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# Cardioprotective and antihyperglycemic activity of vildagliptin in presence of nifedipine on adrenaline induced hyperglycemic rat

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## Abstract

Generally there is higher prevalence of co-morbidity of diabetes and hypertension. Mortality increases more than 7 times when patient is having diabetes along with hypertension. In India 6.4% to 55% prevalence of hypertension among diabetes (Type 2) patients was found. Vildagliptin is an oral anti hyperglycemic agent of new class dipeptidyl peptidase-4 (DPP-4) inhibitor. Nifedipine is an antihypertensive drug that comes under the class of calcium channel blockers. The present study is to find out the effect of co administration of Nifedipine and Vildagliptin on cardioprotective and antihyperglycemic activity in adrenaline induced hyperglycemic rats. In acute and chronic condition study glucose level and lactate dehydrogenase (LDH) estimation in blood was done with the help of Glucometer and Lactate dehydrogenase assay kit respectively. Albino Rats heart muscles were subjected to histopathological examination. After co-administration of drugs initial glucose level (142.77 ± 12.9 mg/dl) and final blood glucose level (135.1 ± 48.7 mg/dl) in acute condition and initial glucose level (160.2 ± 9.3 mg/dl) and final blood glucose level (154.6 ±14.8 mg/dl) in chronic condition were found. In chronic condition initial LDH level (455.9 ±17.1 IU/L) and final LDH level (236 ±24.1 IU/L) in blood were found. In microscopic examination of endocardium layer of adrenaline induced hyperglycemic rats treated with co-administration of drugs necrosis was not found, it confirms their cardioprotective activity. On the basis of study conclusion was that when co-administration of Nifedipine and Vildagliptin, nifedipine significantly reducing the antihyperglycemic activity but it has no markedly effect on cardioprotective activity.

**Keywords:** Vildagliptin, Nifedipine, Lactate dehydrogenase, Dipeptidyl peptidase-4 inhibitor.

## Introduction

Diabetes is a metabolic disorders characterized by hyperglycemia due to insufficiency in insulin secretion or insulin action or both. The symptoms of diabetes include polyurea, polydypsea, blurred vision, retinopathy, neuropathy and fatigue.[1,2] Largest number of people with diabetes is in India, China and the U.S. with India leading the list. Diabetes and Hypertension tends to occur together because they share certain physiological traits.[3] The prevalence of hypertension among T2DM patients varies across countries and is reported to range from 20.6% to 78.4% in the Southeast Asian region, and 9.7% to 70.4% in the African region, in India it is 6.4% to 55%. Mortality is increased more than 7 times when patient is having diabetes along with hypertension.[4]

Generally in current treatment strategy the calcium channel blockers and angiotensin converting enzyme inhibitors were the drugs of choice for treatment of hypertensives and diabetic hypertensives condition.[5,6] Vildagliptin is an oral anti hyperglycemic agents of new class dipeptidyl peptidase-4 (DPP-4) inhibitor which lowers the hyperglycemic state of body. DPP-4 inhibitor acts by blocking the action of DPP-4, an enzyme which destroys the hormone incretin. Incretin helps the body produce more insulin only when it is needed and reduce the amount of glucose being produced by the liver.[7] Nifedipine is an antihypertensive drug that comes under the class of calcium channel blockers. As calcium ions play a major role in insulin secretion from pancreatic beta cells by the process of exocytosis. Calcium channel blockers block the entry of calcium ion into the pancreatic beta cells due to which the required concentration of calcium does not reach to the cells to attain the threshold potential for the release of insulin and hence affect blood glucose level.[8]

The objective of present study is to find out the effect of co administration of Nifedipine and Vildagliptin on Cardioprotective and Antihyperglycemic activity in adrenaline induced hyperglycemic rats. In this research work we have determined glucose level, LDH level and histopathological study of heart muscles of adrenaline induced hyperglycemic rat.

## Materials and Method

**Drugs and Chemicals:** Glucometer (Accusure, Dr. Gene Health and Wellness) was used for analysis of glucose. Lactate dehydrogenase assay kit was procured from Merck Diagnostic Ltd. India. Vildagliptin (Galvus Novartis) and Nifedipine (Calcigard, Torrent) were procured from market. Adrenaline was procured from market (Vasocon, Neon lab ltd) for the purpose of induce hyperglycemia in rats.

**Experimental Animals:** Albino rats of either sex weighing 150-200 gm were used for the studies. Animal was kept at 12-hour light and 12-hour dark sequence with the help of artificial lightening in animal room. Animal was on common laboratory diet feeding with regular supply of drinking water. This study was permitted by the Institutional Animal Ethical Committee with Reg. No. (1239 /ac/ 10 / CPCSEA).

