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EFFECTS OF BETA-ADRENOCEPTOR BLOCKERS ON THE PLATELET AND CARDIOMETABOLIC INDICES IN UNCONTROLLED HYPERTENSION

Zahraa A. G. Mohammed Ali*

Department of Clinical Pharmacy, College of Pharmacy, Al-Mustansiriyah University, Baghdad, Iraq.

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Correspondence to Author:
Zahraa A. G. Mohammed Ali

Assistant Lecturer,
Department of Clinical Pharmacy,
College of Pharmacy, Al-Mustansiriyah University, Baghdad, Iraq.

E-mail: zahraaaalbasry@yahoo.com

ABSTRACT: Background: Metabolic derangement in term of glucose dysregulation, dyslipidemia, and electrolyte disturbances are the adverse reactions of beta-adrenoceptor blockers that limit their use. **Aims:** To investigate the effect of BARBs on the cardio-metabolic risk factors and platelet indices that play a role in accelerating the atherogenicity. **Materials and methods**: This observational clinical study was done in the Department of Clinical Pharmacy, College of Pharmacy, Al-Mustansiriya University in Baghdad, Iraq from 1st August 2016 to 31st December 2016. A total number of 54 uncontrolled hypertensive patients were enrolled in this study. They grouped into Group I (*n*=25): hypertensive patients treated with angiotensin receptor blockers (ARBs) or angiotensin converting enzyme inhibitors (ACEIs), and Group II (*n*=29): hypertensive patients treated with beta-adrenoceptor agents in addition to the ARBs or ACEIs. The anthropometric, blood pressure, fasting serum glucose and lipid profile, and the platelet indices were determined. **Results**: Group II patients have significant low fasting serum glucose and non-significant high serum levels of triglycerides and cholesterol. Significant negative correlation between fasting serum triglycerides and plateletcrit (r=0.444, df=23, p=0.0250 observed in Group I patients. **Conclusion:** BARBs carried a metabolic derangement in term of alterations in the fasting serum glucose, triglycerides and cholesterol, but they offered a favorable effect on the platelet function and thereby reduced the risk of coronary artery disease.

INTRODUCTION: There are many classes of antihypertensive agents act *via* different mechanisms are used in management of hyper - tension and none of them is free from adverse reactions. Metabolic derangement in term of hyper-glycemia or hypoglycemia, dyslipidemia, and electrolyte disturbances are the adverse reactions that limit the use of these drugs in hypertension comorbidities *e.g*. diabetes mellitus [1 - 4].

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Angiotensin converting enzyme inhibitors (ACEIs) are commonly used in management of hypertension and their main adverse reactions included dry cough, hyperkalemia, proteinuria and hyper-sensitivity reactions [5, 6]. There is no evidence that ACEIs exerts a beneficial or harmful effect on the lipid profile or the blood glucose levels even in experimental studies [7, 8].

There is evidence that angiotensin receptor blockers (ARBs) can improve the dyslipidemia that occurred in diabetic patients with nephropathy complications [9] and they also attenuate the harmful effects of hyperglycemia [10, 11]. Beta-adrenoceptor blocking agents (BADRBs) induced many adverse reactions that depended on their cardio selectivity and intrinsic sympathetic activity.

BADRBs interfere with glucose regulation leading to cause hyperglycemia as an adverse reaction, in addition to their inhibitory effects on the hepatic gluconeogenesis [12]. Dyslipidemia in term of increase plasma levels of triglycerides occurred with using the BARBs even those with cardio selective effect *e.g*. atenolol [13]. BARBs are known compounds that inhibit the aggregation of the blood platelet and there is evidence that propranolol is more effective than atenolol in this concern [14]. On the other hands, platelet indices and hypertension are interrelated, and these indices used as a diagnostic or prognostic markers [15].

The rationale of this study that the metabolic derangement and changes in the platelet indices that induced by BADRBs may be influenced by using other antihypertensive drugs. The aims of this study were to explore the effect of BARBs on the cardio-metabolic risk and platelet indices that play a role in accelerating the atherogenicity.

MATERIALS AND METHODS: This observational clinical study was done in the Department of Clinical Pharmacy, College of Pharmacy, Al-Mustansiriya University in Baghdad, Iraq from 1st August 2016 to 31st December 2016. The protocol of the approved by the Institutional Scientific Committee. The study included hypertensive patients who attended the private clinics for follow-up of essential hypertension. All patients provided informed consent to participate in the study. The criteria of inclusion were essential hypertension treated with antihypertensive drugs (not more than two drugs related to different classes, one of them related to the beta-adrenoceptor blocking agents). The criteria of exclusion included secondary hypertension, diabetes mellitus, pregnancy, renal and hepatic failure.

