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Original Research Article

Evaluation of effect of amitriptyline and pregabalin on heart rate variability in neuropathic pain in non-diabetic patients

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ABSTRACT

Background: The effects of amitriptyline and pregabalin on heart rate variability (HRV) in patients with neuropathic pain in non-diabetic patients are poorly understood in India. The present study was conducted to evaluate the effect of amitriptyline and pregabalin on heart rate variability (HRV) and neuropathic pain in non-diabetic patients.
Methods: Forty adult patients (aged 18-65 years) of either sex diagnosed with neuropathic pain were divided into two groups. The study was prospective open label and observational study. Amitriptyline 10 mg once a day was given to group 1 while group 2 received pregabalin 75 mg once a day and HRV and pain score were recorded; and post-treatment data at 2 and 4 weeks were compared with pre-treatment values (control). All the statistical analysis was performed by using Statistical package for social sciences (SPSS) 20.0 software.
Results: Both amitriptyline and pregabalin have increased HRV and reduced neuropathic pain intensity after 2- and 4-weeks treatment. The correlation between HRV and neuropathic pain was not observed.
Conclusions: To conclude both the drugs have significantly increased HRV and reduced the pain intensity; but no correlation was observed between increased HRV and reduced pain intensity.

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

INTRODUCTION

Neuropathic pain (NP) may be due to multiple reasons. The common non-diabetic causes are nerve injury, nerve compression, viral infection (e.g. herpes zoster; postherpetic neuralgia), autoimmune disease (e.g. multiple sclerosis) and cancer. Neuropathic pain (irrespective of the cause) had been shown to affect heart rate variability. Many studies available showed 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; HRV can be measured by the variation in the "RR interval". A high degree of HRV is observed in healthy individuals and indicates the ability to adapt quickly to physical or psychological demands of the environment; while lower levels of HRV are associated with cardiac damage, including myocardial infarction, impaired ventricular ejection and in extreme cases sudden cardiac death.

Chronic neuropathic pain is associated with abnormality in autonomic nervous system and involves the affective and evaluative components.[1,2] Patients have lower HRV if they have neuropathic pain, that can be determined by HRV time domain parameter SDNN.[3] Patients with diabetic neuropathy have also shown altered HRV indices.[4] It has been observed that treatment of depression

with tricyclic antidepressants including amitriptyline was associated with decrease in HRV.[5] Pregabalin increases the heart rate variability; and thus improves cardiac autonomic functions. Amitriptyline also affects QT interval leading to its prolongation; thus, may contribute to cardiac morbidity and mortality in long term outcomes.

Drugs like duloxetine, low dose amitriptyline, gabapentin and pregabalin were shown to relieve 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. However, the effects of amitriptyline and pregabalin on cardiac autonomic function i.e. effect on HRV in non-diabetic neuropathic patient in India are poorly understood.

Thus, present study was conducted to evaluate the effect of amitriptyline and pregabalin on HRV and whether alteration in neuropathic pain is related with HRV. The safety of amitriptyline and pregabalin (with respect to heart rate variability) 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 40 non-diabetic patients, suffering from neuropathic pain. The study period was from January 2018 to December 2018. Before the commencement of study, the study was approved by institutional ethical committee. 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 40 patients of either sex aged 18-65 years non-diabetic who have been diagnosed with neuropathic pain.

They were further subdivided into 2 groups. Group-1 amitriptyline group with 20 patients (14 males and 6 females) as 2 patients lost to follow up; and group-2 pregabalin group with 19 patients (13 males and 6 females) as 1 patient 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) and pain score were recorded. Pretreatment value of heart rate variability and pain score of the same patient were served as control. The data recorded for pretreatment and post-treatment/follow up at 2 and 4 weeks were compared. The following inclusion and exclusion criteria were used to select the patient.

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 non-diabetic patients of 6 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 with diabetes or H/O diabetes, patients with cardiovascular disease, patients not giving consent for enrollment in study, 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.

Heart rate variability (HRV) was calculated by root mean square deviation of successive differences between adjacent RR intervals (RMSSD). The ECG was recorded for 5 minutes by physio Pac 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.”

Statistical analysis

The Statistical package for social sciences (SPSS) 20.0 software was used to perform all the statistical analysis. 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

The present study includes 40 non-diabetic patients of either sex aged 18-65 years who have been diagnosed with neuropathic pain. In amitriptyline group there were 20 patients (14 males and 06 females) while and in pregabalin group there were 19 patients (13 males and 06 females). The statistically significant effect was produced by amitriptyline on heart rate variability after 2 weeks (66.30±8.84) [$p<0.005$] and 4 weeks (80.840±11.2) [$p<0.005$] treatment as compared to pretreatment values. On pair-wise comparison, the effect of amitriptyline on HRV after 4 weeks treatment as compared to 2 weeks treatment was statistically significant indicating further increase in HRV (Table 1, 2).

