Original Article

Evaluation of efficacy and safety of cilnidipine and losartan in hypertensive patients with type 2 diabetes mellitus

Abstract

Objective: To compare the efficacy and safety of cilnidipine and losartan in hypertensive patients with type 2 diabetes mellitus (type 2 DM). **Materials and Methods:** In this observational, prospective study, hypertensive patients with type 2 DM receiving cilnidipine and losartan were included. Demographic details, clinical history, serum potassium, and urinary albumin were recorded in a case record form. Patients were followed up every monthly up to 24 weeks and observed for clinical and laboratory parameters and adverse drug reactions (ADRs). Data were analyzed using paired *t*-test, unpaired *t*-test, and Fisher's exact test. **Results:** Out of 114 patients, 59 received cilnidipine and 55 patients received losartan. By 24 weeks, both cilnidipine and losartan significantly ($P < 0.01$) improved mean blood pressure and urinary albumin. However, mean decrease in urinary albumin was significant ($P < 0.005$) with cilnidipine (20.6 ± 20.4 mg/day) as compared to losartan (18.3 ± 14.3 mg/day). Mean serum potassium was increased significantly ($P < 0.05$) in patients treated with losartan (0.9 ± 2.8) as compared to patients treated with cilnidipine. A total of 19 ADRs were observed in both groups and out of these, 36.8% ADRs were caused by cilnidipine and 63.2% ADRs by losartan. **Conclusion:** Cilnidipine is equally effective as losartan in reducing blood pressure in hypertensive patients with type 2 DM. However, cilnidipine is more effective in the prevention of albuminuria and better tolerated by patients as compared with losartan.

Key words: Albuminuria, cilnidipine, essential hypertension, losartan, serum potassium, type 2 diabetes mellitus

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INTRODUCTION

Hypertension like diabetes mellitus is "a silent killer," with a global prevalence of more than one billion people estimated in 2013.[1] Both hypertension and diabetes mellitus frequently coexist.[2] Usually, at initial stage of hypertension, there are few symptoms such as occipital headache.[3] Hypertension, if untreated for long-term, can lead to catastrophic outcomes such as cerebrovascular accident, coronary artery disease, chronic renal failure, and congestive heart failure.[4] There is frequently coexistence of hypertension and diabetes mellitus in patients and both accentuate the development of process of renal failure.[5] Renin angiotensin aldosterone system and over activity of sympathetic system play a crucial part in the evolution of heart failure and renal failure in hypertensive and diabetic patients, and merely control of mean arterial blood pressure and blood glucose is not sufficient in these patients.[6]

Losartan, an angiotensin receptor blocker (ARB), acts as an antihypertensive agent by blocking angiotensin type I (AT_1) receptor and inhibiting the action of AT_2.[7-9] Losartan, indirectly produces

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vasodilation, inhibits the release of aldosterone, and blocks vascular and cardiac hypertrophy and remodeling action of AT_2.[8-10] ARBs are used as primary antihypertensive agent in hypertensive–diabetic patients, as they slow the progression of diabetic nephropathy.[11] However, ARBs can produce adverse effects such as hyperkalemia, hypotension, angioedema, dry cough, and renal failure (in case of bilateral renal artery stenosis).[4] Cilnidipine, a novel dihydropyridine calcium channel blocker (CCB), inhibits the L-type and the N-type calcium channel. The N-type calcium channel is abundantly expressed in peripheral sympathetic nerve endings. Hence, cilnidipine reduces excessive release of catecholamine and suppresses reflective tachycardia compared with amlodipine (a L type CCB) in hypertensive patients.[12-14] In addition, a recent study showed that the L-type CCBs dilate the afferent, but not the efferent, arterioles of glomeruli; whereas cilnidipine dilates both the afferent and efferent arterioles, and prevents proteinuria.[15] Cilnidipine was shown to have a superior effect to amlodipine in preventing the progression of proteinuria in hypertensive patients. Among the available antihypertensive agents, both cilnidipine and losartan seem to have renoprotective effects However, there are no comparative data on the renoprotective effects of cilnidipine and losartan in hypertensive patients with noninsulin-dependent diabetes mellitus (NIDDM). The aim of the present study was to compare the efficacy and safety of cilnidipine and losartan in hypertensive patients with NIDDM.

