Original Article

To compare the effect of Telmisartan with Metoprolol on arterial stiffness in hypertension: Prospective randomized parallel group trial

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ABSTRACT

Background: Hypertension is often complicated by increased arterial stiffness and is an independent predictor of adverse cardiovascular (CV) outcome. Beta blockers and angiotensin receptor blockers (ARBs) are commonly used antihypertensive agents. The effect of beta blockers and ARBs on arterial stiffness has not been compared adequately. The aim of the present study is to compare the effect of telmisartan with metoprolol on arterial stiffness in hypertensive patients in prospective open label randomized parallel group intervention study.

Methods: 100 patients of hypertension, not on any antihypertensive agents, were enrolled after obtaining informed consent. Baseline recording of data related to demographics, CV risk factors, anthropometry and BP were made. Arterial stiffness was measured non-invasively by recording pulse wave velocity (PWV) using periscope (Genesis medical system). Left ventricular (LV) mass was measured using 2D guided M-mode echocardiography. Blood sugar, renal function, lipids and uric acid estimations were done in fasting state. Patients were randomized to receive metoprolol and telmisartan using stratified randomization technique. Dose of the study drugs were titrated to achieve target BP of <140/90 mmHg. Data related to PWV, BP, anthropometry and blood biochemistry was repeated after 6 months of treatment with study drugs.

Results: Telmisartan resulted in significantly greater reduction in arterial stiffness index (ASI) in left and right lower limb arterial bed (39.9 ± 11.7 vs. 46.8 ± 17.0 m/s, $p < 0.02$) and (36.4 ± 9.6 vs. 44.86 ± 15.1 m/s, $p < 0.002$) respectively and systolic blood pressure (SBP) (-4.9 mmHg with 95% C.I. of -8.0–1.7 mmHg, $p < 0.003$) compared to metoprolol. Reduction in diastolic blood pressure (DBP) in telmisartan and metoprolol groups was not different

statistically (−1.0 mmHg with 95% C.I. of −3.3—1.2 mmHg, $p < 0.3$). The change in LV mass was not significantly different between the study groups (135.5 ± 37.6 vs. 143.2 ± 41.5, $p < 0.3$).

1. Introduction

Cardiovascular diseases (CVD) are the leading cause of morbidity and mortality and contribute to about 30% of the total mortality. Hypertension ranks number one as a risk factor for non-communicable diseases related disability-adjusted life years (DALYS).[1] The underlying cause of morbidity and mortality in hypertension is primarily due to vascular damage thus affecting heart, brain and kidneys. In hypertension, the structure and function of the arterial wall have been reported to be altered even in an early stage of the disease resulting in increased arterial stiffness.[2,3] Increased arterial stiffness is very important risk marker of CVD in patients of hypertension.[4—9] The stability, resilience and compliance of the vascular wall are dependent on relative contributions of its two prominent scaffolding proteins: collagen and elastin.[10—13] The relative content of these molecules is normally held stable by slow but dynamic process of production and degradation. Dysregulation of this balance mainly due to stimulation of inflammatory milieu, leads to overproduction of abnormal collagen and diminished quantities of normal elastin which contribute to vascular stiffness. Stiffness is not uniformly distributed throughout the vascular tree but is often patchy.[14] Increased arterial stiffness leads to increased systolic and lower diastolic pressure in the central aortic artery. This translates into increased ventricular afterload and decreased coronary perfusion pressure leading to left ventricular hypertrophy (LVH) and subendocardial ischemia. Thus, LVH and subendocardial ischemia could trigger the onset of hypertensive heart disease. Increased systolic pressure in central aorta and conduit arterial tree as a result of increased arterial stiffness, leads to decreased impedance gradient between major conduit arterial tree and distal small resistant arterial bed.[15—18] Thus, transmission of increased arterial pressure from central arterial tree to distal microcirculatory bed could also play a role in hypertensive microangiopathy. Therefore, management of hypertension should address not only the control of BP, but also should aim to prevent progression or reverse the process of arterial stiffness that would be more effective means to reduce the risk of CVD. The available antihypertensive agents lower the BP through diverse mechanisms. The arterial stiffness has been documented to decrease with use of Angiotensin converting enzyme inhibitors (ACE-Is) and ARB[19,20] but there were conflicting results with beta-blockers and diuretics in number of small studies.[21] These studies are limited by shorter duration of treatment and limited comparative trials. Beta-blockers and ARBs have favorable effect on structural remodeling of heart in congestive heart failure, however there are no studies comparing their effect on arterial stiffness in patients of hypertension. Present study compared the effect of metoprolol and telmisartan on arterial stiffness as measured by PWV in newly diagnosed and or diagnosed hypertensive not on antihypertensive agents.