Treatment with pregabalin has also produced statistically significant effect on heart rate variability after 2 weeks

(58.22±19.4) [p<0.0001] and 4 weeks (86.10±19.4) [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 non-diabetic patients (estimates).

Heart rate variability	Mean	Std. Error	95% Confidence interval		
			Lower bound	Upper bound	P value
Pre-treatment	61.875	3.917	53.677	70.073	
After 2 weeks	66.305	4.425	57.043	75.567	<0.005
After 4 weeks	80.840	5.614	69.090	92.590	

Table 2: Effect of amitriptyline on HRV in non-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-treatment	After 2 weeks	-4.430	2.373	.077	-9.396	.536
	After 4 weeks	-18.965*	5.980	.005	-31.482	-6.448
After 2 weeks	Pre-treatment	4.430	2.373	.077	-.536	9.396
	After 4 weeks	-14.535*	5.472	.016	-25.988	-3.082
After 4 weeks	Pre-treatment	18.965*	5.980	.005	6.448	31.482
	After 2 weeks	14.535*	5.472	.016	3.082	25.988

Based on estimated marginal means. N=20. *. The mean difference is significant at the .05 level. a. Adjustment for multiple comparisons: Bonferroni: Least Significant Difference

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

Heart rate variability	Mean	Std. deviation	95% Confidence interval		
			Lower bound	Upper bound	P value
Pre-treatment	53.5105	20.50571	43.627	63.394	<0.0001
After 2 weeks	58.2211	19.40320	48.869	67.573	
After 4 weeks	86.1000	19.42158	76.739	95.461	

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

(I) HRV	(J) HRV	Mean difference (I-J)	Std. Error	Sig.[a]	95% Confidence interval for difference[a]	
					Lower bound	Upper bound
Pre-treatment	After 2 weeks	-4.711*	1.522	0.006	-7.909	-1.512
	After 4 weeks	-32.589*	6.091	p<0.0001	-45.386	-19.793
After 2 weeks	Pre-treatment	4.711*	1.522	0.006	1.512	7.909
	After 4 weeks	-27.879*	6.101P	p<0.0001	-40.696	-15.061
After 4 weeks	Pre-treatment	32.589*	6.091	p<0.0001	19.793	45.386
	After 2 weeks	27.879*	6.101	p<0.0001	15.061	40.696

Based on estimated marginal means. N=19. *. The mean difference is significant at the .05 level. a. Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).

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

Pain score	Mean	Std. Error	95% Confidence interval		
			Lower bound	Upper bound	P value
Pre-treatment	8.265	.142	7.969	8.561	p<0.00001
After 2 weeks	6.950	.110	6.719	7.181	
After 4 weeks	4.250	.073	4.097	4.403	

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

(I) Pain score	(J) Pain score	Mean difference (I-J)	Std. Error	Sig.[a]	95% Confidence interval for difference[a]	
					Lower bound	Upper bound
Pre-treatment	After 2 weeks	1.315*	0.142	<0.00001	1.017	1.613
	After 4 weeks	4.015*	0.170	<0.00001	3.659	4.371
After 2 weeks	Pre-treatment	-1.315*	0.142	<0.00001	-1.613	-1.017
	After 4 weeks	2.700*	0.126	<0.00001	2.436	2.964
After 4 weeks	Pre-treatment	-4.015*	0.170	<0.00001	-4.371	-3.659
	After 2 weeks	-2.700*	0.126	<0.00001	-2.964	-2.436

Based on estimated marginal means. N=20. *. The mean difference is significant at the .05 level. a. Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).

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

Pain score	Mean	Std. Error	95% Confidence interval		
			Lower bound	Upper bound	P value
Pre-treatment	8.537	.098	8.331	8.743	
After 2 weeks	6.963	.131	6.688	7.238	<0.0001
After 4 weeks	3.863	.064	3.729	3.998	

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

(I) Pain score	(J) Pain score	Mean difference (I-J)	Std. Error	Sig.[a]	95% Confidence interval for difference[a]	
					Lower bound	Upper bound
Pre-treatment	After 2 weeks	1.574*	0.137	p<0.0001	1.285	1.862
	After 4 weeks	4.674*	0.117	p<0.0001	4.429	4.919
After 2 weeks	Pre-treatment	-1.574*	0.137	p<0.0001	-1.862	-1.285
	After 4 weeks	3.100*	0.144	p<0.0001	2.797	3.403
After 4 weeks	Pre-treatment	-4.674*	0.117	p<0.0001	-4.919	-4.429
	After 2 weeks	-3.100*	0.144	p<0.0001	-3.403	-2.797

Based on estimated marginal means. N=19. *. The mean difference is significant at the .05 level. a. Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).

