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TO COMPARE THE EFFECTIVENESS OF AMITRIPTYLINE AND PREGABALIN IN THE MANAGEMENT OF DIABETIC NEUROPATHY IN SKBZ/CMH MUZAFFARABAD

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Abstract

Objectives: *To compare amitriptyline and pregabalin in the management of diabetic neuropathy in terms of mean pain score.*

Study design: *Randomized controlled trial.*

Place and duration of study: *H.H Sheikh Khalifa Bin Zayed Al-Nahyan Hospital/ CMH, Muzaffarabad from December 2023 to June 2024.*

Methodology: *Sixty two patients with diabetic neuropathy were given either amitriptyline or pregabalin for eight weeks. Numeric pain rating scale was assessed at baseline, four weeks and eight weeks after therapy and compared between groups. Data was analyzed by Statistical Package for Social Sciences software version 20.00.*

Results: *Mean age of patients was 46.37 ± 8.44 years. There were 42 (67.74%) male and 20 (32.26%) female patients. Mean duration of diabetes was 5.82 ± 2.44 years. Mean HbA1C% was 9.13 ± 1.39%. Mean baseline numeric pain rating scale (NPRS) score was 8.04 ± 1.55. Mean NPRS score at four weeks follow up in amitriptyline group (A) was 6.03 ± 1.49 while in pregabalin group (B) it was 4.93 ± 1.74 ($p = 0.010$). Mean NPRS score at eight weeks follow up in amitriptyline group (A) was 5.03 ± 1.49 while in pregabalin group (B) it was 2.70 ± 1.59 ($p < 0.001$).*

Conclusion: *Pregabalin is better in reducing pain related to diabetic neuropathy.*

INTRODUCTION

Type II Diabetes is a disease of endocrine system that is affecting more than 463 million (6.01%) people worldwide and in Pakistan, 10.6 – 19.1% population is affected by type II diabetes with 15.8% population affected being women and 14.8% being men. [1] Long-term diabetes has negative consequences on a number of physiological and anatomical processes in the body, including peripheral neuropathy, which can cause foot ulcers, amputation, and Charcot joints. [2] Chronic, potentially crippling, and painful diabetic neuropathy affects mostly the feet and legs and is characterized by paresthesia, numbness, tingling, and/or burning sensations. According to reports, diabetic neuropathy affects more than 40.3% of diabetic individuals. [3]

Multiple pharmacological agents are in use for management of diabetic neuropathy (DN) including gabapentinoids (pregabalin, gabapentin) and tricyclic

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antidepressants (amitriptyline). [4] Use of pregabalin for management of diabetic neuropathy (DN) was approved by USFDA in 2004 while amitriptyline is recommended drug for its management. Both of these medications have demonstrated effectiveness in treating diabetic neuropathy [5], but prior studies have found varying efficacy comparison results. A study reported that efficacy of amitriptyline, as compared to pregabalin in terms of reduction of pain score, was better (68.12% with amitriptyline and 61.83% with pregabalin, respectively) in an open label, randomized controlled study. [6] In contrast to this, a study conducted the study with similar objective using numeric pain rating system as a tool of assessment of severity of neuropathic pain. They reported that pregabalin was significantly far better drug for providing pain relief in neuropathic pain as compared to amitriptyline [4.38 ± 2.72 versus 6.32 ± 2.31, respectively]. [7]

Neuropathic pain is a difficult condition to treat and most patients suffering from it, due to their agony and inadequate choice of pharmacological agent lose their trust on treating physician and have higher risk of non-compliance. For this purpose, it is essential to find out optimal drug therapy to avoid these circumstances and improved patient outcome. Earlier researches have shown that either of these two medications are useful in neuropathic pain with some favoring pregabalin while others favoring amitriptyline for which it remains unclear which of these drugs is better than the other. For this purpose, present study was conducted with the aim to determine best choice of drug amongst these two for neuropathic pain in diabetic neuropathy patients to optimize patient outcomes.

METHODOLOGY

This randomized controlled trial was conducted at Department of Medicine, H.H Sheikh Khalifa Bin Zayed Al-Nahyan Hospital/ CMH, Muzaffarabad from December 2023 to June 2024. after obtaining approval from ethical committee of institution (IERB #: _____). Appropriate sample size was calculated using OpenEpi sample size calculator using following formula:

$$n = \frac{2\sigma^2(z_{1-\alpha} + z_{1-\beta})^2}{(\mu_1 - \mu_2)^2}$$

For calculations, following assumptions were used:

- Level of significance (α) = 5%
- Power (1-β) = 80%
- Anticipated mean post-treatment pain score in pregabalin group = 4.38 ± 2.72 [7]
- Anticipated mean post-treatment pain score in amitriptyline group = 6.32 ± 2.31 [7]

This gave a sample size (n) of 62 (31 patients in each group).

