90 DPN patients who have been screened using Michigan Neuropathy Score Instrument were randomized into two groups of 45 each to receive either Duloxetine(DLX) 20 mg (dose titration allowed up to 40 mg/day) with Methylcobalamin (MCB) 1500 mcg or Pregabalin (PGB)75 mg (dose titration allowed up to 150 mg/day) with MCB 1500 mcg tablet once daily in the night for 12 weeks. Efficacy was measured by reduction in Visual analog score (VAS) score and sleep interference (SIS) score at week 4, 8 and 12 from baseline. Safety was assessed by monitoring treatment emergent adverse effects. Data analysed by using repeated measure ANOVA, unpaired and paired't' test for continuous data and chi-square test for categorical data.

RESULTS: The mean VAS and SIS score after 12 weeks of treatment was 5.1±1.03 and 4.6±1.07 PGB + MCB in the group and 4.3±1.02 and 3.2±0.97 in DLX + MCB group. PGB + MCB and DLX + MCB both groups effectively reduced VAS and SIS score compared to baseline ($p<0.0001$) at the end of 12 weeks. A greater percentage of patients experienced improvement in sleep and pain in the DLX + MCB group (73%) compared to PGB + MCB (64%). No significant adverse effects were noted.

CONCLUSION: DLX + MCB combination significantly reduced VAS and SIS score as compared to PGB + MCB with no significant adverse effects and thus can be favourable therapeutic option in patients who failed monotherapy with PGB OR DLX in DPN

KEY WORDS: Diabetic peripheral neuropathy; MNSI; Pregabalin; Duloxetine; Methylcobalamin

INTRODUCTION: Diabetic sensorimotor polyneuropathy (DSPN), a common debilitating microvascular complication of diabetes affects approximately 50% of patients and roughly 11 to 20% of these experience painful DSPN, which can impact sleep, mood and daily activities resulting in poor quality of life and economic burden[1,2,3].

The International Consensus Panel on DPN recommends Tricyclic antidepressants, Serotonin-Nor Epinephrine Reuptake Inhibitors, Pregabalin or Gabapentin, out of which Pregabalin(PGB) and Duloxetine(DLX) are approved by both US- FDA and European Medicines Agency[4].
PGB a GABA analogue exerts its analgesic effect by binding to α2δ subunit of presynaptic voltage dependant calcium channel by inhibiting the release of glutamate[4,5]. PGB exhibits linear pharmacokinetics, low inter subject variability, fewer drug- drug interactions[5], no impact on lipid profile & glycemic control but may cause weight gain upto 1.6 kg[6]. The onset of pain relief with PGB is as early as 1St week with a consistent improvement of subjective sleep[7].
DLX a balanced and potent SNRI(Seratonin-Norepinephrine Reuptake Inhibitor) modulates pain via descending inhibitory pain pathways with efficacy of DLX is 1.27 times and improvement in QOL 1.44 times better than that of PGB with less usage of supplemental analgesics[8,9,10]. Further DLX has no adverse effects on metabolic paramaters and QTc interval[11].
Methylcobalamin(MCB) a potent active form of cyanocobalamin, protects against the glutamate induced neurotoxicity, enhances nerve regeneration and exerts analgesic effect by suppressing ectopic spontaneous pain discharges[12,13]. MCB was found to improve somatic and autonomic symptoms significantly [14].

Considering the fact that direct head to head comparative studies are not reported to the best of our knowledge till date for Pregabalin vs Duloxetine with add on MCB in DPN patients, this study is undertaken

Materials & methods : This study is a Randomized, , Open label, Prospective, Comparative Study conducted at Department of Medicine at Victoria hospital attached to Bangalore Medical College and Research Institute, Bengaluru. The protocol was approved with the Ethics Committee of our Institute and adhered to the tenets of the Declaration of Helsinki.

Patients with Type 2 DM with DPN patients attending the diabetic clinic Out-Patient department aged between 18 and 60 years belonging to either gender between November 2018 to May 2020 were included after obtaining written informed consent.

