Original Article

Relationship Of C - Reactive Protein With Essential Hypertension At 1st Presentation And Effect Of Antihypertensive Treatment On Micro Inflammation

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Objective: To determine the relationship of C - reactive protein with essential hypertension at 1st presentation and effect of angiotensin-II receptor blockade on micro-inflammation.

Material & Methods: Twenty healthy controls and forty patients of stage 1 and stage 2 essential hypertension diagnosed at their 1st presentation at outpatient department of Services Hospital Lahore were studied. Blood of all patients was checked for CRP at 1st presentation and at the end of twelve weeks. Patients were divided in two groups A & B, group A received valsartan 80 to 160 mg per day and group B received amlodipine 5 to 20 mg per day. None of the patients required additional antihypertensive therapy.

Results: The mean change in hsCRP was 0.09 mg/L among those allocated to amlodipine compared with 0.08 mg/L among those allocated to valsartan. When the means of hsCRP were compared in three groups, it was found that initial hsCRP levels were high in hypertensive group and after twelve week treatment with antihypertensive medicines there was significant drop in hsCRP levels ($p<0.05$). Within the groups neither amlodipine nor valsartan showed the individual benefit on each other ($p>0.05$), both of them were equally effective in reducing hsCRP. No relationship was observed between hsCRP change and change of blood pressure.

Conclusion: It is concluded that C-reactive protein is high in hypertensive patients and adequate control of blood pressure is required to prevent the vasculature from atherosclerotic damage

Keywords: Hypertension, C - Reactive Protein and Microinflammation.

Introduction

Renin-angiotensin system adversely influences fibrinolytic balance; vascular endothelial function and vascular inflammation all are key components of atherosclerotic progression and adverse coronary outcomes. Results of various studies suggest favorable effects of angiotensin converting enzyme inhibitors (ACE) and angiotensin II receptor blockers (ARBs) over markers of these components including effects on plasminogen activator inhibitor 1, endothelin 1 and nitric oxide by ACE and effect on vascular cell adhesion molecule 1 (VCAM-1) and C-reactive protein (CRP) by ARBs. CRP is the best characterized inflammatory marker.[1-5] CRP levels >10 mg/L are often found in systemic inflammation, levels < 1, 1-3 and > 3 mg/L , respectively identify patients at low, intermediate and high risk for future cardiovascular events.[6] Individuals with LDL cholesterol below 130 mg/dL who have CRP levels = 3 mg/L represent a high-risk group.[7] High plasma concentration of CRP was associated with a 2 fold increase in a risk of stroke, 3 fold increase in risk of MI and 4 fold increase in risk of peripheral vascular disease.[8] CRP adds to the predictive value of total and HDL cholesterol; in men with HDL cholesterol < 50 and CRP >3 mg/L, there is an increased risk for future MI and stroke.[9] CRP is associated with increased risk of fatal coronary events among high risk male smokers,[10] incidental coronary disease among elderly[11,12] and recurrent coronary events in patients with known coronary artery disease.[13-17]

Hypertension is an inflammatory disease. Accumulation of inflammatory cells is seen in arteries of hypertensive rats.[18] CRP also predicts hypertension.[19] C-reactive protein is a predictive risk factor for myocardial infarction and stroke among apparently healthy women.[20]

Material & Methods

It was a single center, open label, prospectively designed randomized trial conducted in SIMS/Services Hospital, Lahore from January 2008 to January 2009. The study center was Medical Unit-II of SIMS/Services Hospital Lahore. It was designed to observe the increased inflammatory activity in

reactive protein and effect of antihypertensive treatment with valsartan and amlodipine on C-reactive protein level. It included men and women between 18 and 75 years of age with stage 1 & 2 hypertension. For the purpose of study stage 2 hypertension was defined as systolic blood pressure 160 mmHg or diastolic blood pressure 100 mmHg based on the measurement of 3 consecutive seated blood pressure readings using a standardized mercury sphygmomanometer.

Similarly stage 1 hypertension was defined as systolic blood pressure of 140-159 and diastolic blood pressure of 90-99 mmHg. Patients having systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg, serum creatinine 2 mg/dL, patients having diabetes mellitus, serum potassium =3.5 and ≥5.5 mEq/L, patients with deranged liver functions and having hepatitis B & C positive liver disease, pregnant or lactating women as well as those with a history of secondary hypertension or history of myocardial infarction, stroke, cardiac revascularization, unstable angina, congestive heart failure and taking statins were excluded from the study. Subjects with chronic inflammatory conditions such as rheumatoid arthritis, osteoarthritis, lupus, or inflammatory bowel disease were also excluded from study. Forty patients of essential hypertension diagnosed at their first outpatient presentation at Services Hospital Lahore were studied. Similar observation was made in twenty normal healthy individuals. Detailed history regarding symptoms related to hypertension and to exclude secondary hypertension such as headache, somnolence, palpitations, sweating, pallor, weakness, polyuria and nocturia was taken. General physical examination especially of peripheral pulses and blood pressure in both arms was checked and orthostatic drop in blood pressure was recorded. Cardiovascular examination to look for left ventricular heave and pre-systolic (S4) gallop was done. Abdominal examination for renal bruit and chest examination for basilar crepitations was done. Blood of all patients was checked for CRP at first presentation and at the end of three months. Patients were divided in two groups A & B, group A received valsartan 80 to 320 mg per day and group B received amlodipine 5 to 20 mg per day. Patients were followed up at weekly intervals. All blood samples were processed at SIMS laboratory and underwent hsCRP evaluation. Statistical analysis was done using SPSS version 16. Comparison of the treatment groups was done by analysis of variance (ANOVA). Paired 't' test was applied to see before and after treatment effect. Spearman's correlation coefficient was computed to see the correlation of blood pressure and CRP.