Each patient asked to answer specific questions related to the demographic characteristics and his/her illness history and then the patients subjected to the following measurements, blood pressure, anthropometric indices, fasting serum lipid profile, complete blood count and the related hematological indices. The blood pressure was measured in sitting position and the mean of three readings was taken.

The anthropometric measurements included height, weight and waist circumference. Body mass index (BMI) was calculated by applying the Quetlete's equation:

$$\text{Body mass index (kg/m}^2\text{)} = \text{weight (kg)} / \text{height}^2 \text{ (m)}$$

Peripheral venous blood drew immediately after admission into a plane and EDTA-tubes Plane tubes that contained blood were centrifuging at 2500 RPM for 10 min, and the sera were separated for determination of lipid profile. The determinants of lipid profile included fasting serum total cholesterol (TC), triglycerides (TG), and high-density lipoprotein-cholesterol (HDL-c). Low-density lipoprotein-cholesterol (LDL-c) was calculated by using the following equation:

$$\text{LDL-c (mg/dl)} = \text{TC- (HDL-c+[0.2} \times \text{TG])}$$

The EDTA tubes were used for determination of blood platelet indices using hematology analyzer. The platelet indices included platelet count, plateletcrit (PCT), mean platelet volume (MPV), and platelet width distribution (PWD).

A total number of 54 hypertensive patients were enrolled in this study. They grouped into:

Group I (*n*=25): hypertensive patients treated with one medication related to the angiotensin receptor blockers (ARBs) (candesartan, losartan, valsartan) or one of angiotensin converting enzyme inhibitors (ACEIs) (capropril, enalopril, lisinopril).

Group II (*n*=29): hypertensive patients treated with one medication related to the beta-adrenoceptor agents (atenolol, bisprolol, metoprolol) and one medication either related to the angiotensin receptor blockers (ARBs) (candesartan, losartan, valsartan) or one of angiotensin converting enzyme inhibitors (ACEIs) (capropril, enalopril, lisinopril).

Statistical Analysis: The statistical analysis was performed by using SPSS v.20.0 for Windows (IBM Corp., Armonk, NY, USA).

The results are expressed as a number, percentage and mean ± SD. Difference between percentages test was used to compare categorical variables. The differences in means were analyzed by using the two- tailed unpaired t-test and a simple correlation test was used to determine the relationship between platelet indices and the variables related to the metabolic derangement determinants. The level of statistical significance was set at $p \leq 0.05$.

RESULTS: Table 1 shows the characteristics of the study. There was non-significant differences between Group I and II regarding the age, duration of hypertension, smoking or past history of ischemic heart disease. There was non-significant differences between Group I and II in respect to the using the antihypertensive agents of ACEIs and/or ARBs.

TABLE 1: CHARACTERISTICS OF THE PATIENTS ENROLLED IN THE STUDY

	Group I (*n*=25)	Group II (*n*=29)	P value
Gender (Male : Female)	4:21	11:18	
Age (year)	64.3±7.9	63.5±8.7	0.727
Duration of hypertension (year)	14.1±4.1	14.2±5.2	0.938
Current smoking	16(64)	11(37.9)	0.056
History of ischemic heart disease	11(44)	8(27.6)	0.208
Current antihypertensive agents:			
ARBs	15(60)	11(37.9)	0.106
ACEIs	10 (40)	18(62.1)	0.106
BARBs	0	29(100)	

The results are expressed as number (%) and mean ± SD. Group I: patients not treated with beta-adrenoceptor blocking agents; Group II: patients treated with beta-adrenoceptor blocking agents. ARBs; angiotensin receptor blockers, ACEIs; angiotensin converting enzyme inhibitors, BARB; beta-adrenorecetor blockers.

Table 2 shows the determinants of the cardio-metabolic risk factors. There was non-significant differences in the levels of blood pressure or the anthropometric measurements presented with BMI and waist circumference.