2. Methods

2.1. Study design

Prospective, randomized, parallel group, open label, blinded, end point clinical intervention trial in hypertensive patients. Investigator measuring the PWV was blinded for the assigned treatment group.

2.2. Patient population screened

All consecutive patients of newly diagnosed and established hypertension not on antihypertensive agents attending Cardiology OPD of IGMC hospital were screened for enrollment in the study.

2.3. Patient selection

Patients of newly detected hypertension i.e. recording of BP > 140/90 mmHg on two different occasions at 2—4 weeks interval first time, or known hypertensives but not on antihypertensive medications with BP > 140/90 mmHg were enrolled if found eligible after obtaining informed consent. Hypertensive patients with peripheral vascular disease, Heart failure, Heart rate (HR) less than 70/minutes, cerebrovascular accident, chronic kidney disease, Bronchial asthma, significant chronic obstructive airway disease, patients with atrial fibrillations and those on antihypertensive agents were excluded. The study protocol was approved by Institutional ethical committee.

Sample size; as a pilot study 106 eligible patients consenting to participate were enrolled for the study.

2.4. Data collection

Data related to demographics and status of CV risk factors recorded using structured questionnaires, followed by clinical examination to record BP using mercury sphygmomanometer. Average of two readings, recorded at an interval of 3—5 min, using appropriate size BP cuff, following standard guidelines were taken as the BP value. Anthropometric measurement included weight, height and waist circumference using standard procedure. About 7—8 cc venous blood was drawn after overnight fasting for estimation of blood urea, creatinine, uric acid and lipid profile using standard kits in fully automatic auto analyzer, KONE LAB-30. Blood sugar was estimated by GOD POD method (glucose oxidase peroxidase method) on semiautomatic analyzer, ERBA CHEM 5 plus by

TRANSASIA. Arterial stiffness was measured by recording PWV in both brachial and femoral arteries noninvasively with PERISCOPE™ (Genesis Medical Systems) based on oscillometric principle. Arterial stiffness value in carotid femoral arterial segment was calculated automatically by inbuilt software of periscope.

2.5. Measurement of LV mass

LV mass was measured using 2D guided M mode scan in parasternal long axis view at the level of tip of mitral leaflets following the standard guidelines of American Society of Echocardiography (ASE) for calculating LV mass by measuring (intact ventricular septum) IVS, left ventricular internal dimension (LVID) and LV posterior wall thickness at end of diastole using I E 33 Echo machine of Philips medical System with adult phased array probe.

2.6. Estimation of arterial stiffness

Arterial stiffness was measured by recording PWV and ASI noninvasively using oscillometric principle with PERISCOPE™ (Genesis Medical Systems). The subject was made to lie on the bed for at least 10 min in quit room at comfortable temperature. BP cuffs were wrapped around both upper and lower limbs and 4 ECG electrodes were applied at standard positions over anterior chest wall to record ECG signals to obtain ECG gated trigger for simultaneous inflation of BP cuff in all four limbs for detection of pulse wave signals by oscillometric method. Before performing the test, the nature of the procedure was explained to allay the anxiety and was instructed to refrain from coffee and tobacco smoking at least for 3 h before study. Following parameters were recorded as indices of arterial stiffness.

2.7. Pulse wave velocity

PWV was measured by recording of pulse transit time measured from R wave of ECG signals to the foot of the pulse wave recorded at left and right brachial artery and left and right ankle arteries through ECG triggered simultaneous inflation of BP Cuffs at these sites by inbuilt calibrating software.

2.8. Arterial stiffness index (ASI)

It is another measure of arterial stiffness. It quantifies the shape of oscillometric envelope. As the arterial stiffness increases, it becomes harder to collapse the arteries by applying pressure. Hence the oscillometric envelope becomes flatter as the stiffness increases. The higher the stiffness, higher the ASI value.