Results

Mean age of control group was 30 years. Mean age of hypertensive patients receiving valsartan was 42 years. Mean age of hypertensive patients receiving amlodipin was 45 years. **Table1 & 2** present the clinical characteristics about age**,** blood pressure and hsCRP levels of the study population before and after treatment. It was found on statistical analysis that mean value of CRP was significantly high among the hypertensive patients at the start of study. One way ANOVA comparing the means of CRP in three groups showed that antihypertensive treatment significantly reduced the CRP levels **(Fig-1).** Paired t test was applied to see before and after treatment effects, and it showed that none of the treatment showed statistical advantage over the other (p>0.05). . No correlation was observed in blood pressure reduction and CRP levels **(Table 3).**

Table-1: Descriptive statistics about age and hsCRP of the study population.

Treatment groups	Age in Years	Pre/Post treatment	hsCRP Level
Amlodipine group	29.55±11.16	Before treatment	2.00950±292
		After treatment	1.91500±0.171
Valsartan group	41.75±13.73	Before treatment	1.84950±0.443
		After treatment	1.70550±0.112
Control group	38.74±14.64	Before treatment	1.70550±0.112
		After treatment	1.70550±0.112

One way ANOVA to compare means of control and treatment group,p<0.05
Paired t-test to compare both treatment group (Amlodipine) p=0.392 and P value for valsartan=0.207

Table-2: Descriptive statistics about blood pressure of study population before & after treatment

Blood pressure	Min BP	Max BP	Mean blood pressure ± SD
Systolic blood pressure before treatment (n=40)	135	170	150.00±9.058
Diastolic blood pressure before treatment (n=40)	95	120	104.13±6.29
Systolic blood pressure after treatment (n=40)	110	140	126±8.350
Diastolic blood pressure after treatment (n=40)	95	120	104.13±6.293

Table-3: Spearman's correlation coefficient between change in blood pressure and change in hsCRP

Change in hsCRP	Change in Systolic Blood Pressure	Change in diastolic BP
Total Cohort	-0.148 (p=0.361)	-0.48 (p=0.77)
Valsartan	-0.374 (p=0.104)	+0.009 (p=0.009)
Amlodipine	+0.119 (p=0.618)	-0.05 (p=0.835)

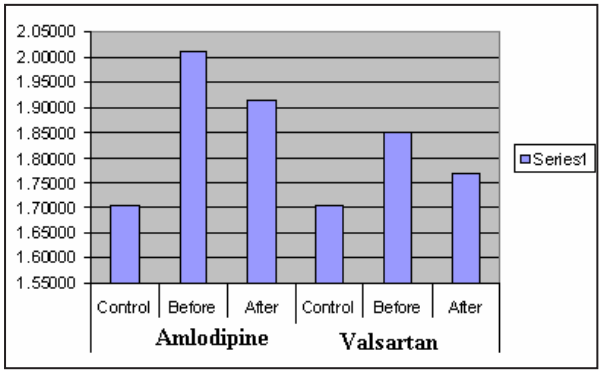

Fig-1: Mean Comparison of CRP in controls and two treatment groups

Discussion

Evidence from a number of studies suggests that angiotensin receptor blockade has anti-inflammatory effect, and reduction of hsCRP was observed in the patients taking angiotensin receptor blockers. In this study valsartan and amlodipine monotherapy was used for treatment of hypertension in stage 1 and 2 hypertensive patients. C reactive protein was found to be high in all hypertensive patients at the start of study. Blood pressure was adequately controlled in both these groups with antihypertensive medications used. After twelve weeks of treatment significant drop in CRP was observed in both treatment groups.