Type 2 diabetic patients (ADA criteria) diagnosed with diabetic neuropathy as per clinical signs and symptoms with A score of more than 7 on the MNSI (Michigan Neuropathy Screening Instrument) questionnaire (part I) or a score more than 2.0 on the MNSI examination score (part II) and A pain score of at least 40 mm on the 100 mm visual analogue scale (VAS) and patients with HbA1c value $\leq$10 gm%

Exclusion of other causes of neuropathy by history and clinical examination was done. Patients with hypersensitivity and/ or contraindications to study drugs, pregnant or lactating females and patients with medical conditions like hepatic, cardiac or renal failure were excluded.

90 patients newly diagnosed DPN with DM will be allotted into two groups of 45 each and randomized in 1:1 ratio using computer random sequence generator to receive either PGB 75 mg (dose titration allowed upto 150 mg/day) with MCB 1500 mcg or DLX 20 mg (dose titration allowed upto 40 mg/day) with MCB 1500 mcg tablet once daily as decided by the consultant physician based on the

clinical status. At screening, the eligibility criteria for inclusion were pain attributed to DPN based on history, clinical examination, MNSI Questionnaire, monofilament testing. Each patient will be given a unique identity number. Demographic data, medical history, concomitant medications, physical examination, clinical examination including recording of vital signs and details of drug prescription by the treating physician will be recorded in the study proforma and relevant blood investigations will be done at baseline visit (visit 1).
The primary efficacy parameter is reduction in severity of pain rating recorded by patients in daily diaries using 11 point VAS (0- no pain and 10- worst possible pain).The monthly mean VAS score for pain is calculated for each patient. The reduction in mean VAS score value from baseline to 12 weeks post treatment is considered as the primary end point.

Secondary efficacy end points is the monthly mean sleep interference score from daily sleep diary. Sleep interference is rated on 11 point scale that described how pain had interfered with patients's sleep during 24 hours in a day (0- did not interfere and 10- unable to sleep due to pain). Also presence/ absence of positive symptoms like parasthesia, dysesthesia, spasm and negative symptoms like hyposthesia, anaesthesia and weakness are documented at baseline and at the end of 12 weeks.

Follow-up visits will be at 4 weeks (visit 2), 8 weeks (visit 3) and 12 weeks (visit 4) after administering the study drugs. A deviation of ±2 days for first follow-up and ±1 week for subsequent follow-ups will be accepted. At follow-up visits reduction in VAS and sleep interference score will be recorded.

Concomitant medications that are necessary will be given at the discretion of the physician and will be recorded.
Relevant laboratory investigations will be repeated on Day 90 (Visit 4/Week 12). Adverse events will be recorded using CDSCO-ADR form and graded according to severity.

Sample size calculation: The sample size was calculated at a confidence level of 95%, A sample size of **90** was taken for better validation of results. The study subjects will be randomly assigned into 2 groups of 45 patients each.

Statistical analysis:
The Continuous data in this study will be assessed using repeated measure ANOVA and un paired 't' test. Categorical data will be assessed using chi-square test. Data was collected and continuous variables were expressed as Mean ± Standard Deviation (parametric data) or as median and inter quartile range (non-parametric data). The continuous data in this study was analysed using repeated measure ANOVA (analysis of variance) for intragroup comparison and unpaired 't' test (parametric data) for intergroup comparison. Non-parametric continuous variables were analysed using Mann Whitney 'U' test for intergroup comparison. Categorical data was expressed as percentages /proportions and was analysed using chi-square test. $p < 0.05$ was considered statistically significant. Statistical analysis was performed using Vassar Stats software.

Results:
100 patients were screened for the study of whom 90 patients who met the inclusion and exclusion criteria and gave written informed consent to participate were enrolled in the study. The flow chart of recruitment, randomization and follow up is depicted in figure 1. Group 1 received PGB(75 mg, Dose titration allowed up to 150 mg) with MCB (1500 mcg) tablet once daily and DLX(20 mg, dose titration allowed up to 40 mg) with MCB (1500 mcg) tablet once daily for 12 weeks.