2.9. Randomization procedure

Randomization was stratified for age and sex with blocks of age groups at 5-years age interval for each gender. The treatment codes for each stratified groups were assigned in random order using random number table. The investigator implementing the assigned treatment code was blinded for the allocation sequence. After baseline evaluation patients were randomized to telmisartan or metoprolol group choosing the appropriate block based on given age and sex of the patient and the treatment was assigned based on generated allocation sequence on the given block. Starting dose of metoprolol was 25 mg–50 mg and was 20 mg–40 mg in telmisartan group depending upon baseline BP and HR. Patients were followed up within 2 weeks time to titrate the dose in both arms to ensure control of BP by 4 weeks time. Maximum dose of metoprolol used was 200 mg and 160 mg of telmisartan. Patients were followed up for 6 months. At the end of 6 months of study drug exposure each patients underwent repeat recording of BP, anthropometry, estimation of blood sugar, blood urea, creatinine, uric acid, lipid profile, PWV and Echo study for estimation of LV mass using same protocol. Patients in both study groups were counseled to adopt healthy lifestyle as a part of usual practice.

2.10. Statistical analysis

It was a pilot study and 50 patients in each group were enrolled to compare the effect on arterial stiffness. The demographic and clinical characteristics of the study population in each group was described as percentages and mean ± SD for categorical and continuous variables respectively and differences in the distribution between two study groups were compared by X^2 and unpaired t test or Mann Whitney test as appropriate. The effect of study drugs on arterial stiffness was compared using unpaired t test or Man Whitney test as appropriate with estimation of 95% C.I. of the effect size. 2 tailed significance at <0.05 were considered as statistically significant. Statistical analysis were done using Epi info version 3.4.

3. Results

3.1. Patient enrollment and dropouts

A total of 106 patients were enrolled, 100 completed the study follow up. Total of 6 patients were lost to follow up as 3 patients dropped out from each study group. In telmisartan group 2 patients discontinued medicines in between as they felt better after briefly taking medicines and another patient diagnosed as a case on lung carcinoma whereas in metoprolol group 1 patient was withdrawn from study as he complained of weakness due to study drug and 2 patients were lost to follow up.

3.2. Demographic and clinical characteristics of the study population

The characteristics of the study population in metoprolol and telmisartan groups are described. The two study groups were well matched for age (45.0 ± 10.6 vs. 45.0 ± 10.3, p 0.67) and gender distribution; men (69.1% vs. 76.5%, p 0.39). The distribution of CV risk factors; overweight and obesity (32.7% vs. 33.3%, p 0.95), dyslipidemia (78.2% vs. 82.4%, p 0.59), diabetes (3.6% vs. 2.0%, p 0.60) and tobacco consumers was also similar in two study groups (38.2% vs. 37.3%, p 0.92). The median dose

of metoprolol and telmisartan used were 50 and 80 mg respectively with range of 25—200 mg for metoprolol and 20—160 mg for telmisartan (Table 1).

3.3. Distribution of impaired arterial stiffness index

Frequency distribution of impaired arterial stiffness was similar in two study groups, but varied greatly in different arterial territories and was highest in carotid femoral arterial segment (78.2 vs. 78.4%, p 0.98) followed by in lower limb; left ankle (7.3% vs. 5.9%, p 0.77), right ankle (7.3% vs. 2.0%, p 0.2) and least in upper limb arterial segments; right brachial (3.6% vs. 2.0%, p 0.60), left brachial (0.0% vs. 2.0%, p 0.30) in metoprolol and telmisartan group respectively (Table 1).

3.4. Study groups means of cardio metabolic risk factors, serum levels of blood urea, creatinine, uric acid and lipids in the study groups

The study groups were well matched for distribution of various cardio metabolic risk factors, indices of renal function and uric acid levels. In brief mean level of SBP, (151.5 ± 13.5 vs. 157.8 ± 20.0, p 0.60) DBP (99.6 ± 8.2 vs. 99.6 ± 11.3, p 0.98), HR (82.1 ± 13.8 vs. 78.1 ± 13.4, p 0.14), LV Mass (134.9 ± 28.5 vs. 129.4 ± 33.2, p 0.36), BMI (26.1 ± 3.9 vs. 25.7 ± 4.3, p 0.60), waist circumference (93.6 ± 6.7 vs. 91.9 ± 9.8, p 0.31), blood sugar levels were similar in two groups (93.5 ± 18.0 vs. 94.9 ± 21.4, p 0.70). The mean total cholesterol level was significantly higher in metoprolol group (203.4 ± 45.7 vs. 185.3 ± 35.7, p < 0.02) (Table 2).