MATERIALS AND METHODS

This was an observational, continuous, prospective, single center study conducted at the department of medicine of a tertiary care hospital in western part of India. This study was approved by Institutional Ethic Committee. Patients, who were recently diagnosed with essential hypertension and type 2 diabetes mellitus (type 2 DM), of either gender, 18 years or older and willing to participate in the study and gave written informed consent, treated with either tablet cilnidipine (10 mg/day) or tablet losartan (50 mg/day) were enrolled into study from June 5, 2014 to May 31, 2015. Patients with severe renal or hepatic disease, overt cardiovascular disease, malignancy, and who had been treated with other antihypertensive drugs were excluded from study. Patients were randomized into two groups. First group received tablet cilnidipine 10 mg once a day for 24 weeks and second group received tablet losartan 50 mg once a day for 24 weeks. Demographic details and details of clinical examination, laboratory investigation, and drug treatment were recorded in a pretested case record form (CRF). Patients were followed up monthly for 24 weeks and observed for clinical improvement, changes in laboratory parameters such as serum potassium and albuminuria, and adverse drug reactions (ADRs). To evaluate the effect of cilnidipine and losartan on serum potassium and their renoprotective effect (by observing urinary albumin) in patients treated by these drugs, serum potassium and albuminuria were included into CRF. Data were recorded in Microsoft Excel Worksheet and analyzed using Fisher's exact test, repeated measure ANOVA, paired *t*-test, and unpaired *t*-test with the help of GraphPad Prism 5.0 (GraphPad Software, Inc., La Jolla, CA 92037 USA). $P < 0.05$ was considered as statistically significant.

RESULTS

Baseline characteristics

Out of 122 patients, 78 (63.9) were men and 44 (36.1%) were women. Of these, 63 were treated with cilnidipine and 59 with losartan. Four patients were lost to follow-up in both groups. Hence, at the end of 24 weeks, 59 patients were treated with cilnidipine and 55 patients were treated with losartan [Table 1].

Clinical assessment

A significant improvement ($P < 0.01$) in headache and dizziness was observed in patients treated with cilnidipine and losartan at 12 weeks. All patients were symptom-free at 24 weeks in both treatment groups [Table 2]. In both treatment groups, mean systolic and diastolic blood pressure (mm of Hg) were significantly ($P < 0.05$) decreased by 12 weeks and 24 weeks [Table 3], respectively, as compared to baseline.

Laboratorial assessment

A significant ($P < 0.001$) improvement in mean serum potassium and urinary albumin was observed in patients treated with cilnidipine at 24 weeks as compared to baseline [Table 4]. By 24 weeks, in patients treated with losartan, there was significant ($P < 0.01$) reduction in urinary albuminuria; however, mean potassium level was increased significantly ($P < 0.05$).

Table 1: Baseline characteristics of the patients of hypertension with noninsulin-dependent diabetes mellitus in the study (*n*=114)

Parameter	Cilnidipine	Losartan	Total
Number of patients	59	55	114
Mean age (years)	49.5±14.6	47.4±8.3	-
Gender			
Men	45	33	78
Women	18	26	44
Clinical symptoms			
Headache	24	31	-
Dizziness	08	11	-
Palpitation	07	03	-
Polyuria/polydipsia/polyphagia	14	05	-
Family history			
NIDDM	47	39	
Renal disease	04	07	
Heart disease	08	02	
Mean arterial blood pressure (mm of Hg)			
Systolic blood pressure	148.3±8.7	145.1±12.3	
Diastolic blood pressure	91.6±5.4	92.5±6.2	
Laboratory parameters			
Potassium (mEq/L)	4.3±1.9	4.2±1.7	
Urinary albumin (mg/day)	47.9±25.1	54.6±19.9	

Values are absolute number and mean±SEM. NIDDM = Noninsulin dependent diabetes mellitus, SEM = Standard error of mean

Table 2: Comparison of clinical symptoms of patients at different time intervals (*n*=114)

Study groups	Symptoms	Baseline (0 week)	3rd follow-up (12 weeks)	6th follow-up (24 weeks)
Cilnidipine (*n*=59)	Headache	24 (100)	04 (16.6)*	0 (0)*
	Dizziness	08 (100)	2 (25)*	0 (0)*
	Palpitation	07 (100)	1 (14.2)*	0 (0)*
	Polyuria/polydipsia/ polyphagia	14 (100)	03 (21.4)*	0 (0)*
Losartan (*n*=55)	Headache	31 (100)	13 (41.9)#	0 (0)#
	Dizziness	11 (100)	3 (27.2)#	0 (0)#
	Palpitation	03 (100)	0 (0)#	0 (0)#
	Polyuria/polydipsia/ polyphagia	05 (100)	3 (60.1)	0 (0)#