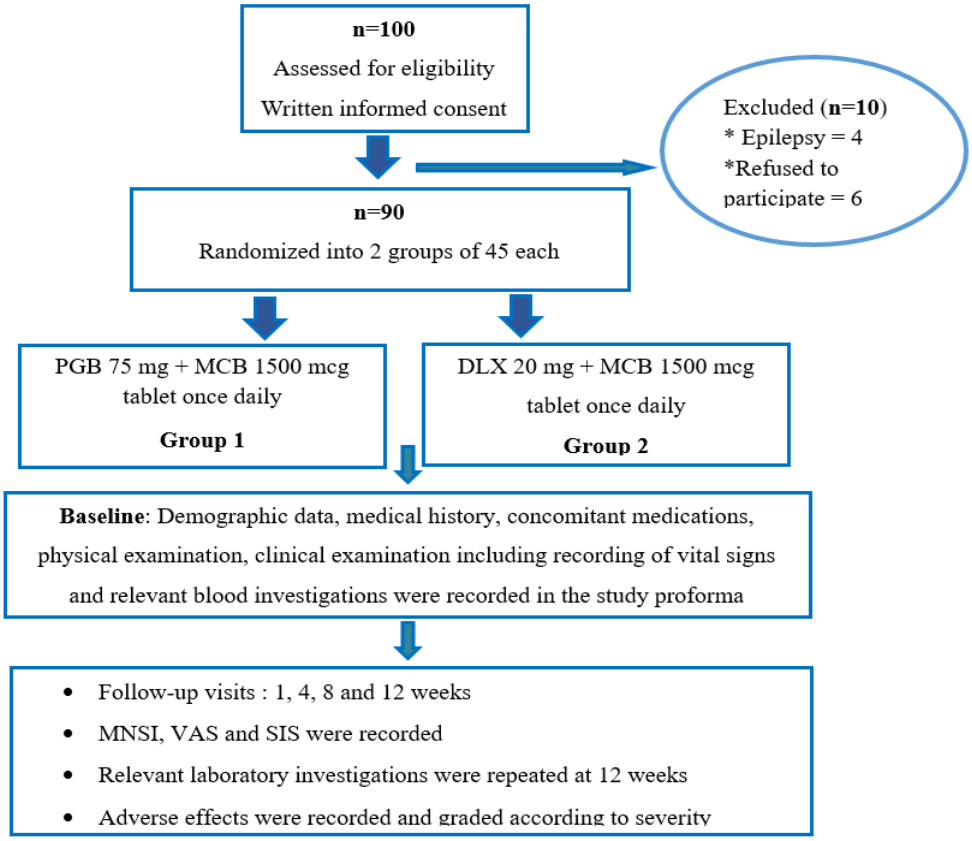


Figure I: Flow chart of recruitment, randomization and follow up

Demographic Characteristics

Table I represents the demographic profile of the patients included in the study. Both the treatment groups were matched with respect to baseline demographic characteristics

Table I: Baseline demographic characteristics

Parameters	**Group 1** PGB 75 mg + MCB 1500 mcg tablet once daily **(n=45)**	**Group 2** DLX 20 mg + MCB 1500 mcg tablet once daily **(n=45)**	***p value***
Age (years) (Mean ± SD)	63.11± 4.9	62.57 ± 5.3	0*
Gender- n (%)			
Male	27 (60%)	26 (57.7%)	0.8303**
Female	18 (40%)	19 (43.3%)	
Co-morbidities n (%)			
Dyslipidaemia	4	5	
Hypertension	17	20	0.**
Hypothyroidism	4	5	
Ischemic heart disease	2	3	
COPD			
No	1	2	
	17	10	

* Data analysed using unpaired t test, **Data analysed using Chi-square, p <0.05 is considered statistically significant, DM=Type 2 diabetes mellitus, CVA=Cerebrovascular accidents

Assessment of neuropathy using Michigan Neuropathy Screening Instrument

The MNSI includes two parts, the first part is related to the patient's perception of symptoms in relation to diabetic peripheral neuropathy and the second part consists of set of a set of examinations done to detect DPN among the patients. The examination includes,

i) vibration test using 128 Hz tuning fork

ii) elicitation of muscle jerk reflex at ankle joint and

iii) monofilament testing.

Mean score of MNSI in PGB + MCB group 7.2±1.19 and DLX + MCB 6.9±0.8 which was matched using independent t test with *p value 0.08*

Measurement of Reduction in VAS score:

The baseline mean VAS score was comparable between the two groups ($p = 0.16$). VAS was 8.3±0.9 in PGB + MCB group and 8.1±1.02 in DLX + MCB group.