The statistically significant [p<0.0001] reduction in neuropathic pain intensity was observed in patients treated with amitriptyline.

On pair-wise comparison, there was further reduction in pain intensity after 4 weeks treatment (statistically significant) as compared to 2 weeks treatment (Table 5, 6).

Pregabalin 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 pregabalin on pain after 4 weeks treatment as compared to 2 weeks treatment was also statistically significant (Table 7, 8). There was no difference between effect of amitriptyline and pregabalin on HRV in non-diabetic neuropathy patients indicating their similar effect on HRV. On analysis, no co-relation was observed between HRV and neuropathic pain in non-diabetic patients (data not shown).

DISCUSSION

The patients with ischemic heart disease and heart failure due to low HRV have shown increased risk of sudden cardiac death.[4,6] After 2 and 4 weeks treatment as compared to pretreatment values in non-diabetic patients, amitriptyline has produced statistically significant effect on heart rate variability (HRV). However, when used in cases of depression, amitriptyline was associated with decrease in HRV.[5] Pregabalin has produced similar effect on HRV as amitriptyline. Patients with neuropathic pain have lower HRV.[3] Pregabalin improves cardiac autonomic functions by increasing the heart rate variability and similar results were obtained in earlier studies.[7,8] Wei et al have also demonstrated the improvement in HRV after pregabalin treatment for 4 week in patients of diabetic neuropathy.[9]

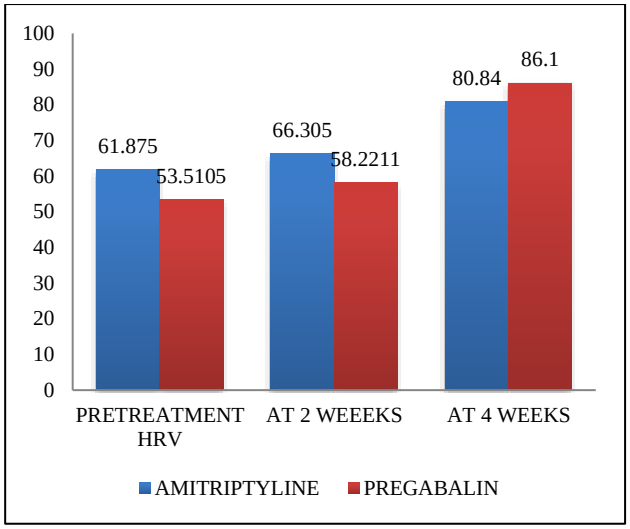

Figure 1: Comparing effect of amitripyline and pregabalin on HRV (mean) in non-diabetic neuropathy patient.

In our study, the improvement of HRV was not correlated with reduction in pain intensity. On the contrary, in another study HRV positively correlated with short form McGill pain questionnaire (SF-MPQ) scores in patients after abdominal surgery. In their study, assessment of pain was done by multidimensional pain assessment tool i.e. SF-MPQ than the single-dimensional assessment tool (VAS). In our study, amitriptyline has produced significant reduction in neuropathic pain intensity as observed on VAS after 2- and 4-weeks treatment as compared to pretreatment values. Similarly, one study has shown improvement of pain by amitriptyline after 4 weeks of treatment though improvement was slow; but adverse effects were more out of which 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 complete pain relief was not observed (>50% improvement of pain score).

The mechanism of improved HRV by pregabalin may possibly be due to reduced release of neurotransmitters (glutamate, noradrenaline, 5-HT, dopamine, and substance P) from the presynaptic neurons, leading to reduced sympathetic activity and augmented parasympathetic activity; thus produced improvement in HRV apart from increased GABA level.[12] It produced relief in neuropathic pain by similar neurotransmitter mechanisms.[13-15] The activation of KATP channels due to pregabalin may also be associated with pain relief.[16] Devi et al have shown significant reduction in pain score by pregabalin.[17] However, they have titrated the dose based on response of the patients to pain while dose was fixed (75 mg once a day) in our study due to safety concern.

The pain intensity was significantly reduced but complete pain relief was not obtained; possibly due to non-compliance 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). A positive correlation between HRV and postoperative pain with SF-MPQ scores was shown by Chang et al in patients after abdominal surgery.[18]

CONCLUSION

Based on our study, we conclude that both the amitriptyline (10 mg OD) and pregabalin (75 mg OD) have significantly increased HRV and significantly reduced the pain intensity after 2 weeks and 4 weeks treatment; but no correlation was observed between increased HRV and reduced pain intensity. In our study, we have used low dose of these drugs; and these doses were safe as revealed by no significant adverse effect. On the basis of this study, both amitriptyline and pregabalin can safely be used in the lower doses for the treatment of non-diabetic neuropathic pain. It is suggested to investigate other drugs used for neuropathic pain in further studies with and longer duration of treatment to substantiate the finding of present study.

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