Inclusion criteria: All male and female patients aged between 18 to 60 years who presented with diabetic neuropathy (DN) and numeric pain rating scale (NPRS) score ≥ 4 at baseline were included in this study. Diabetic neuropathy was defined as "diabetic neuropathy score (DNS) > 1". [8]

Exclusion criteria: Patients with serum creatinine level > 1.3mg/dl, liver enzyme levels raised > 3 times of normal value, known allergy/contraindication to any of the study medication, history of urinary retention, pregnant females and lactating mothers were excluded from the study.

Patients were selected through non-probability consecutive sampling technique. Prior to inclusion in this study, a written informed consent was signed by all the patients. After this, baseline characteristics of the patients including the age (in years), gender (male/female), duration of diabetic disease (in years), HbA1C%, diabetic neuropathy (DNS) score and numeric pain rating scale (NPRS) score were documented prior to administration of any therapy. All these patients were then divided into two groups randomly by paper lottery method into two equal groups of thirty one patients each. Group A (n = 31) included patients who were prescribed tablet amitriptyline 25mg once daily for a period of eight weeks. Group B (n = 31) included patients who were prescribed capsule pregabalin 50 mg once daily for a period of eight weeks. Patients were then called for follow up visits at weeks four and eight after initiation of therapy to assess the efficacy of both

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these drugs by evaluating and documenting follow up numeric pain rating scale (NPRS) score.

Data was analyzed using SPSS version 26.0. The numeric variables (age, duration of diabetic disease, DNS score, HbA1C%, pre- and post-treatment NPRS) were expressed as mean ± standard deviation. The categorical variables (gender) was represented as frequency and percentages. Data was stratified by age, gender, duration of diabetic disease and pre-treatment NPRS to deal with effect modifiers. Post-stratification Student t-test was used. To compare post-treatment NPRS between two groups, Student t-test was used. Significant level was set at p-value ≤ 0.05.

RESULTS

In this study, 62 patients with diabetic neuropathy were included. Mean age of patients was 46.37 ± 8.44 years. There were 42 (67.74%) male and 20 (32.26%) female patients. Mean duration of diabetes was 5.82 ± 2.44 years. Mean HbA1C% was 9.13 ± 1.39%. Mean diabetic neuropathy score (DNS) was 6.11 ± 2.50. Mean baseline numeric pain rating scale (NPRS) score was 8.04 ± 1.55. Comparison of baseline characteristics between study groups is given below in table I:

Table I: Comparison of baseline characteristics of study groups (n = 62)

Parameter	Study groups		p-value
	Amitriptyline Group A (n = 31)	Pregabalin Group B (n = 31)	
Mean age	47.25 ± 8.58 years	45.48 ± 8.34 years	0.413
18-45 years	14 (45.16%)	17 (54.84%)	0.446
46-60 years	17 (54.84%)	14 (45.16%)	
Gender			
Female	10 (32.26%)	10 (32.26%)	1.000
Male	21 (67.74%)	21 (67.74%)	
Mean duration of diabetes	6.25 ± 2.33 years	5.38 ± 2.51 years	0.163
≤ 5 years	7 (22.58%)	13 (41.94%)	0.103
> 5 years	24 (77.42%)	18 (58.06%)	
Mean HbA1C%	8.94 ± 1.50 %	9.33 ± 1.26 %	0.278
Mean diabetic neuropathy score (DNS)	5.90 ± 2.27	6.32 ± 2.73	0.514
Mean baseline numeric pain rating scale (NPRS) score	8.03 ± 1.49	8.06 ± 1.63	0.936
< 8	12 (38.71%)	12 (38.71%)	1.000
≥ 8	19 (61.29%)	19 (61.29%)	

Mean NPRS score at four weeks follow up in amitriptyline group (A) was 6.03 ± 1.49 while in pregabalin group (B) it was 4.93 ± 1.74 (p = 0.010). Mean NPRS score at eight weeks follow up in amitriptyline group (A) was 5.03 ± 1.49 while in pregabalin group (B) it was 2.70 ± 1.59 (p < 0.001). This is demonstrated below in table II:

Table II: Comparison of mean four and eight weeks post-therapy NPRS score between group (n = 62)

Parameter	Study groups		p-value
	Amitriptyline Group A (n = 31)	Pregabalin Group B (n = 31)	
Mean NPRS score at 4 weeks follow up	6.03 ± 1.49	4.93 ± 1.74	0.010
Mean NPRS score at 8 weeks follow up	5.03 ± 1.49	2.70 ± 1.59	< 0.001

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Stratification of mean four and eight weeks follow up NPRS score by age, gender, duration of diabetic disease and pre-treatment NPRS is given below in table III:

Table III: Stratification of mean four and eight weeks follow up NPRS score by age, gender, duration of diabetic disease and pre-treatment NPRS (n = 62)