Table 7 shows the mean VAS in the PGB + MCB group and DLX + MCB groups at baseline and at each of the follow up visits. The mean VAS after 12 weeks of treatment was 5.1±1.03 in the g PGB + MCB group and 4.3±1.02 in the DLX + MCB group. PGB + MCB group and DLX + MCB effectively reduced VAS score compared to baseline ($p <$) at the end of 12 weeks. Figure 22 and 23 represents the mean VAS score in both the groups at baseline and at each follow up visits respectively.

Table II: Mean VAS at follow up visits

Groups	**Group 1** **PGB 75 mg/day + MCB 1500 mcg/day (n = 45)**	**Group 2** **DLX 40 mg/day + MCB 1500 mcg/day (n = 45)**	**p value**
(Mean±SD)	**VAS**	**VAS**	
Baseline	8.3±0.9	8.1±1.02	p<0.0001*
4 weeks	6.9±0.9	6.6±1.1	<0.0001*
8 weeks	5.8±0.9	5.4±1.09	<0.0001*
12 weeks	5.1±1.03	4.3±1.02	<0.0001*

Data analysed by repeated measures ANOVA (intra-group comparison), * $p < 0.05$ is considered statistically significant. Post hoc analysis using Tukey HSD test showed $p < 0.05$ between each visit is statistically significant

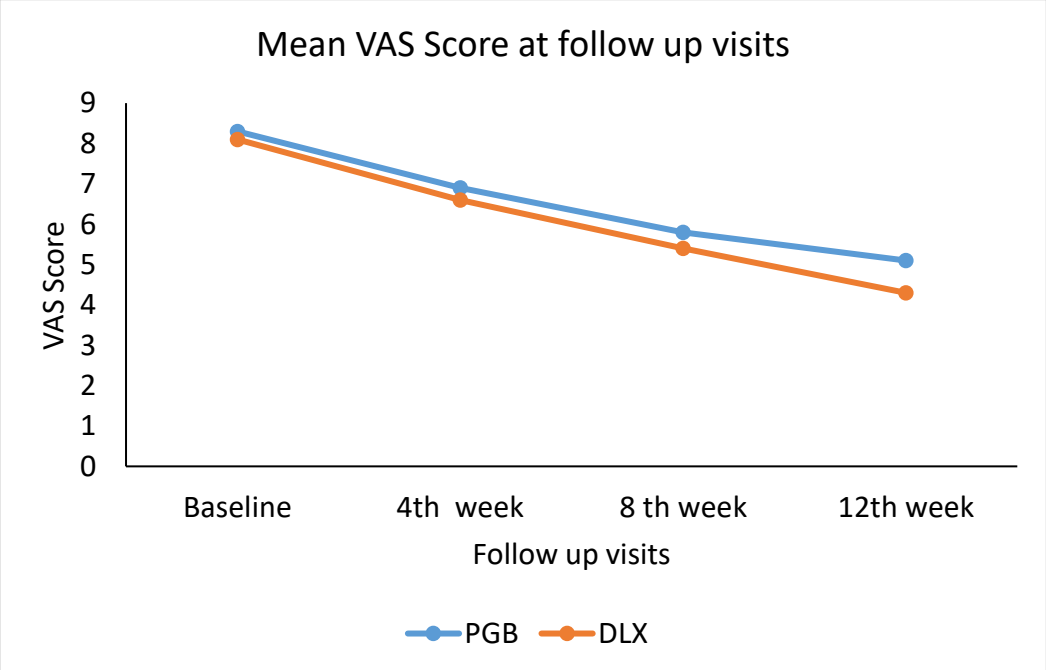


Figure II: Mean VAS Score at follow up visits

Measurement of Reduction in SIS score:

The baseline mean SIS score was comparable between the two groups (p = 0.06). SIS score was in 8.4±0.78 PGB + MCB group and 8.08±1.16 in DLX + MCB group.