3.5. Study groups means of PWV in different arterial territories at baseline

The means of PWV in different arterial segments in metoprolol and telmisartan groups were similar at baseline (Table 3.) right brachial artery (34.9 ± 10.6 vs.33.2 ± 10.6 m/s, p 0.59), left brachial artery (30.0 ± 8.0 vs. 31.2 ± 9.2 m/s, p 0.48), right ankle (41.2 ± 19.7 vs. 44.5 ± 12.3 m/s, p 0.31) and left ankle (45.2 ± 17.7 vs.47.7 ± 19.5 m/s, p 0.83) and carotid femoral artery (1072.4 ± 366.7 vs. 1043.7 ± 465 m/s, p 0.72) respectively (Table 3).

3.6. Comparison of effect of metoprolol and telmisartan on arterial stiffness, BP and LV mass

- **Brachial artery stiffness Index;** Brachial artery stiffness index in right brachial artery was not significantly different among telmisartan and metoprolol group (33.6 ± 16.8 vs. 34.3 ± 12.4 m/s, p 0.84. but there was trend of greater reduction in left brachial artery stiffness in telmisartan group compared to metoprolol (29.05 ± 7.8 vs. 32.9 ± 11.6 m/s, p < 0.055).
- **Lower limb Arterial Stiffness Index;** Both left and right lower limb arterial stiffness indices decreased significantly in telmisartan group compared to metoprolol group (39.9 ± 11.7 vs. 46.8 ± 17.0 m/s, p < 0.023) and (36.4 ± 9.6 vs. 44.8 ± 15.1 m/s, p < 0.002) respectively.
- **Carotid femoral pulse wave velocity (CFPWV);** There was no significant difference in CFPWV between telmisartan and metoprolol study groups (1011 ± 337.8 vs. 1045 ± 694 m/s, p < 0.75) although there was a trend in favor of telmisartan group.
- **BP;** Reduction in SBP was significantly higher in telmisartan group compared to metoprolol group (124.7 ± 7.8 vs. 129.7 ± 7.9, p < 0.003) but no significant difference in the reduction in DBP was observed between study groups (81.3 ± 5.4 vs. 82.4 ± 5.9, p < 0.35).
- **HR;** The mean HR was significantly lower in metoprolol group than telmisartan group as was expected 67.6 ± 8.5 vs. 78.2 ± 10.4 p < 0.001.
- **LV Mass;** Although there was a trend of greater reduction in mean LV mass in telmisartan group than in metoprolol group but was statistically not significant (135.5 ± 37.6 vs. 143.2 ± 41.5, p 0.33) Table 4.

Table 1 — Baseline characteristics of the study groups.			
Characteristics	Metoprolol group n = 50	Telmisartan group n = 50	Sig. at 2 tailed
Age (mean ± SD)	45.0 ± 10.6	45.0 ± 10.3	0.67
Sex (male) %	38 (69.1%)	39 (76.5%)	0.39
Overweight/obesity	18 (32.7%)	17 (33.3%)	0.95
Central obesity	46 (83.6%)	33 (64.7%)	0.02
Dyslipidemia	43 (78.2%)	42 (82.4%)	0.59
Diabetes	2 (3.6%)	1 (2.0%)	0.60
Impaired fasting glucose	3 (5.5%)	5 (9.8%)	0.39
Tobacco consumers	21 (38.2%)	19 (37.3%)	0.92
Family H/O hypertension	27 (49.1%)	21 (41.2%)	0.41
Increased arterial stiffness %			
Right brachial artery	2 (3.6%)	1 (2.0%)	0.60
Left brachial artery stiffness	0 (0%)	1 (2.0%)	0.29
Right lower limb arterial stiffness	4 (7.3%)	1 (2.0%)	0.20
Left lower limb arterial stiffness	4 (7.3%)	3 (5.9%)	0.77
Carotid femoral arterial stiffness	43 (78.2%)	40 (78.4%)	0.98

