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Efficacy and Safety Outcome (in Terms of Hyponatremia) of Duloxetine in the Treatment of Diabetic Peripheral Neuropathic Pain

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Abstract

Objective: To determine the efficacy and safety outcomes (in terms of hyponatremia) of duloxetine among patients with diabetic peripheral neuropathic pain at a tertiary care hospital.

Material and methods: This descriptive case series study using non–probability purposive sampling technique was done at diabetic outdoor of Nishtar hospital, Multan. Detailed history and physical examination of study participants was done and all the relevant baseline investigations were carried out and patients were prescribed with Duloxetine 60 mg once daily for 12 weeks. Data was entered and analyzed using SPSS-25.

Results: Three seventy-seven patients with diabetic peripheral neuropathic pain were taken in the study, of which 70.6% (n=266) were males and 29.4% (n=111) were female patients with their mean age; 61.71 ± 9.21 years (range; 45 years–79 years) and 52.5% (n=198) were aged >60 years. Of these 377 patients, 52% (n=196) were from urban localities, 63.9 % (n=241) were poor and 53.1% (n=200) were hypertensive. Mean duration of DPNP was 4.31 years±2.12 years and 63.9% (n=241) had duration more than 2 years. Mean BMI was 26.34 kg/m^2± 2.23 kg/m^2 and 30% (n=113) were obese. Efficacy was noted in 57.6% (n=217) and mean serum sodium level was 137.23 nmol/L ± 2.41 nmol/L and hyponatremia was noted in 3.2% (n=12).

Conclusion: Duloxetine is found to be safe, well tolerate and effective in Diabetic Peripheral Neuropathic Pain (DPNP) and can be employed safely to relieve symptoms of DPNP. Efficacy was significantly associated with younger age groups, residential status, hypertension and obesity. Duloxetine induced hyponatremia was most prevalent side effect which was associated with female gender and older ages.

Keywords: Duloxetine; Efficacy; Diabetic peripheral neuropathic pain

Introduction

Diabetic neuropathy is encountered in estimated 70 % diabetic patients and Diabetic Peripheral Neuropathic Pain (DPNP) is a common, debilitating and one of the most devastating complications of the Type 2 Diabetes Mellitus (T2DM) [1-3]. Despite its debilitating impacts on quality of life, management yet remains to be poor and approximately 35% patients remain untreated while those who are treated; often receive medication with low or little efficacy [4]. Diabetic neuropathy is generally associated with neuronal apoptosis as well as inhibitory mechanism nerve regeneration as a result of elevated blood sugar levels and it leads to the development of high deficits of tactile sensitivities, vibrational senses, proprioception of lower limbs and kinaesthesia. The commonest form of DPNP is "distal sensorimotor polyneuropathy" and is usually specified by the sensory symptoms regarded as "glove and stocking distribution" [5]. Apart from causing chronic pains, numbness, paresthesia and lack of sensitivity it is also associated with sleep disorders, depressive mood symptoms, increased risk of foot injuries, burns and has a negative impact on quality of life and daily routine work as it hinders routine activities [6].

Duloxetine is relatively balanced selective Serotonin/ Norepinephrine Reuptake Inhibitor (SNRI) and it is employed to treat major depressive disorders, diabetic neuropathies, generalized anxiety disorder, Diabetic Peripheral Neuropathic Pain (DPNP), fibromyalgia and chronic musculoskeletal pains and it is approved by FDA for the treatment of DPNP along with pregabalin [7,8].

Duloxetine in reduction of patient's perception of pain by enhancing mechanism of descending pain pathways which reduce signals of pain that arise from peripheries [9,10]. Duloxetine induced hyponatremia is quite low and is usually prevalent among patients having depressive symptoms and chronic neuropathy pain and is associated with female gender and increasing age, however mechanism of duloxetine induced hyponatremia remains unclear [11].

We conducted this study to ascertain effectiveness, safety and burden of duloxetine induced hyponatremia in Diabetic Peripheral Neuropathic Pain (DPNP). Duloxetine induced hyponatremia is associated with significant morbidity, female gender with older ages, so early management followed by diagnosis remains cornerstone for the treatment of these patients.

Material and Methods

This descriptive case series study using non–probability purposive sampling technique was done at diabetic outdoor of Nishtar hospital, Multan. In this study we recruited 377 patients with DPNP from January 01, 2021 to March 31, 2021, assessed clinically, of either sex aged 40 years–80 years. Patients with history of diuretic use, pre-existing hyponatremia, excessive intake of salt and water and don't give consent of participation were excluded from our study. Sample size was calculated using 43% efficacy [12] of Duloxetine in DPNP as hypothesized frequency of efficacy, 95% CI and 5% margin of error on EPI–info software of CDC. Informed consent was taken from the

patients describing them objectives of this study, ensuring them confidentiality of the information provided and fact that there was no risk involved to the patient while taking part in this study. Detailed history and physical examination of study participants was done and all the relevant baseline investigations were carried out and patients were prescribed with Duloxetine 60 mg once daily for 12 weeks. These patients were called for follow up every week to document resolution of symptoms of DPNP (at least 50% reduction in pain from baseline using VAS was considered as efficacious) and three ml of venous blood sample was drawn. This blood sample was sent to central laboratory of Nishtar hospital for serum sodium level estimation and Patients were considered hyponatremic, if they have serum Na+ levels<135 nmol/L.