Table III shows the mean SIS in the PGB + MCB group and DLX + MCB groups at baseline and at each of the follow up visits. The mean SIS after 12 weeks of treatment was 4.6±1.031.07 in the g PGB + MCB group and 3.2±0.97 in the DLX + MCB group. PGB + MCB group and DLX + MCB effectively reduced SIS score compared to baseline (p <0.0001) at the end of 12 weeks.

Table III: Mean SIS score at follow up visits

Groups	**Group 1 PGB 75 mg/day + MCB 1500 mcg/day (n = 45)**	**Group 2 DLX 40 mg/day + MCB 1500 mcg/day (n = 45)**	**p value**
(Mean±SD)	**SIS**	**SIS**	
Baseline	8.4±0.78	8.08±1.016	p<0.01*
4 weeks	6.7±0.94	5.7±1.27	p<0.01*
8 weeks	5.9±1.06	4.4±1.15	p<0.01*
12 weeks	4.6±1.07	3.2±0.97	p<0.01*

Data analysed by repeated measures ANOVA (intra-group comparison), * p < 0.05 is considered statistically significant. Post hoc analysis using Tukey HSD test showed p < 0.05 between each visit is statistically significant.

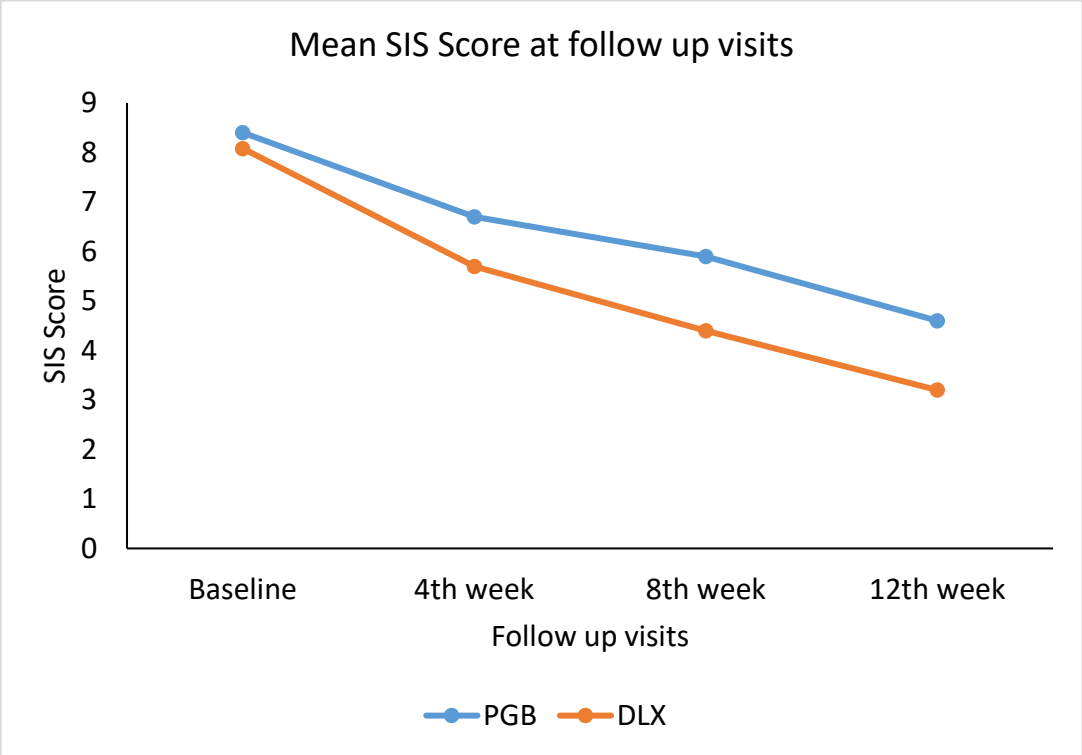


Figure III: Mean SIS Score at follow up visits

Evaluation of DPN symptoms:

DPN positive symptoms like paraesthesia, dysesthesia, spasm and negative symptoms like hypoesthesia, anaesthesia and weakness were documented at baseline and at the end of 12 weeks. Positive symptoms were matched at baseline and there was no statistically significant reduction of positive symptoms between the groups (p=0.7). Negative symptoms were matched at baseline and there was no statistically significant reduction of negative symptoms between the groups (p=0.26). There was a significant reduction in positive (p=0.04) and negative symptoms (p=0.03) in PGB + MCB

group from baseline to 12 weeks. There was a significant reduction in positive (p=0.03) and negative symptoms (p=0.01) in DLX + MCB group from baseline to 12 weeks.

