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Original Research Article

Effect of amitriptyline and pregabalin on heart rate variability and electrolytes in neurotrophic pain in diabetic patients

Rohan Srivastava[1]*, N. D. Kantharia[2]

[1]Department of Medicine, Breach Candy Hospital, Mumbai, Maharashtra, India
[2]Department of Pharmacology, Government Medical College, Surat, Gujarat, India

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***Correspondence:**
Dr. Rohan Srivastava,
Email: drrohan3005@gmail.com

ABSTRACT

Background: The data regarding effects of amitriptyline and pregabalin on heart rate variability in patients with neuropathic pain in diabetic patients are poorly understood in India. The present study was conducted to evaluate the effect of amitriptyline and pregabalin on heart rate variability in diabetic patients with neuropathic pain and their effect on serum electrolyte (sodium and potassium).
Methods: The patients include 60 diabetic patients of either sex aged 18-65 years diagnosed with neuropathic pain and divided into two groups. The study was prospective open label and observational study. Group 1 was treated with amitriptyline 10 mg once a day while group 2 with pregabalin 75 mg once a day and HRV, serum sodium and serum potassium levels and pain score were recorded; and data of post-treatment at 2 and 4 weeks were compared with pretreatment values (control). All the statistical analysis was performed by using SPSS 20.0 software.
Results: Both the drugs have increased HRV and reduced neuropathic pain intensity after 2 and 4 weeks treatment. The sodium and potassium level were not altered by these drugs. No correlation was observed between HRV and neuropathic pain.
Conclusions: In conclusion, both the amitriptyline and pregabalin have significantly increased HRV and reduced the neuropathic pain intensity; but no correlation was observed between increased HRV and reduced neuropathic pain intensity.

Keywords: Heart rate variability, Amitriptyline, Pregabalin, Neuropathic pain, Electrolytes

INTRODUCTION

Multiple causes of neurpathic pain (NP) have been described, the commonest being diabetes mellitus. Neuropathic pain (irrespective of the cause) had been demonstrated to affect heart rate variability. Autonomic neuropathy is usually manifested in the patients of diabetes mellitus and too affects heart rate variability. Many studies have shown that patients suffering from cardiovascular disease with low heart rate variability (HRV) have risk for mortality. Heart rate variability (HRV) is the physiological phenomenon of variation in the time interval between heartbeats. It is measured by the variation in the "RR interval". A high degree of HRV reflects the ability to adapt quickly to physical or psychological demands of the environment as seen in healthy individuals, while lower levels of HRV are associated with cardiac damage, including myocardial infarction, impaired ventricular ejection and sudden cardiac death. Chronic NP involves the affective and evaluative components and associated with abnormality in autonomic nervous system.[1,2] Patients with neuropathic pain have lower HRV, which can be determined by HRV

time domain parameter SDNN.[3] Patients with diabetic neuropathy have also shown altered HRV indices.[4] Studies have shown that treatment with tricyclic antidepressants including amitriptyline in cases of depression was associated with decrease in HRV.[5] Pregabalin increases the heart rate variability and thus improves cardiac autonomic functions. Also, amitriptyline affects QT interval resulting in its prolongation; thus may contribute to cardiac morbidity and mortality in long term outcomes.

Drugs like pregabalin, low dose amitriptyline, duloxetine and gabapentin have proved to be beneficial in relieving pain in the patients of neuropathic pain. Studies outside India have shown that low dose amitriptyline and pregabalin produced significant effects on heart rate variability. The data regarding effects of amitriptyline and pregabalin on cardiac autonomic function i.e. effect on HRV in neuropathic patient in India are limited and poorly understood. Thus, present study was conducted to study effect of amitriptyline and pregabalin on HRV and whether HRV is related with alteration in neuropathic pain. Serum sodium and potassium level were also measured to find out any correlation between HRV and sodium and potassium level. The safety (with respect to heart rate variability) of amitriptyline and pregabalin in neuropathic pain was also compared.