It was observed in the previous studies as well that there was accumulation of inflammatory cells in arteries of hypertensive rats.[18] hsCRP was found to predict the future risk of developing hypertension in normotensive individuals.[20] Angiotensin II activates nuclear factor $\kappa\beta$ in human vascular smooth muscles.[21] Angiotensin induces interleukin 6 production by human vascular smooth muscle cells. Angiotensin II increases oxidant stress.[22] Angiotensin II by activation of nuclear factor kappa B(NFkB), induces production of interleukin 6 by human vascular smooth muscles and increases monocyte adhesion and monocyte recruitment by increasing cellular expression of vascular cell adhesion molecule (VMCA) and macrophage chemo-attractant protein (MCP-1) and also increases oxidant stress and promotes hypertension.[23,24] Angiotensin II promotes dimidiation of angiotensin 1 receptors (AT) which increases monocyte adhesion to endothelium.[25]

In our study no antihypertensive treatment was found to be superior to other. In our study both amlodipine and valsartan reduced blood pressure effectively and also reduced hsCRP equally. Studies with other angiotensin II receptor blockers also showed similar results as observed in our study. Angiotensin II receptor blockade significantly reduces micro inflammation in patients with essential hypertension as early as week 6 of therapy with olmesartan medoxomil alone and in co-therapy with HMG Co-A reductase inhibitor and shows significant reduction in serum levels of high sensitivity C-reactive protein, high sensitivity tumor necrosis factor alpha (hsTNF α) and interleukin (IL-6) after 6 weeks of therapy.[26-28] Reduction in hsCRP level was also observed in those patients who were taking statins.[29] Hypertension control appears to be mandatory to reduce vascular inflammation.

Conclusion

Hypertension is an inflammatory disease and strict control of blood pressure is required to prevent the atherosclerotic damage.

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Medical News

Dapagliflozin Improves Diabetes Control Without Weight Gain

NEW YORK (Reuters Health) Aug 12 - The investigational glucose-lowering drug dapagliflozin improved glycemic control in patients with type 2 diabetes already on metformin, and it promoted significant weight loss, in a phase II trial reported in Diabetes Care online August 4. "Dapagliflozin is a potential valuable alternative to sulfonylureas as add-on therapy when metformin monotherapy fails to maintain adequate glycemic control," the authors conclude. Adverse events were no more common with dapagliflozin, the authors report. That was not the case in later studies, however, and last month a U.S. federal advisory committee declined to recommend approval of dapagliflozin because of safety concerns, including a possible increased risk of breast and bladder cancers. A final decision by the U.S. Food and Drug Administration is expected in late October. Dapagliflozin, a selective sodium-glucose cotransporter 2 inhibitor, reduces glucose resorption from the proximal tubule of the kidney, leading to increased urinary glucose excretion and net caloric loss. The authors of the current paper, led by Dr. Michael A. Nauck, with the Diabetes Centre in Bad Lauterberg, Germany, compared dapagliflozin to the sulfonylurea glipizide as add-on therapy in 814 patients with type 2 diabetes inadequately controlled on metformin. Patients took the assigned treatment for a year. Mean HbA1c -- 7.7% at baseline -- fell more rapidly at first in the glipizide group but then rose, while the dapagliflozin group showed a steadier drop. The result was an identical decrease in HbA1c of 0.52% in both groups at 52 weeks. Secondary endpoints were significantly different, however. The mean adjusted weight dropped by 3.2 kg with dapagliflozin but increased by 1.2 kg with glipizide. Also, the proportion of patients with at least one episode of hypoglycemia was 40.8% with glipizide but only 3.5% with dapagliflozin. Serious adverse events related to treatment occurred in six patients on dapagliflozin and in four on glipizide. "Higher proportions of patients receiving dapagliflozin reported events suggestive of genital infections or lower UTIs compared with glipizide," Dr. Nauck and colleagues report. "This head-to-head comparison of dapagliflozin versus glipizide added to metformin in type 2 diabetic patients poorly controlled with metformin monotherapy demonstrated similar glycemic efficacy at 52 weeks but markedly divergent effects on weight and hypoglycemia," the research team concluded.

First Triple Combo With Aliskiren Gets US Approval

The US FDA has approved for marketing a triple antihypertensive combination therapy containing the direct renin inhibitor, aliskiren, along with the calcium channel blocker amlodipine and the diuretic, hydrochlorothiazide (HCTZ) . This is the first such combination containing a direct renin inhibitor, says Novartis, which will market the product as Amturnide; it is not indicated as initial therapy, rather use must be reserved for those whose blood pressure is not adequately controlled with any of its two components. Amturnide joins other three-drug combination pills for hypertension approved in the US. These include Exforge HCT (also Novartis)--a three-drug combo of amlodipine, the angiotensin-receptor blocker (ARB) valsartan and HCTZ, cleared last year-- and Tribenzor (Daiichi Sankyo), which combines the ARB olmesartan, amlodipine and HCTZ, which was approved by the FDA in July. The same product has also just been cleared for marketing in Germany, its first European country, where it will be known as Sevikar HCT. Many experts believe these new triple combinations of antihypertensive drugs will help hard-to-treat patients reach their blood-pressure goals, but an American Society of Hypertension position paper [2,3] published earlier this year cautioned that branded combinations are typically more expensive than combining two or three single-drug pills, particularly if the single medications