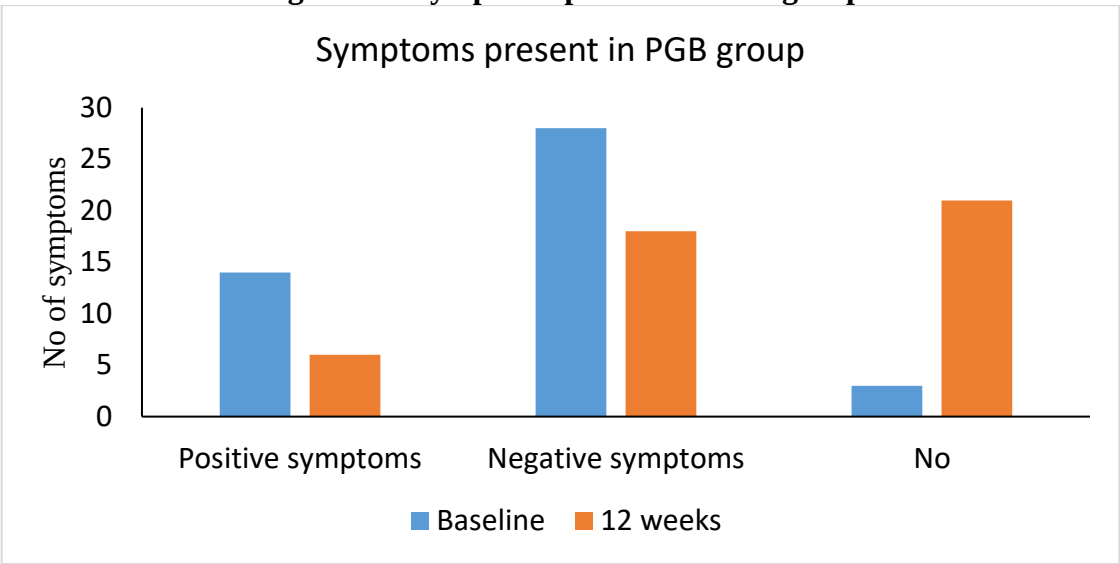
Table IV: Positive and Negative symptoms in both the groups

Symptoms	**Group 1 PGB + MCB (n = 45)**		**Group 2 DLX + MCB (n = 45)**		***P value****
Positive	**Baseline**	**12 weeks**	**Baseline**	**12 weeks**	
Paraesthesia	06	03	07	03	**0.7**
Dysesthesia	03	--	04	03	
Spasm	05	03	05	02	
Negative					
Hypoesthesia	09	08	08	04	0.26
Anaesthesia	07	03	06	04	
Weakness	12	07	10	04	

* Data analysed using Chi-square with Yate's correction, $p > 0.05$ is considered not statistically significant

$\chi^2 = 3.32$, df = 1, $p = 0.7$ and p= 0.