*P<0.01 as compared to baseline (Fisher's exact test). #P<0.0001 as compared to baseline (Fisher's exact test), values are absolute count (%)

Table 3: Comparison of mean blood pressure of patients at different time intervals (*n*=114)

Study groups	Mean blood pressure	Baseline (0 week)	3rd follow-up (12 weeks)	6th follow-up (24 weeks)
Cilnidipine (*n*=59)	Systolic blood pressure	148.3±11.7	134.6±4.8*	132.1±5.4*
	Diastolic blood pressure	91.6±5.4	82.5±3.1**	81.1±2.2**
Losartan (*n*=55)	Systolic blood pressure	145.1±12.3	135.4±5.2*	133.3±3.5*
	Diastolic blood pressure	92.5±6.2	82.2±4.3**	80.9±1.7**

*P<0.05 as compared to baseline (repeated measure ANOVA), **P<0.02 as compared to baseline (repeated measure ANOVA), values are mean±SEM. SEM = Standard error of mean

Table 4: Comparison of laboratory parameters of patients at different time intervals (*n*=114)

Study groups	Laboratory parameters	Baseline (0 week)	3rd follow-up (12 weeks)	6th follow-up (24 weeks)
Cilnidipine (*n*=59)	Mean potassium (mEq/L)	4.3±1.9	4.1±1.8	4±1.2
	Mean urinary albumin (mg/day)	47.9±25.1	32.1±10.3*	27.3±4.7#
Losartan (*n*=55)	Mean potassium (mEq/L)	4.2±1.7	4.5±1.4*	4.9±0.9#
	Mean urinary albumin (mg/day)	54.6±19.9	41.2±8.9*	36.3±5.6**

*P<0.02 as compared to baseline (repeated measure ANOVA), #P<0.01 as compared to baseline (repeated measure ANOVA), **P<0.03 as compared to baseline (repeated measure ANOVA, values are mean±SEM. SEM = Standard error of mean

Comparison between cilnidipine- and losartan-treated groups

There was a significant ($P < 0.005$) increase in mean serum potassium in patients treated with losartan at the end of the study as compared with cilnidipine-treated patients, which showed no significant change in potassium level in patients. By 24 weeks, there was a significant ($P < 0.005$) improvement in mean urinary albumin in patients treated with cilnidipine and losartan; however, mean decrease in urinary albumin was higher in patients treated with cilnidipine at the end of treatment [Table 5, Figures 1 and 2].

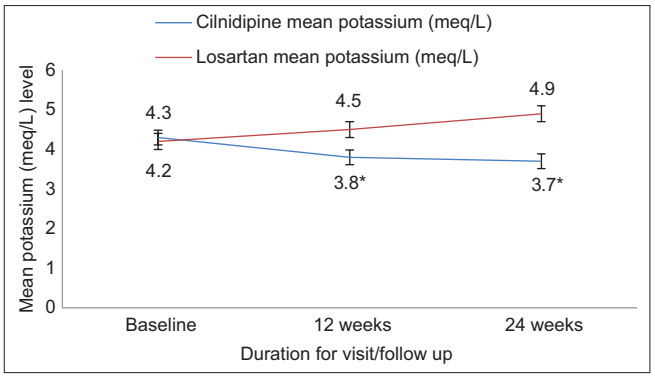

Figure 1: Mean potassium (meq/L) level in patients treated with cilnidipine and losartan at different time intervals ($n = 114$). *$P < 0.01$ as compared to baseline (Paired Student's *t*-test)

Adverse drug reactions

A total of 19 ADRs were observed in 114 patients during the study period. Out of these 19 ADRs, 7 were observed into patients treated with cilnidipine and 12 were into patients treated with losartan. In patients treated with cilnidipine, the most common ADR was headache, (04) followed by dizziness (02). Most common ADRs observed in losartan-treated group were dizziness (04) and headache (03), followed by rashes (02) and hyperkalemia (02). ADRs were categorized as mild based on modified Hartwig and Siegel scale [Table 6]. None of the ADR required withdrawal of causal drug. Majority of ADRs (19) were possibly related to the drug WHO-UMC scale except for dry cough and hyperkalemia in patients treated with losartan, which was probable in nature [Table 6].