**Study Design for Acute and Chronic condition:** The whole study was completed in 2 phases (Acute and Chronic). In first phase we determine the effect of drugs in acute administration with the help of only glucose level estimation in blood. In the second phase we determine the effect of drugs in chronic dose with the help of glucose and LDH level estimation in blood. For the purpose of this study we have prepared following groups of animal which is described in the Table no. 01.[9] In Acute condition after two hours of treatment blood was taken from animal tail and glucose level was estimated by using a standard Glucometer. For chronic study every day blood was taken from animal tail to determine glucose and LDH level both for 15 days.[10,11]

**Histopathological study:** Histopathological study of cardiac tissue was done after chronic administration of drugs. The cardiac tissue was collected from anesthetized animal. Anesthetized animal whole heart was removed by sacrificing the animal and preserved in 10% formalin solution. After that collection of heart immediately a section of 5µm thickness was taken by using paraffin technique.[12] Further staining was done with the help of hematoxylin and eosin (H & E) for histological examination.[13] The histopathological study was carried out in Department of Pathology, VSS medical college, Burla, Sambalpur, Odisha.

**Statistical Analysis:** The obtained data were analyzed by one way ANOVA followed by Dunnet's t-test. The values were considered statistically significant when p less than 0.05 ($p<0.05$).

## Result and Discussion

**Acute condition:** The effect of Vildagliptin (10 mg/kg) alone and in combination with Nifedipine (5 mg/kg) on the blood glucose level of adrenaline induced hyperglycemic rats at acute condition was shown in table no. 2 and graph no.1. Data of this table indicates that there is no significant change occurs in initial and final blood glucose level of Group 1. In Group 2, after administration of adrenaline blood glucose level significantly increases from 89.3 ±13.9 mg/dl to 143.0 ± 22.2 mg/dl. It means that adrenaline induces hyperglycemia. In Group 3, adrenaline induced hyperglycemic rats treated with vildagliptin shows decrease of blood glucose level (110.2 ± 39.1mg/dl) from initial glucose level (142.77 ± 12.9 mg/dl). It indicates that vildagliptin plays a significant role on lowering of blood glucose level in adrenaline induced hyperglycemic rats. In Group 4, adrenaline induced hyperglycemic rats treated with combination of Vildagliptin and nifedipine there is no significant change occurs in blood glucose level. This observation indicates that nifedipine inhibits blood glucose lowering effects of vildagliptin.[14]

**Chronic condition:** The effect of Vildagliptin (10 mg/kg) alone and in combination with Nifedipine (5 mg/kg) on the blood glucose level and LDH level of adrenaline induced hyperglycemic rats at chronic condition was shown in table no. 3 and graph no. 2. On the basis of obtain data after 15 days it clearly indicate that adrenaline produced both hyperglycemia and cardiotoxicity (Group 2). In Group 3, when animals are treated with vildagliptin there is significant reduction in the blood glucose and LDH level as compare to Group 2. This finding very much indicates that vildagliptin has the activity of normalizing hyperglycemia and carditoxicity. In group 4 when concurrent administration of nefidipine and vildagliptin is done there is no significant reduction in blood glucose level. It means that nifedipine extensively blocks the anti-hyperglycemic activity of vildagliptin. In case of LDH level significant reduction is observed but the reduction is not similar as compared to vildagliptin alone. Both the drug vildagliptin and nifedipine have cardioprotective activity[15,16] but our observation shows that when both the drugs are used concurrently then their cardio protective activity gets lowered. This observation was further confirmed by the histopathological study done on animal's heart muscles.

**Histopathological study:** In histopathological study further vildagliptin cardioprotective activity was assessed on the basis of necrosis found or not in the cardiac muscles of the animals. In this study, we consider endocardium layer of animal's heart muscle. Histopathological study result was shown in figure no.1 to figure no.4. Endocardium layer of adrenaline treated animal heart muscle shows clear evidence of microscopic changes occur as compared with normal control group. In microscopic examination of endocardium layer of adrenaline treated animal heart muscle black spot was seen that indicates necrosis (Fig. 2). In case of other treated groups there was no evidence of necrosis found in the microscopic examination of endocardium layer (Fig. 1, 3 and 4). This study confirms the cardioprotective activity of vildaglipatin and nifedipine.