Figure IV: Symptoms present in PGB group



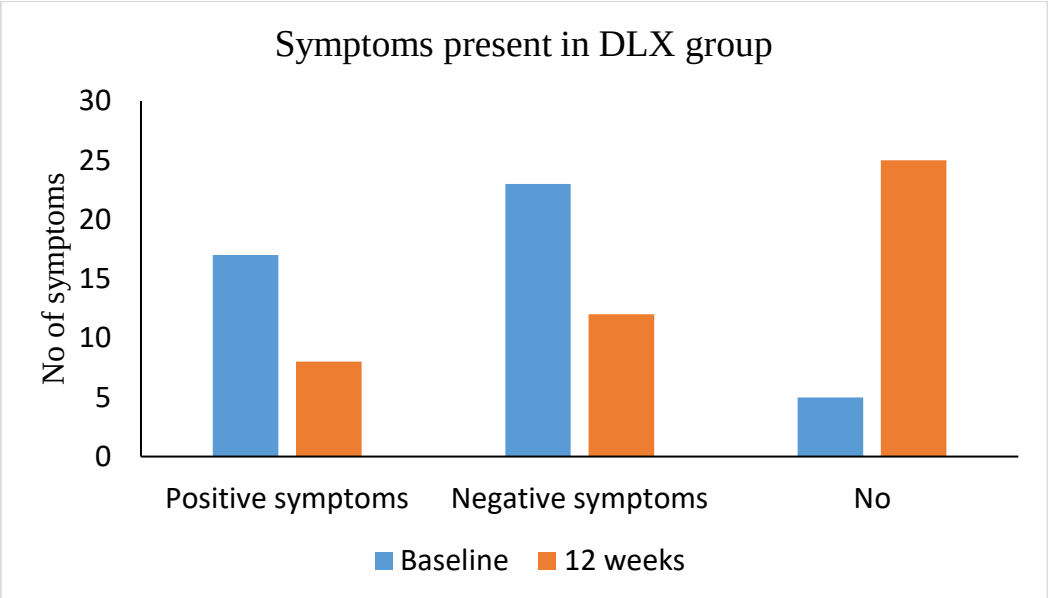


Figure IV: Symptoms present in DLX group

Evaluation of Safety parameters

The adverse drug reactions (ADRs) encountered were mild to moderate in nature and there was no statistically significant difference between the groups (p = 0.67), though the total number of ADRs was slightly higher in PGB + MCB group compared to DLX + MCB group.

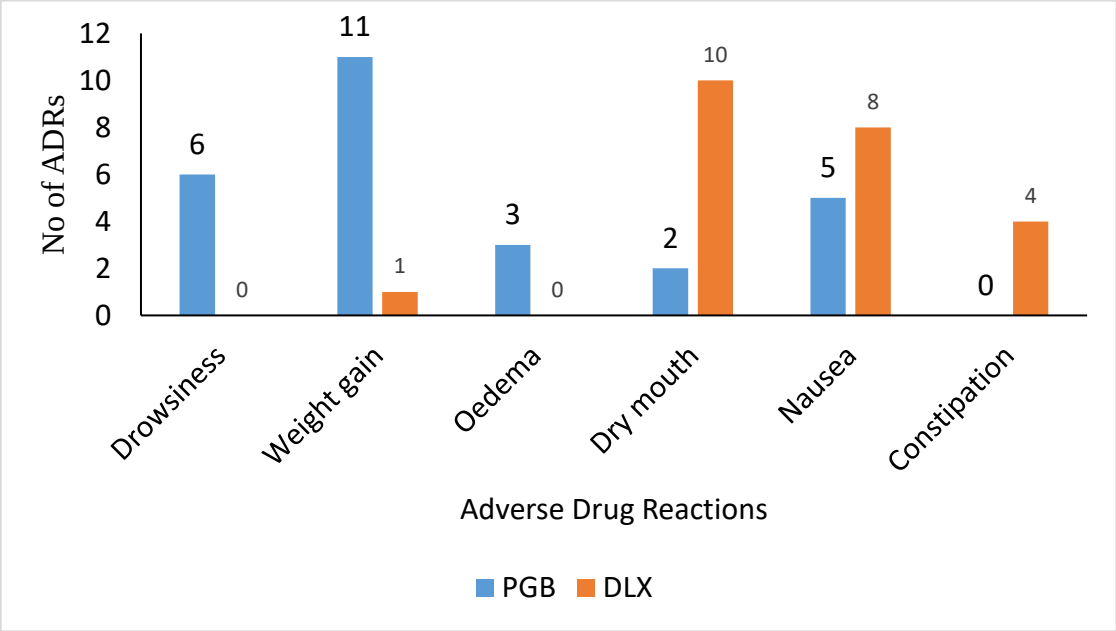


Figure V: Adverse Drug Reactions of both groups

DISCUSSION

Diabetic peripheral neuropathy (DPN) is the most common microvascular complication in type I and type II diabetes mellitus, an average 30% of patients with clinical manifestation as a painful neuropathy. DPN means the presence of symptoms and/or signs of peripheral nerve damage that occur to people with diabetes, excluding all other causes of neuropathy. Neuropathies develop about 5-10% of the patients in initial years, and 60-70% of the patients after 20 years the duration of diabetes. Patients with diabetic sensory neuropathy have a 25% greater risk of developing an ulcer on the feet and amputation of the limbs. The three-year survival of patients with diabetic neuropathy is about 20% lower compared to patients without diabetic neuropathy

There is Male preponderance in our study with 60% in PGB + MCB in group and 57.7% in DLX + MCB in group. A randomised control study in 2019 on DPN management among Indian population done by Shahid W et.al also reported that 57.7% male population in their study. [15].