DISCUSSION

Essential hypertension and type 2 DM very commonly coexist and lead to the progression of diabetic nephropathy and cardiovascular disease.[6] Many clinical trials have recommended that the use of ARBs such as losartan slows the progression of diabetic nephropathy and it is commonly used as an antihypertensive drug in patients with essential hypertension with type 2 DM,[6,7] although the use of ARBs alone for this purpose is not enough and is often prescribed with hydrochlorothiazide. Losartan frequently causes hyperkalemia, dry cough, rashes, and rarely angioedema-like severe ADRs in patients.[7,8] Contrary to this, some studies have suggested that losartan and other ARBs are not efficacious to prevent the development of macroalbuminuria (≥300 mg/day urinary albumin) in hypertensive patients with type 2 DM having microalbuminuria (≤30–300 mg/day urinary albumin).[2,3] However, cilnidipine, a third generation dihydropyridine, CCB is vasoselective and is a dual blocker of L-type and N-type calcium channels. L-type calcium channel blockade produce vasodilation of peripheral resistance vessels. Inhibition of neuronal N-type calcium channels disrupts sympathetic nervous outflow, lowering plasma catecholamine levels, and produces vasodilation of both pre- and post-capillary resistance vessels, reducing capillary hypertension and consequent hyperfiltration of fluid into the interstitium.[9,10,15] These dual mechanisms of cilnidipine

Table 5: Comparison of difference in the mean value of laboratory parameters of patients treated with cilnidipine and losartan (*n*=114)

Parameters	Mean difference 3rd follow-up (12 weeks) compare to baseline		Mean difference 6th follow-up (24 weeks) compare to 3rd follow-up		Total mean difference (24 weeks)	
	Cilnidipine (*n*=59)	Losartan (*n*=55)	Cilnidipine (*n*=59)	Losartan (*n*=55)	Cilnidipine (*n*=59)	Losartan (*n*=55)
Mean potassium (mEq/L)	−0.2±1.6	0.3±2.3	−0.1±0.6	0.4±0.5	−0.3±2.2	0.9±2.8**
Mean urinary albumin (mg/day)	−15.8±14.8*	−13.4±11	−4.8±5.6	−4.9±3.3#	−20.6±20.4**	−18.3±14.3**

P<0.002 as compared to losartan-treated group (unpaired Student's *t*-test), #*P*<0.01 as compared to losartan group (unpaired Student's *t*-test), ##*P*<0.05 as compared to cilnidipine group (unpaired Student's *t*-test), **P*<0.005 as compared to losartan-treated group (unpaired Student's *t*-test), values are mean±SEM. SEM = Standard error of mean

Table 6: Details of adverse drug reactions observed among patients treated with cilnidipine and losartan (*n*=114)

ADRs	Cilnidipine *n* (%)	Losartan *n* (%)	WHO-UMC causality scale	Severity (based on modified Hartwig and Siegel cale)
Headache	04 (57.1)	03 (25)	Possible	Mild
Dizziness	02 (28.5)	04 (33.3)	Possible	Mild
Rashes	01 (14.2)	02 (15.3)	Possible	Mild
Hyperkalemia	00 (00)	02 (15.3)	Probable	Mild
Dry cough	00 (00)	01 (8.3)	Probable	Mild
Total	7 (100)	12 (100)	-	-

ADRs = Adverse drug reactions

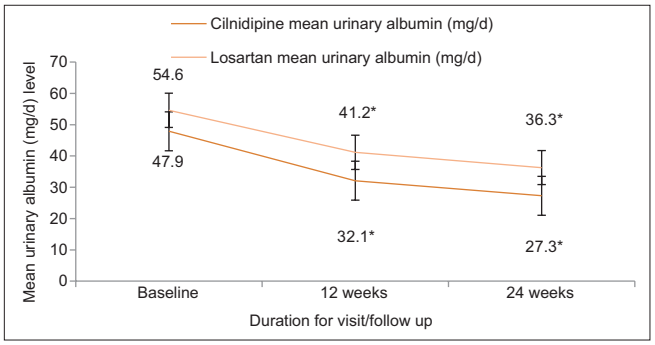

Figure 2: Mean urinary albumin (mg/day) level in patients treated with cilnidipine and losartan at different time intervals (*n* = 114). *$P < 0.05$ as compared to baseline (Paired Student's *t*-test)

explain both the low incidence of ankle edema and antihypertensive action without the reflex tachycardia. Cilnidipine effectively prevents the development of diabetic nephropathy and cardiovascular diseases in hypertensive patients with type 2 DM.[10,11,15]