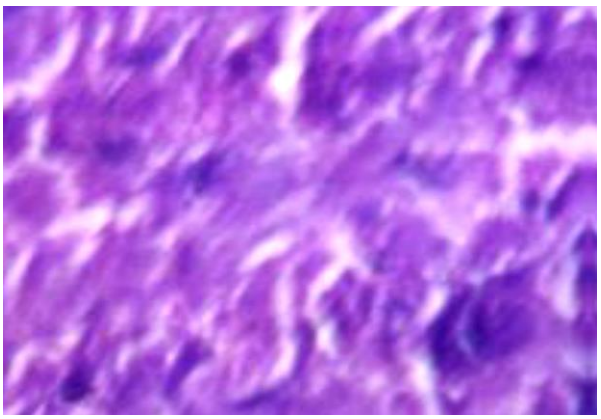

**Fig. 1: Histopathological study endocardium of heart of animal treated with vehicle (Group 1)**

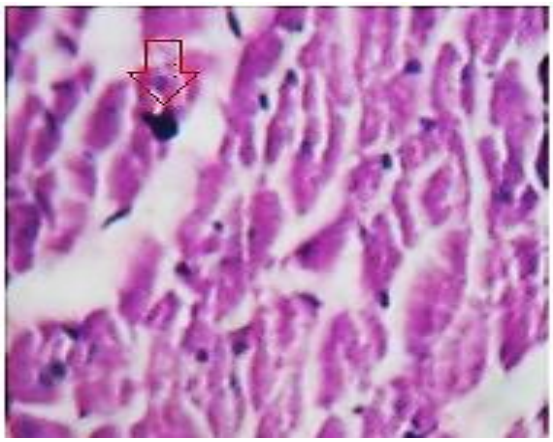

**Fig. 2: Histopathological study of endocardium of heart of animal treated with adrenaline (Group 2). Red arrow indicates necrosis**

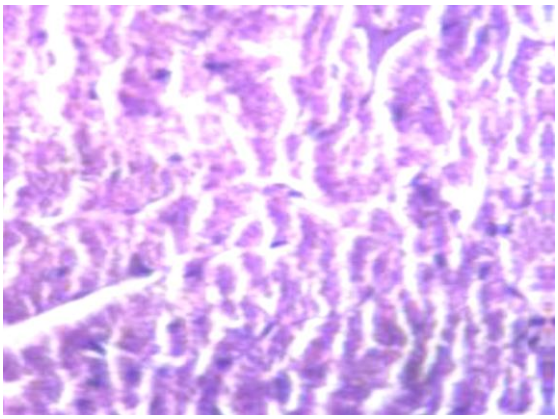

**Fig. 3: Histopathological study of endocarium of heart of animal treated with Vildagliptin and Adrenaline**

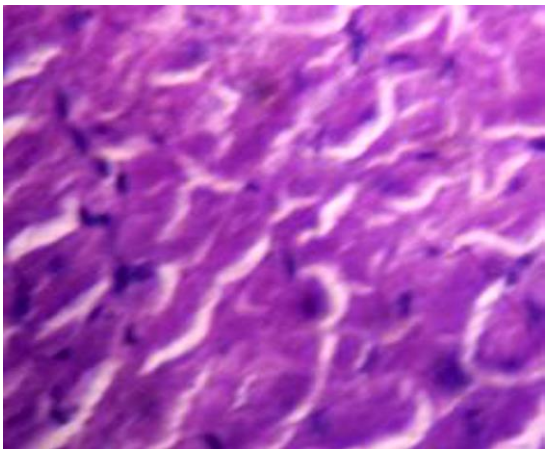

**Fig. 4: Histopathological study of endocarium of heart of animal treated with Adrenaline and Vildagliptin and nifedipine combination**

## Conclusion

There is a higher prevalence of co-morbidity of hypertension and diabetes. Hypertension has a significant relation with other cardiovascular complication also. These three complications are highly interrelated. Calcium channel blockers are very commonly used in treatment of hypertension. When there is co-morbidity condition of hypertension and diabetes, calcium channel blocker blocks excess release of insulin from beta cells of pancreas. In normal conditions calcium channel blocker does not show any inhibitory action on normal insulin release. Vildagliptin is newer class of antihyperglcemic drug that comes under the classification of DPP4 inhibitor. Vildagliptin when administered alone to adrenaline induced rat it is very effective in lowereing blood glucose level but when used in combination with calcium channel blocker (nifedpine) there is inhibition of antihyperglycemic activity of vildagliptin. Vildagliptin and nifedipine both drugs have cardioprotective activity as they maintain LDH level in heart muscles. When both vildagliptin and nefidipine used alone they have remarkable activity in maintaining LDH level in heart muscles but in combination same response is not seen. On the basis of our observation we conclude that co administration of calcium channel blocker (nifedipine) and DPP4 inhibitor (vildagliptin) should not be choice of drug treatment in co morbidity condition of hypertension and diabetes.

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## Conflict of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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