METHODS

Study population

The subjects/patients were recruited from the medicine outpatient department of tertiary care hospital (New Civil hospital, Government medical college, Surat) with a sample size of 60 diabetic patients, suffering from neuropathic pain. The study period was from Janaury 2017 to June 2018. The study was approved by institutional ethical committee before the commencement of study. Written informed consents were taken from the participants (patients) before their enrollment for study.

Study design

Our study is a prospective open label, observational study with a follow up period of 4 weeks. The present study includes 60 patients of either sex aged 18-65 years diabetic who have been diagnosed with neuropathic pain. They were further subdivided into 2 groups. Group-1 amitriptyline group with 28 patients (13 males and 15 females) as 2 patients lost to follow up; and group-2 pregabalin group with 27 patients (16 males and 11 females) as 3 patients lost to follow up. The group -1 was treated with amitriptyline (10 mg once day i.e. OD); while group-2 with pregabalin (75 mg OD). In each group, heart rate variability (ECG), serum sodium and potassium levels and pain score were recorded. Pretreatment value of heart rate variability, serum potassium, serum sodium and pain score of the same patient were served as control. The parameters recorded were compared for pretreatment and post-treatment/follow up at 2 and 4 weeks.

Inclusion criteria

The inclusion criteria were patients of either sex between the ages of 18-65 years, patients who are giving informed consent, newly diagnosed patients of diabetic neuropathic pain, not exposed to earlier treatment with amitriptyline and pregabalin and undergoing therapy for the duration of minimum 4 weeks.

Exclusion criteria

The exclusion criteria were patients not giving consent for enrolment in study, patients with cardiovascular disease, patients with history of substance abuse within a year, patients with suicidal tendencies (depression), concurrent major illness or systemic dysfunction involving hepatic and renal system, children, pregnant and lactating women and patients with history of allergy to any of the above medication.

Procedure

Heart rate variability (HRV) was calculated by root mean square deviation of successive differences between adjacent RR intervals (RMSSD). ECG was recorded for 5 minutes by physiopac digital polygraph software after 20 minutes of rest. The pain was assessed by using an 11 point visual analog scale (VAS; 0-10 cm) representing the pain intensity, where 0 represents “no pain” and 10 indicates “unbearable pain.” The blood samples of patients were taken to determine the sodium and potassium level before the treatment (pre-treatment) and 2 and 4 weeks after the treatment (post-treatment).

Statistical analysis

All the statistical analysis was performed by using SPSS 20.0 software. All values obtained were expressed as mean±SD. The final statistical analysis was performed by repeated measure analysis of variance (ANOVA) test to find put any significant difference with Greenhouse-Geisser correction; followed by post hoc analysis with Bonferroni correction. The $p<0.05$ was taken as minimal level of significance.

RESULTS

Amitriptyline has produced statistically significant effect on heart rate variability after 2 weeks (56.10±8.54) ($p<0.0001$) and 4 weeks (68.989±10.8) ($p<0.0001$) treatment as compared to pretreatment values. On pair-wise comparison, the effect of amitriptyline on HRV after 4weeks ($p<0.0001$) treatment as compared to 2 weeks ($p<0.003$) treatment was statistically significant indicating further increase in HRV (Table 1-2). Pregabalin has also produced statistically significant effect on heart rate variability after 2 weeks (54.89±9.06)

(p<0.0001) and 4 weeks (69.03±10.6) (p<0.0001) as compared to pretreatment values. Comparing the effect of pregabalin on HRV between 2 weeks and 4 weeks treatment was statistically significant indicating further increase in HRV (Table 3-4).

Table 1: Effect of amitriptyline on HRV in diabetic patients (estimates).