Table 2 — Baseline comparison of population means of the CV risk factors and indices of renal function in the study groups.			
Characteristics	Metoprolol (mean ± SD)	Telmisartan (mean ± SD)	p Value
BMI	26.1 ± 3.9	25.7 ± 4.3	0.6
Waist circumference	93.6 ± 6.7	91.9 ± 9.8	0.31
SBP	151.5 ± 13.5	157.8 ± 20.0	0.06
DBP	99.6 ± 8.2	99.6 ± 11.3	0.98
LV mass	134.9 ± 28.5	129.4 ± 33.2	0.36
Fasting blood sugar	93.5 ± 18.0	94.9 ± 21.4	0.70
Total cholesterol	203.5 ± 45.7	185.3 ± 35.7	0.02
LDL-C	122.4 ± 35.9	108.4 ± 27.1	0.02
HDL-C	46.9 ± 11.2	45.7 ± 10.4	0.60
TG	179.6 ± 95.7	176.0 ± 71.6	0.86
TG/HDL ratio	4.0 ± 2.1	3.9 ± 2.0	0.89
Blood urea	28.7 ± 7.0	28.3 ± 6.8	0.73
S. creatinine	0.87 ± 0.18	0.87 ± 0.18	0.93
Uric acid	6.1 ± 1.3	6.4 ± 1.5	0.28

Table 3 – Baseline comparison of study groups means of arterial stiffness (PWV) in different regional.				
Regional arterial segments	Metoprolol meters	Telmisartan meters	Mean difference on meters	95% C.I. of mean difference
Right brachial artery	34.9 ± 20.6	33.2 ± 10.6	1.73	−4.6–8.1
Left brachial artery	30.0 ± 8.0	31.2 ± 9.2	−1.2	−4.4–2.1
Right ankle	41.2 ± 19.7	44.5 ± 12.3	−3.2	−9.6–3.7
Left ankle	45.2 ± 17.7	47.7 ± 19.5	−2.5	−9.7–4.6
Carotid femoral artery	1072.4 ± 366	1043.7 ± 465.2	28.7	−132–189

3.7. Comparison of effect of telmisartan and metoprolol on blood biochemistry

- **Blood sugar and lipid profile, renal function and uric acid levels;** There was no significant difference in the level of blood sugar, lipid profile, blood urea and serum creatinine levels between telmisartan and metoprolol groups. Although there was a trend of greater reduction in the level of uric acid in telmisartan group but was statistically not significant (5.6 ± 1.2 vs. 7.2 ± 1.3, p 0.1) (Table 4).

4. Discussion

Increased arterial stiffness in hypertensive patients has prognostic importance and is mediated by inflammatory process. Activation of local RAAS system is believed to be one of the important trigger in initiation of inflammatory process mediated through oxidative stress pathways.[14] Thus inhibition of oxidative stress by blocking the effect of Angiotensin- II with telmisartan which has the highest affinity for AT1 receptor with longest plasma half-life[22–24] can be a rational choice. In the present study telmisartan was more effective than metoprolol in reducing arterial stiffness in hypertensive patients; right lower limb (36.4 ± 9.6 vs. 44.8 ± 15.1 m/s, p < 0.002), left lower limb arterial stiffness of (39.9 ± 11.7 vs. 46.8 ± 17.0 m/s, p < 0.02). There was no significant difference between study drugs on arterial stiffness in upper limb arterial bed. This could be due to lower prevalence of increased arterial stiffness in upper limb compared to lower limb vessels in both groups. There are number of factors that could influence the arterial stiffness e.g. age, sex, HR, hypertension, diabetes, dyslipidemia, obesity, tobacco consumption status etc. Since both the intervention groups were well matched for these confounders/risk factors, thus the observed decrease in PWV with telmisartan cannot be attributed to other confounding factors. Change in the cardiac cycle duration is likely to affect the PWV. Studies shows increase in HR increases the PWV[25]. In the metoprolol group, as expected, HR was significantly lower than in the telmisartan group thus at the most HR could have undermined the effect of telmisartan on PWV as compared to metoprolol. The lack of effect of telmisartan on arterial stiffness of carotid femoral arterial segment observed in the study is not known. It is likely that the structural changes in central arterial conduit vessels may be more advanced thus needs longer duration of drug exposure to show its reversal. Although there was a trend of greater reduction in the LV mass in telmisartan group (135.5 ± 37.6 vs. 143.2 ± 41.5) but was statistically not significant. Both telmisartan and metoprolol had no significant effect on glucose and lipid metabolism and on renal function. Telmisartan has also been found to be effective in lowering arterial stiffness by other investigators.[26,27] The effect of telmisartan on arterial stiffness in patients with