Our study showed the treatment outcomes of total 114 patients of hypertension with type 2 DM treated with cilnidipine and losartan for 24 weeks. At the end of 24 weeks, all patients had significant clinical improvement and normalization of laboratory parameters. Mean age of patients in both cilnidipine- and losartan-treated groups was 49.5 ± 14.6 years and 47.4 ± 8.3 years, respectively, which was lower than the mean age observed in a study conducted by Nishida *et al.*,[14] in which mean age for ARBs was 61.7 years and for CCBs 66.8 years.

There were more men (63.9%) than women (36.1%) in our study. Similar observation was observed in a study carried out by Abe *et al.*[15] In our study, headache and dizziness were the most common presenting symptoms. Headache was because of an increased mean arterial blood pressure and severe hypertension. Similar findings had been reported in studies conducted by Nishida *et al.*[14] Serum potassium and urinary albumin were used to determine the effect of cilnidipine and losartan on potassium homeostasis and in the prevention of albuminuria.

Cilnidipine and losartan treatment resulted in a significant improvement in headache and dizziness at 12 weeks and all patients were symptom-free at the end of 6 months treatment with cilnidipine and losartan. Our observations are similar to the studies conducted by Nishida *et al.*[14] and Abe *et al.*[15] Treatment with cilnidipine and losartan decreases blood pressure and improves the signs and symptoms of essential hypertension.

A parallel improvement in laboratory parameters was noted in the present study. However, a significant increase in serum potassium was observed in patients treated with losartan as compared with cilnidipine. This observation suggested that losartan tends to increase serum potassium as compared to cilnidipine, which has no significant effect on serum potassium. Similar results were observed in studies conducted by Nishida *et al.*,[14] Kurnik *et al.*,[16] and Formica *et al.*[17] There was a significant ($P < 0.005$) improvement in albuminuria in patients treated with cilnidipine and losartan in our study, and such observations have been observed in studies carried out by Nishida *et al.*[14] Abe *et al.*,[15] and Formica *et al.*[17] Although the mean age of patients in the study done by Nishida *et al.*[14] was higher, compared with the mean age of patients treated with cilnidipine and losartan in the present study, in both these studies, newly diagnosed hypertensive patients with type 2 DM were enrolled. However, in the present study, reduction in urinary albumin in patients treated with cilnidipine was more than in patients treated with losartan. This may be due to dual blockade of cilnidipine on L-type and N type of calcium channels which produces vasodilation of both pre -and post-capillary resistance vessels, reducing capillary hypertension and consequent hyperfiltration of fluid into the interstitium. In addition to this, cilnidipine decreases plasma AT_2 and aldosterone level. Losartan is a selective antagonist of AT_1 receptor and does not completely block the effect of AT_2, which continues to produce albuminuria, especially in patients of NIDDM with hypertension. Similar results were observed in studies conducted by Kurnik *et al.*[16] and Formica *et al.*[17]

In the present study, ADRs were more common in patients receiving losartan (63.2%) as compared with patients receiving cilnidipine (36.8%). Headache (57.1%) and dizziness (33.3%) were the most

common observed ADRs in cilnidipine- and losartan-treated patients, respectively. ADRs such as peripheral edema and palpitation, which are commonly observed during treatment with amlodipine (a dihydropyridine CCB), were not observed in patients treated with cilnidipine during the present study. This may be attributed to dual blockage of both L- and N-type of calcium channels by cilnidipine. However, in patients treated with losartan, two cases of hyperkalemia and one case of dry cough were observed in our study. Similar observations were observed during the study conducted by Nishida *et al*.[14] All 19 ADRs observed in the present study were mild in severity (modified Hartwig and Siegel scale) and none of the ADR required withdrawal of patients from the study. All 19 ADRs were possible in nature except hyperkalemia and dry cough, which were probable in nature according to the WHO-UMC scale.