Heart rate variability	Mean	Std. Error	95% Confidence interval		P value
			Lower bound	Upper bound	
Pretreatment	51.146	4.325	42.273	60.020	<0.0001
After 2 weeks	56.107	4.271	47.343	64.871	
After 4 weeks	68.989	5.405	57.898	80.080	

Table 2: Effect of amitriptyline on HRV in diabetic patients (pairwise comparisons based on table 1).

(I) HRV	(J) HRV	Mean difference (I-J)	Std. Error	P value	95% Confidence interval for difference[a]	
					Lower bound	Upper bound
Pre treat	After 2 weeks	-4.961*	1.730	0.008	-8.511	-1.410
	After 4 weeks	-17.843*	4.440	<0.0001	-26.952	-8.734
After 2 weeks	Pretreatment	4.961*	1.730	0.008	1.410	8.511
	After 4 weeks	-12.882*	3.967	0.003	-21.022	-4.742
After 4 weeks	Pretreatment	17.843*	4.440	<0.0001	8.734	26.952
	After 2 weeks	12.882*	3.967	0.003	4.742	21.022

Based on estimated marginal means, *the mean difference is significant at the 0.05 level. a. adjustment for multiple comparisons.

Table 3: Effect of pregabalin on HRV in diabetic patients (estimates).

Heart rate variability	Mean	Std. Error	95% Confidence interval		P value
			Lower bound	Upper bound	
Pretreatment	50.481	4.517	41.196	59.767	<0.0001
After 2 weeks	54.896	4.503	45.640	64.153	
After 4 weeks	69.033	5.375	57.985	80.081	

Table 4: Effect of pregabalin on HRV in diabetic patients (pairwise comparisons based on table 3).

(I) HRV	(J) HRV	Mean difference (I-J)	Std. Error	P value	95% Confidence interval for difference[a]	
					Lower bound	Upper bound
Pre treat	After 2 weeks	-4.415*	0.689	<0.0001	-5.832	-2.998
	After 4 weeks	-18.552*	4.296	<0.0001	-27.382	-9.721
After 2 weeks	Pretreatment	4.415*	0.689	<0.0001	2.998	5.832
	After 4 weeks	-14.137*	4.393	0.003	-23.167	-5.107
After 4 weeks	Pretreatment	18.552*	4.296	<0.0001	9.721	27.382
	After 2 weeks	14.137*	4.393	0.003	5.107	23.167

Based on estimated marginal means, *the mean difference is significant at the 0.05 level, a. adjustment for multiple comparisons: Bonferroni: least significant difference

Table 5: Effect of amitriptyline on neuropathic pain in diabetic patients (estimates).

Pain score	Mean	Std. Error	95% Confidence interval		P value
			Lower bound	Upper bound	
Pretreatment	8.168	0.108	7.946	8.389	<0.0001
After 2 weeks	6.414	0.073	6.265	6.563	
After 4 weeks	4.175	0.106	3.958	4.392	

Table 6: Effect of amitriptyline on neuropathic pain in diabetic patients (Pairwise comparisons based on table 5).

(I) Pain score	(J) Pain score	Mean difference (I-J)	Std. Error	P value	95% Confidence interval for difference[a]	
					Lower bound	Upper bound
Pre treat	After 2 weeks	1.754*	0.118	<0.0001	1.511	1.996
	After 4 weeks	3.993*	0.150	<0.0001	3.685	4.301
After 2 weeks	Pretreatment	-1.754*	0.118	<0.0001	-1.996	-1.511
	After 4 weeks	2.239*	0.113	<0.0001	2.008	2.471
After 4 weeks	Pretreatment	-3.993*	0.150	<0.0001	-4.301	-3.685
	After 2 weeks	-2.239*	0.113	<0.0001	-2.471	-2.008

Based on estimated marginal means, *the mean difference is significant at the 0.05 level, a. adjustment for multiple comparisons: least significant difference (equivalent to no adjustments).

Table 7: Effect of pregabalin on neuropathic pain in diabetic patients (estimates).