TABLE 2: MEASUREMENTS OF THE CARDIO-METABOLIC RISK FACTORS

Risk factor	Group I (*n*=25)	Group II (*n*=29)	P value
Blood pressure (mmHg)			
Systolic	151.2±19.1	151.4±21.3	0.971
Diastolic	97.4±8.3	98.3±10.7	0.734
Body mass index (kg/m^2)	30.8±5.4	31.7±8.2	0.641
Waist circumference (cm)	99.9±17.1	100.4±22.5	0.928
Waist to Height ratio	0.616±0.107	0.615±0.140	0.977
Fasting serum glucose (mg/dL)	115.8±19.3	105.4±14.4	0.028
Fasting serum lipid profile (mg/dL)			
Total cholesterol	183.1±32.6	192.5±28.6	0.264
Triglycerides	136.7±50.8	158.0±55.3	0.149
High density lipoprotein-cholesterol	47.1±5.8	52.4±14.7	0.097
Low density lipoprotein-cholesterol	108.7±24.1	108.5±31.2	0.979

The results are expressed as mean ± SD. Group I: patients not treated with beta-adrenoceptor blocking agents; Group II: patients treated with beta-adrenoceptor blocking agents.

Despite there is no significant difference between waist to height ratio between Group I and Group II, the value of this ratio exceeded the cut off value of 0.5, which indicated that the patients of both groups were at risk of cardiovascular events. The mean levels of fasting serum glucose were within normal range in both groups but Group I patient had a significant high level compared with Group II. The fasting lipid profile levels did not show significant difference between Group I and Group II but the patients of Group II had a mean level of serum triglycerides that exceeded the cut off value of 150mg/dl, which indicated the evidence of metabolic syndrome.

Table 3 shows the non-significant differences in the platelets indices between Group I and II. The levels of fasting serum triglycerides were significantly correlated in an inverse pattern with the plateletcrit (r= -0.447, df =23, p=0.025) in Group I patients (**Table 4**).

TABLE 3: MEASUREMENTS OF THE PLATELETS INDICES

Platelets indices	Group I (*n*=25)	Group II (*n*=29)	P value
Platelet counts (per mm^3)	302.68 ±87.7×10^3	321.14±87. 47×10^3	0.444
Plateletcrit (%)	0.148±0.03	0.155±0.04	0.476
Mean platelet volume(fL)	5.0±0.91	4.97±0.77	0.896
Platelet width distribution (%)	17.2±0.74	17.2±0.87	1.000

The results are expressed as number (%) and mean ± SD. Group I: patients not treated with beta-adrenoceptor blocking agents; Group II: patients treated with beta-adrenoceptor blocking agents.

TABLE 4: CORRELATIONS BETWEEN PLATELET INDICES WITH TRIGLYCERIDES AND HIGH DENSITY LIPOPROTEIN-CHOLESTEROL

Correlation	Group I (*n*=25)	P value	Group II (*n*=29)	P value
PCT *vs* TG	-0.447	0.025	0.060	0.757
PCT *vs* HDL-c	-0.160	0.444	0.091	0.639
MPV *vs* TG	0.187	0.371	-0.095	0.624
MPV *vs* HDL-c	0.058	0.783	-0.091	0.639
PWD *vs* TG	0.299	0.146	0.242	0.205
PWD *vs* HDL-c	0.093	0.658	-0.204	0.288

The results are expressed as a correlation factor (r). Group I: patients not treated with beta-adrenoceptor blocking agents; Group II: patients treated with beta-adrenoceptor blocking agents. PCT; plateletcrit, MPV; mean platelet volume, PWD; platelet width distribution, TG; triglycerides, HDL-c; high-density lipoprotein-cholesterol.

DISCUSSION: The results showed that hypertensive patients treated with BARBs have a significant low serum glucose level and non-significant high serum triglycerides and cholesterol levels compared with those patients did not treat with BADRBs. This observation may relate to the BARBs in addition to the other factors for the following reasons:

First: the characteristic features of participants enrolled in the study did not show significant difference between Group I and II. The number of smokers in Group II was less than corresponding number of Group I (p=0.056) and this finding is in agreement with other studies that show active smoking is a risk factor of diabetes. The fasting serum glucose among Group I patients who are non-diabetic was significantly higher than corresponding level of Group II patients [16].

Second: the number of Group II patients who used ARBs was non-significantly less corresponding number of Group I. This observation is in favor that low fasting serum glucose level among Group II patients is due to the using BARBs because ARBs reduced the serum glucose [17].