Data was entered and analyzed using SPSS-25. Descriptive statistics was applied to calculate mean and standard deviation for the age of the patients and serum sodium levels. Frequencies and percentage were tabulated for the categorical variables like efficacy of duloxetine, age groups, gender and hyponatremia (Yes/No). Effect modifiers like age, disease duration and gender were controlled by making stratified tables by applying chi– square test (95% CI).

Results

Three seventy-seven patients with diabetic peripheral neuropathic pain were taken in the study, of which 70.6% (n=266) were males and 29.4% (n=111) were female patients with their mean age; 61.71 years ± 9.21 years (range; 45 years-79 years) and 52.5% (n=198) were aged >60 years. Of these 377 patients, 52% (n=196) were from urban localities, 63.9% (n=241) were poor and 53.1% (n=200) were hypertensive. Mean duration of DPNP was 4.31 years ± 2.12 years and 63.9% (n=241) had duration more than 2 years. Mean BMI was 26.34 kg/m^2 ± 2.23 kg/m^2 and 30% (n=113) were obese. Efficacy was noted in 57.6% (n=217) and mean serum sodium level was 137.23 nmol/L ± 2.41 nmol/L and hyponatremia was noted in 3.2% (n=12) (Table 1).

Study variables	Efficacy		P value
	Yes	No	
Gender			
Male (n= 266)	150	116	0.48
Female (n=111)	67	44	
Age groups			
Up to 60 years (n= 198)	181	17	0.002
More than 60 years (n=179)	36	143	
Residential status			
Rural (n=181)	116	65	0.01
Urban (n=196)	101	95	
Socioeconomic status			
Poor (n=241)	130	111	0.065
Middle income (n=136)	87	49	
Disease duration			
Up to 2 years(n=136)	74	62	0.386
More than 2 years (n=241)	143	98	
Hypertension			
Yes (n=200)	74	126	0.002
No (n=177)	143	34	
Obesity			
Yes (n=113)	79	34	0.002
No (n=264)	138	126	

Table 1: Stratification of efficacy of duloxetine with regards to study variables.

Discussion

Diabetic Peripheral Neuropathic Pain (DPNP) complicates almost 47% diabetic patients and economic burden of diabetes is increasing in South Asian nation including Pakistan and Pakistan is among 5 top

countries harboring burden of diabetes which is expected to increase by year 2030. Duloxetine that selectively inhibits serotonin and noradrenaline reuptake has been associated with superior efficacy of DPNP in term of relief of symptoms and positive impact on quality of life on short and long term basis [13].

Three seventy-seven patients with diabetic peripheral neuropathic pain were taken in the study, of which 70.6% (n=266) were males and 29.4% (n=111) were female patients. Wernicke et al. [12] has also reported 64.9% male gender preponderance in DPNP. A Japanese study conducted by Yasuda et al. [14] also reported 76% male patients with DPNP, similar to our results. Wasan et al. [15] also reported 60% male patients with DPNP. A Canadian study by Raskin et al. [16] has also reported 61.5% male patients.

Mean age of our study cases was 61.71 years ± 9.21 years (range; 45 years-79 years) and 52.5% (n=198) were aged >60 years. Wernicke et al. [12] has also reported 59.7 years ± 11.2 years mean age. A Japanese study conducted by Yasuda et al. [14] also reported 60.1 years ± 10 years mean age among patients with DPNP, same as our results. Wasan et al. [15] also reported 53.4 years ± 7.9 years mean age of patients with DPNP. A Canadian study by Raskin et al. [16] has also reported 59.7 years ± 10.7 years mean age, close to our results.

Of these 377 patients, 52% (n=196) were from urban localities, 63.9% (n=241) were poor and 53.1% (n=200) were hypertensive. A Canadian study by Raskin et al. [16] has also reported similar results.

Mean duration of DPNP was 4.31 years ± 2.12 years and 63.9% (n=241) had duration more than 2 years. A Japanese study conducted by Yasuda et al. [14] also reported 4.1 years ± 3.6 years mean duration of DPNP. Wasan et al. 18 also reported 3.6 years ± 3.7 years mean duration of DPNP. A Canadian study by Raskin et al. [16] has also reported 3.9 years ± 4.5 years mean duration of symptoms, similar to our results. Mean BMI was 26.34 kg/m^2 ± 2.23 kg/m^2 and 30% (n=113) were obese. A Japanese study conducted by Yasuda et al. and Wasan et al. [15] also reported similar results. A Canadian study by Raskin et al. has reported 101 kilograms ± 24 kilograms weight of the patients with DPNP, showing compliance with our results.

Efficacy of duloxetine was noted in 57.6% (n=217). Wernicke et al. [12] has also reported 43 % efficacy of duloxetine. A Japanese study conducted by Yasuda et al. [14] also reported significant improvement (P<0.001) in relieving symptoms, consistent with our study results. A Canadian study by Raskin et al. [16] has reported 50% efficacy of duloxetine. Mean serum sodium level was 137.23 nmol/L ± 2.41 nmol/L and hyponatremia was noted in 3.2% (n=12). All hyponatremic patients (n=12) were females and aged more than 70 years encountered within first week of start of therapy which is consistent with available literature [17,18].

Conclusion

Duloxetine is found to be safe, well tolerate and effective in Diabetic Peripheral Neuropathic Pain (DPNP) and can be employed safely to relieve symptoms of DPNP. Efficacy was significantly associated with younger age groups, residential status, hypertension and obesity. Duloxetine induced hyponatremia was most prevalent side effect which was associated with female gender and older ages.

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