Table 4 – Comparison of effect of metoprolol with telmisartan on arterial stiffness in different arterial beds, BP, LV Mass and on blood biochemistry in study groups.					
Regional arterial beds	Telmisartan	Metoprolol	Mean difference	95% C.I. of mean difference	Sig. at 2 tailed
Right brachial artery	33.6 ± 16.8	34.3 ± 12.4	−0.71	(−6.6–5.2)	0.81
Left brachial artery stiffness	29.0 ± 7.9	32.9 ± 11.6	−3.91	−7.9–0.1	0.055
Right ankle arterials stiffness	36.4 ± 9.6	44.9 ± 15.1	−8.4	−13.5 to −3.3	0.002
Left ankle arterial stiffness	39.9 ± 11.7	46.8 ± 17.0	−6.8	−12.6 to −0.9	0.02
Carotid femoral artery stiffness	1011.0 ± 337.8	1045.0 ± 694.0	−33.8	−24.6–181.9	0.75
Fasting blood sugar	88.2 ± 11.4	90.5 ± 10.3	−2.3	−6.6–1.9	0.28
Total cholesterol	191.3 ± 39.9	191.2 ± 37.0	0.14	−15.2–15.4	0.98
LDL-C	117.3 ± 31.8	112.9 ± 28.8	4.4	−7.7–16.5	0.47
HDL-C	45.4 ± 9.4	44.2 ± 8.2	1.2	−2.3–4.7	0.51
TG	163.6 ± 63.6	178.3 ± 62.0	−14.7	−39.7–10.3	0.24
TG/HDL-C ratio	3.8 ± 1.9	4.2 ± 1.8			0.32
Blood urea	29.1 ± 6.2	30.5 ± 7.5	−1.35	−4.1–1.4	0.33
S. creatinine	0.85 ± 0.10	0.86 ± 0.22	−0.002	−0.7–0.07	0.95
Uric acid	5.7 ± 1.2	7.2 ± 1.3	−1.5	−3.5–0.5	0.15
SBP	124.7 ± 7.8	129.7 ± 7.9	−4.9	−8.1 to −1.7	0.003
DBP	81.3 ± 5.4	82.4 ± 5.9	−1.1	−3.3–1.2	0.35
HR	78.2 ± 10.4	67.6 ± 41.5			0.001
LV mass	135.5 ± 37.6	143.2 ± 41.5			0.33

isolated systolic hypertension where the arterial stiffness is increased needs further studies. In present study, population with isolated systolic hypertension formed the very small group (<3%) thus observation made in present study cannot be translated into this subset of hypertensive patients. It would also be of interest to evaluate the correlation between changes in cardiac loading conditions due to changes in arterial stiffness in response to different antihypertensive agents on regional myocardial systolic and diastolic function with use of more sensitive tools e.g. strain imaging with speckle tracking methods. These observations may help improving our mechanistic understanding of impact of arterial stiffness on cardiac function and would form the basis for making informed decision in selection of antihypertensive drugs in future.

5.   Conclusions

Telmisartan was more effective in lowering arterial stiffness in lower limb vessels compared to metoprolol in newly detected and known hypertensive patients not on antihypertensive medications.

6.   Study Limitations

- Small sample size limited the statistical power to detect true differences between metoprolol and telmisartan on arterial stiffness in upper limbs, LV mass.
- Findings are not generalizable to patients with isolated systolic hypertension.
- Study exposure period of six months probably may be inadequate to bring significant impact on structural remodeling of arterial wall favorably.

Conflicts of interest

All authors have none to declare.

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