Pain score	Mean	Std. Error	95% Confidence interval		P value
			Lower bound	Upper bound	
Pretreatment	8.407	0.074	8.256	8.559	<0.001
After 2 weeks	6.396	0.081	6.230	6.562	
After 4 weeks	3.763	0.081	3.596	3.930	

Table 8: Effect of pregabalin on neuropathic pain in diabetic patients (pairwise comparisons based on table 7).

(I) Pain score	(J) Pain score	Mean difference (I-J)	Std. Error	P value	95% Confidence interval for difference[a]	
					Lower bound	Upper bound
Pre treat	After 2 weeks	2.011*	0.105	<0.0001	1.795	2.227
	After 4 weeks	4.644*	0.116	<0.0001	4.407	4.882
After 2 weeks	Pretreatment	-2.011*	0.105	<0.0001	-2.227	-1.795
	After 4 weeks	2.633*	0.110	<0.0001	2.407	2.860
After 4 weeks	Pretreatment	-4.644*	0.116	<0.0001	-4.882	-4.407
	After 2 weeks	-2.633*	0.110	<0.0001	-2.860	-2.407

Based on estimated marginal means, *the mean difference is significant at the 0.05 level, a. adjustment for multiple comparisons: Bonferroni: least significant difference

Table 9: Effect of amitriptyline on serum sodium and potassium in diabetic patients.

Drugs	Variable	Mean	Std. Error	95% Confidence Interval		P value
				Lower bound	Upper bound	
Na	Pretreatment	140.236	0.470	139.271	141.201	0.562
	After 2 weeks	140.243	0.556	139.101	141.384	
	After 4 weeks	140.000	0.358	139.266	140.734	
K	Pretreatment	4.204	0.065	4.069	4.338	0.816
	After 2 weeks	4.050	0.064	3.918	4.182	
	After 4 weeks	4.193	0.044	4.103	4.283	

Amitriptyline has produced reduction in neuropathic pain intensity as observed on VAS after 2 and 4 weeks treatment as compared to pretreatment values. The reduction in pain was statistically significant (p<0.0001). On pair-wise comparison, the effect of amitriptyline on pain after 4 weeks treatment as compared to 2 weeks treatment was also statistically significant (Table 5-6). The patients treated with pregabalin have shown reduced neuropathic pain intensity which was statistically significant (p<0.0001). On pair-wise comparison, there was further reduction in pain intensity after 4 weeks treatment as compared to 2 weeks treatment. This reduction in pain intensity was also statistically significant (Table 7-8). There was no significant difference on sodium and potassium level after 2 and 4 weeks treatment with amitriptyline as compared to pretreatment values. The pair-wise analysis was not applied as the serum values were within normal range (Table 9). Similaly, no significant difference was observed on sodium and potassium level after 2 and 4

weeks treatment with pregabalin as compared to pre-treatment values. The serum values were within normal range, therefore, pair-wise analysis was not applied (Table 10).

Table 10: Effect of pregabalin on serum sodium and potassium in diabetic patients.

Drugs	Variable	Mean	Std. Error	95% Confidence Interval		P value
				Lower bound	Upper bound	
Na	Pretreatment	140.159	0.482	139.169	141.149	0.063
	After 2 weeks	140.107	0.481	139.119	141.096	
	After 4 weeks	141.430	0.364	140.681	142.178	
K	Pretreatment	4.063	.061	3.937	4.189	0.092
	After 2 weeks	4.048	.059	3.927	4.170	
	After 4 weeks	4.196	.045	4.103	4.290	

In the present study, no difference was observed between effect of amitriptyline and pregabalin on HRV in diabetic neuropathy patients indicating their similar effect on HRV. Also on anlaysis, no co-relation was observed between HRV and neuropathic pain in diabetic patients (data not shown).