Amitriptyline group			
Age groups			
	18-45 years	**46-60 years**	**p-value**
Mean NPRS score at 4 weeks follow up	6.07 ± 1.49	6.00 ± 1.54	0.897
Mean NPRS score at 8 weeks follow up	5.07 ± 1.49	5.00 ± 1.54	0.897
Gender			
	Female	**Male**	
Mean NPRS score at 4 weeks follow up	5.80 ± 1.61	6.14 ± 1.45	0.559
Mean NPRS score at 8 weeks follow up	4.80 ± 1.61	5.14 ± 1.45	0.559
Duration of Disease groups			
	≤ 5 years	**> 5 years**	
Mean NPRS score at 4 weeks follow up	6.14 ± 1.57	6.00 ± 1.50	0.828
Mean NPRS score at 8 weeks follow up	5.14 ± 1.57	5.00 ± 1.50	0.828
Baseline NPRS groups			
	< 8	**≥ 8**	
Mean NPRS score at 4 weeks follow up	4.41 ± 0.51	7.05 ± 0.84	< 0.001
Mean NPRS score at 8 weeks follow up	3.41 ± 0.51	6.05 ± 0.84	< 0.001
Pregabalin group			
Age groups			
	18-45 years	**46-60 years**	**p-value**
Mean NPRS score at 4 weeks follow up	4.94 ± 1.91	4.92 ± 1.59	0.984
Mean NPRS score at 8 weeks follow up	2.76 ± 1.60	2.64 ± 1.64	0.837
Gender			
	Female	**Male**	
Mean NPRS score at 4 weeks follow up	5.20 ± 1.47	4.80 ± 1.88	0.570
Mean NPRS score at 8 weeks follow up	2.70 ± 1.25	2.71 ± 1.76	0.982
Duration of Disease groups			
	≤ 5 years	**> 5 years**	
Mean NPRS score at 4 weeks follow up	5.07 ± 1.84	4.83 ± 1.72	0.709

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Mean NPRS score at 8 weeks follow up	3.15 ± 1.57	2.38 ± 1.57	0.193
Baseline NPRS groups			
	< 8	**≥ 8**	
Mean NPRS score at 4 weeks follow up	3.00 ± 0.73	6.15 ± 0.83	< 0.001
Mean NPRS score at 8 weeks follow up	1.33 ± 1.30	3.57 ± 1.07	< 0.001

DISCUSSION

Diabetic neuropathy (DN) is a highly common diabetic complication that was the focus of my study. In this study, it is observed that frequency of diabetic neuropathy (DN) showed a male predominance which is consistent with the findings of multiple studies which reported male gender to be strongly associated with development of diabetic neuropathy. [9, 10] This could be due to decreased availability and access of health care to female gender in our society. On the other hand, opposite to findings of present study, Elliot et al. reported female gender to be a major risk factor for developing diabetic neuropathy. [11] Average duration between diagnosis of diabetes and diabetic neuropathy in present study was approximately six years. Compared to this, a study found this gap between diabetes and neuropathy diagnosis to be around eight years. [12] This shows that longer duration of having diabetes significantly increases the chances of developing diabetic neuropathy. [13] Average HbA1C% of patients having diabetic neuropathy was around 9% exhibiting poor glycemic control. This was in line with the findings of another study showing high HbA1C% values to be strongly associated with developing diabetic neuropathy. [14, 15]

In terms of baseline characteristics, no statistically significant difference was observed between study groups ($p > 0.05$). However, in terms of four and eight weeks follow up pain score values, pregabalin group (B) showed significantly lower pain scores as compared to amitriptyline group (A), demonstrating superior efficacy of pregabalin for management of DN. Similar to the findings of present study, Kancherla et al., Soomro et al. and Sharif et al. reported pregabalin to be a superior pharmaceutical agent for managing DN. [7, 16, 17] Contrary to the results of present study, Sankar et al. and Acet et al. found amitriptyline to provide better relief from pain of neuropathic nature as compared to pregabalin. [18, 19] In one study, no statistically significant difference was observed between amitriptyline and pregabalin in terms of effectively relieving neuropathic pain which also not consistent with the findings of present study. [20]

Diabetes is rampant across Pakistani population [21] and thus in future there will be a greater burden of its complications, like neuropathy. Based on evidence of present study, pregabalin appears to be much better drug for achieving reduction in pain associated with diabetic neuropathy for which preferred use of pregabalin is recommended. Limited sample size, shorter follow up duration and study being conducted at a single center were a few limitations of present study.

CONCLUSION

Diabetic neuropathy is one of the commonest complication encountered in clinical setting. Both amitriptyline and pregabalin are useful in management of this complication of diabetes but pregabalin is significantly better treatment option.

CONFLICT OF INTEREST

None.

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