Mean score of MNSI in PGB + MCB group 7.2±1.19 and DLX + MCB 6.9±0.8 which was matched using independent t test with p value 0.08. The present study findings are in accordance with a study done by Popescu S et.al which showed prevalence of DPN according to Michigan Neuropathy Screening Instrument (MNSI) was 28.8%, being significantly and positively correlated with higher age[15].. In our study, it was observed that the VAS score and Sleep Interference Scores significantly reduced compared to the baseline ($p < 0.0001$) in both the groups at the end of 12 weeks.

A comparative study done by Shahid W et.al showed that the mean VAS score decreased from 6.81 ± 0.91 to 4.01 ± 1.12 with 12 weeks of DLX therapy ($p < 0.0001$) and the mean VAS score decreased from 6.99 ± 1.12 to 4.91 ± 0.82 with 12 weeks of PGB therapy ($p < 0.0001$). The mean change in VAS score over time was - 2.80 with DLX group compared to the mean change - 2.82 for Pregabalin group[15]. The above findings are congruent with our study, which showed the mean change in VAS score with DLX + MCB group was −3.8 compared to −3.2 for PGB + MCB group of patients at the end of 12 weeks ($p = 0.0001$).

Methylcobalamin is an essential element in the synthesis of the myelin sheath and helps to restore the function of the nerve in neuropathy. 7 Methylcobalamin as an add on to our study drugs is backed by

yet another study done by Alvarez M.et. Al found that high prevalence of low levels of vitamin B12 in 17% of patients with diabetic neuropathy and altered (low or borderline) vitamin B12 level was 64% (95% CI: 47– 78%) compared to 17% (95% CI: 10–26%) in patients without diabetic neuropathy. [17].

In the present study, the mean SIS score in the PGB + MCB group reduced from 8.4±0.78 to 4.6±1.07 at the end of 12 weeks. In the DLX + MCB group it reduced from 8.08±1.016 to 3.2±0.97 at the end of 12 weeks. Our study showed the mean change in SIS score with DLX + MCB group was −4.8 compared to −3.8 for PGB + MCB group of patients at the end of 12 weeks (p = 0.0001). The present study findings are in line with a study done by Majdinasab N.et.al proved that the mean change in SIS score with DLX group was −4.08 compared to −3.69 for Gabapentin (GBP) group of patients at the end of 12 weeks (p = 0.08) [18].. In contrast to the present study findings, a Randomized, placebo controlled, comparative study done by Boyle J et.al showed that Pregabalin arm had improved ease of getting to sleep and improved quality of sleep by ncreasing sleep efficiency and total sleep time (TST) compared to Duloxetine arm which improved CNS arousal and information processing ability with an increased Critical Flicker Fusion (CFF) threshold[8].

DPN positive symptoms like paraesthesia, dysesthesia, spasm and negative symptoms like hypoesthesia, anaesthesia and weakness were documented at baseline and at the end of 12 weeks. In our study, there was a significant reduction in positive (p=0.04) and negative symptoms (p=0.03) in PGB + MCB group and significant reduction in positive (p=0.03) and negative symptoms (p=0.01) in DLX + MCB group from baseline to 12 weeks. The present study findings are in line with a study done by Dongre Y U et.al showed that significant improvement of positive and negative symptoms from baseline to 14 days[7].

Conclusion : Thus DLX + MCB was found to be an effective and safe combination therapy in Type 2 DM patients with Diabetic peripheral neuropathy compared to PGB + MCB combination.

Limitations: The current study was conducted in a single centre, hence considering multi – centre with larger subset of population would further aids in generalisability of results.

Conflict of interest : None declared

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