DISCUSSION

Increased risk of sudden cardiac death in patients with ischaemic heart disease and heart failure was associated with low HRV as shown by various studies.[4,6] Amitriptyline has produced statistically significant effect on heart rate variability (HRV) after 2 and 4 weeks treatment as compared to pretreatment values in diabetic patients. On the contrary, when used in cases of depression, amitriptyline was associated with decrease in HRV.[5] Effect of pregabalin on HRV was similar to amitriptyline as above. Patients with neuropathic pain have lower HRV.[3] Patients with diabetic neuropathy have shown altered HRV indices.[6] Pregabalin increases the heart rate variability; and thus improves cardiac autonomic functions. Similar results were obtained in earlier studies.[7,8] Jiang et al have also demonstrated the improvement in HRV after pregabalin treatment for 4 week in patients of diabetic neuropathy.[9]

The improvement of HRV was not correlated with reduction in pain intensity in the present study. However, in another study assessment of pain was done by multidimensional pain assessment tool i.e. short form McGill pain questionnaire (SF-MPQ) than the single-dimensional assessment tool (VAS). In this study, HRV positively correlated with SF-MPQ scores in patients after abdominal surgery. Amitriptyline has produced significant reduction in neuropathic pain intensity as observed on VAS after 2 and 4 weeks treatment as compared to pretreatment values. Another study has shown improvement of pain by amitriptyline after 4 weeks of treatment though improvement was slow; but adverse effects were more (sedation was common).[10] The study by Kaur et al have shown that amitriptyline was effective in diabetic neuropathic pain without significant side effect.[11] In their study also, pain relief showed >50% improvement of pain score but complete pain relief was not observed.

The possible mechanism of improved HRV by pregabalin may be due to reduced release of neurotransmitters (glutamate, noradrenaline, 5-HT, dopamine, and substance P) from the presynaptic neurones, leading to reduced sympathetic activity and augmented parasympathetic activity; thus produce improvement in HRV apart from increased GABA level. By similar neurotransmitter mechanism, it produces relief in neuropathic pain.[12-15] P Pain relief due to pregabalin may also be associated with activation of K_{ATP} channels.[16] Devi et al have shown significant reduction in pain score by pregabalin.[17] In their study, dose was titrated based on response of the patients to pain while in our study the dose of pregabalin was fixed (75 mg once a day) on safety concern. Intensity of pain was significantly reduced but no complete pain relief; possibly due to non-compliance or uncontrolled diabetes or use of lower dose of pregabalin used in our study (75 mg OD) as compared to other studies (75 mg to 150 mg twice a day); and assessment of pain by multidimensional pain assessment tool i.e. short form McGill pain questionnaire (SF-MPQ) than the single-dimensional assessment tool (VAS). Chang et al have shown positive correlation between HRV and postoperative pain with SF-MPQ scores in patients after abdominal surgery.[18] There was no significant difference on sodium and potassium level after 2 and 4 weeks treatment with these drugs and no study has shown alteration in sodium or potassium level by these drugs. Heart rate variability analysis can easily be applied for surveillance of diabetic (post-infarction) patients to prevent sudden death due to cardiac problems.

Limitations

The limitation of the study was small sample size as few patients lost to follow up and many patient were excluded based on exclusion criteria. The further study may be conducted with bigger sample size.

CONCLUSION

In conclusion, patients were given treatment and followed up after 2 weeks and 4 weeks. Both the amitriptyline (10 mg OD) and pregabalin (75 mg OD) have significantly increased HRV and significantly reduced the pain intensity but no correlation was observed between

increased HRV and reduced pain intensity. There was no significant change in serum sodium and potassium levels by amitriptyline and pregabalin. In the present study, low dose of these drugs were used; and these doses were safe as no significant adverse effect was observed. Based on our study, both amitriptyline and pregablin can safely be used in the lower doses for the treatment of diabetic neuropathic pain. However, further studies are needed with other drugs used for neuropathic pain and longer duration of treatment and follow up to ascertain maximum efficacy.

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