Limitations of the study

The study duration was of 6 months only and number of patients in both cilnidipine and losartan treated group is small. It was a nonrandomized, observational study. Considering the open-label design of the study, further large scale studies with controlled situation and blinding techniques are recommended to substantiate our observations. Despite these limitations, we believe that the data generated in our study lead to certain important conclusions.

CONCLUSION

Both cilnidipine and losartan are efficacious and safe in patients with essential hypertension and type 2 DM. However, cilnidipine is more efficacious in the prevention of albuminuria in hypertensive patients with type 2 DM and does not cause potassium imbalance. Losartan is associated with more ADRs such as hyperkalemia, dizziness, and dry cough.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. World Health Organization. A Global Brief on Hypertension: World Health Day 2013. Geneva: World Health Organization; 2013.
2. Bakris GL, Williams M, Dworkin L, Elliott WJ, Epstein M, Toto R, *et al*. Preserving renal function in adults with hypertension and diabetes: A consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Am J Kidney Dis 2000;36:646-61.
3. Baker WL, Coleman CI, Kluger J, Reinhart KM, Talati R, Quercia R, *et al*. Systematic review: Comparative effectiveness of angiotensin-converting enzyme inhibitors or angiotensin II-receptor blockers for ischemic heart disease. Ann Intern Med 2009;151:861-71.
4. Casas JP, Chua W, Loukogeorgakis S, Vallance P, Smeeth L, Hingorani AD, *et al*. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: Systematic review and meta-analysis. Lancet 2005;366:2026-33.
5. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: A network meta-analysis. Lancet 2007;369:201-7.
6. Moser M, Setano JF. Hypertensive vascular disease. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, editors. Harrison's Principles of Internal Medicine. 18th International ed. New Delhi: McGraw-Hill; 2011. p. 1345-77.
7. Tsai EJ, Kass DA. Treatment of myocardial ischemia and hypertension. In: Brunton LL, Chabner BA, Knollmann BC, editors. Goodman and Gilman`s the Pharmacological Basis of Therapeutics. 12th ed. USA: McGraw-Hill; 2011. p. 354-89.
8. Benowitz NL. Antihypertensive Agents. Katzung BG`s Basic & Clinical Pharmacology. 12th International ed. New Delhi: McGraw Hill Lange; 2013. p. 249-88.
9. Zillich AJ, Garg J, Basu S, Bakris GL, Carter BL. Thiazide diuretics, potassium, and the development of diabetes: A quantitative review. Hypertension 2006;48:219-24.
10. Taira N. Differences in cardiovascular profile among calcium antagonists. Am J Cardiol 1987;59:24B-9B.
11. Weber MA. Calcium channel antagonists in the treatment of hypertension. Am J Cardiovasc Drugs 2002;2:415-31.
12. Staessen JA, Li Y, Richart T. Oral renin inhibitors. Lancet 2006;368:1449-56.
13. Opie LH, Yusuf S, Kübler W. Current status of safety and efficacy of calcium channel blockers in cardiovascular diseases: A critical analysis based on 100 studies. Prog Cardiovasc Dis 2000;43:171-96.
14. Nishida Y, Takahashi Y, Nakayama T, Asai S. Comparative effect of angiotensin II type I receptor blockers and calcium channel blockers on laboratory parameters in hypertensive patients with type 2 diabetes. Cardiovasc Diabetol 2012;11:53.
15. Abe H, Mita T, Yamamoto R, Komiya K, Kawaguchi M, Sakurai Y, *et al*. Comparison of effects of cilnidipine and azelnidipine on blood pressure, heart rate and albuminuria in type 2 diabetics with hypertension: A pilot study. J Diabetes Investig 2013;4:202-5.
16. Kurnik D, Vesterman-Landes J, Bialik M, Katzir I, Lomnicky Y, Halkin H, *et al*. Hyperkalemia and renal function during monotherapy and dual renin-angiotensin blockade in the community setting. Clin Ther 2011;33:456-64.
17. Formica RN Jr., Friedman AL, Lorber MI, Smith JD, Eisen T, Bia MJ. A randomized trial comparing losartan with amlodipine as initial therapy for hypertension in the early post-transplant period. Nephrol Dial Transplant 2006;21:1389-94.