Third: The anthropometric measurements and the levels of the blood pressure did not show significant difference. Therefore, these factors did not bias the results of low fasting serum glucose among group II patients. This finding is in agreement with other studies that using BARBs resulted in a significant correlation between reduction of the blood pressure and changes in the anthropometric measurements [18]. In this study, the levels of blood pressure are still high as well as the anthropometric measurement.

Fourth: Significant low fasting serum glucose and a non-significant high serum triglycerides and cholesterol levels highlight the guideline of using BARBs in diabetic patients. The use of BARBs increased the risk of dyslipidemia and atherogenic lipids as this study reports this observation [19]. The significant low serum glucose level that observed in this study does not agree with other studies, which most probably due to the heterogenecity of the prescribed BARBs as DiNicolantonio *et al* 2015 mentioned [19]. Therefore, one of the limitations of the study is the small number size that does not allow a significant analysis of the effect of each BARBs on the metabolic derangement.

Fifth: The result of this study do not show significant effect of using BARBs on the platelet indices but there is a non-significant correlation with fasting serum triglycerides whereas a significant negative correlation observed in Group I patients. This indicates that BARBs affect the plateletcrit indirectly irrespective of their effects on the serum triglycerides. There is evidence that there is a dysfunction of the blood platelet when there is metabolic derangement in term of hyperuricemia or dyslipidemia [20]. This observation is of great importance that indicates the patients of Group II are free from the risk for coronary artery disease as previous studies reported a significant alteration in the platelet indices in patients with diabetes [21].

In conclusion, BARBs carried a metabolic derangement in term of alterations in the fasting serum glucose, triglycerides and cholesterol, but they offered a favorable effect on the platelet function and thereby reduced the risk of coronary artery disease.

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CONFLICT OF INTEREST: The author declares that there is no conflict of interest.

REFERENCES:

1. Butakova SS and Nozdrachev AD: Calcium channel blockers inhibit the hyperglycemic effect of calcitonin. Bull Exp Biol Med 2012; 152:553-559.
2. Brown MJ, Williams B, Morant SV, Webb DJ, Caulfield MJ, Cruickshank JK, Ford I, McInnes G, Sever P, Salsbury J, Mackenzie IS, Padmanabhan S, MacDonald TM and British Hypertension Society's Prevention and Treatment of Hypertension with Algorithm-based Therapy (Pathway) Studies Group: Effect of amiloride, or amiloride plus hydrochlorothiazide, versus hydro chlorothiazide on glucose tolerance and blood pressure (Pathway-3): a parallel-group, double-blind randomised phase 4 trial. Lancet Diabetes Endocrinol 2016; 4:136-147.
3. Cooper-De Hoff RM, Wen S, Beitelshees AL, Zineh I, Gums JG, Turner ST, Gong Y, Hall K, Parekh V, Chapman AB, Boerwinkle E and Johnson JA: Impact of abdominal obesity on incidence of adverse metabolic effects associated with antihypertensive medications. Hypertension 2010; 55:61-68.

4. Manrique C, Johnson M and Sowers JR: Thiazide diuretics alone or with beta-blockers impair glucose metabolism in hypertensive patients with abdominal obesity. Hypertension 2010; 55:15-17.
5. Desai AS, Vardeny O, Claggett B, McMurray JJ, Packer M, Swedberg K, Rouleau JL, Zile MR, Lefkowitz M, Shi V and Solomon SD: Reduced risk of hyperkalemia duringt treatment of heart failure with mineralocorticoid receptor antagonists by use of sacubitril/valsartan compared with enalapril: A secondary analysis of the Paradigm-HF Trial. Jama Cardiol 2017; 2:79-85.
6. Clase CM and Mann JF. Adding lisinopril to losartan increased hyperkalemia and acute kidney injury in type 2 diabetes and proteinuria. Ann Intern Med 2014; 160:JC3.
7. Galeeva ZM and Galiavich AS: A fixed-dose lisinopril and amlodipine combination in conjunction with rosuvastatin in patients with hypertensive disease and coronary heart disease. Ter Arkh 2014; 86:71-76.
8. Akbar DH, Hagras MM, Amin HA and Khorshid OA: Comparison between the effect of glibenclamide and captopril on experimentally induced diabetic nephropathy in rats. J Renin Angiotensin Aldosterone Syst. 2013; 14:103-115.
9. Srivastava A, Adams-Huet B, Vega GL and Toto RD: Effect of losartan and spironolactone on triglyceride-rich lipoproteins in diabetic nephropathy. J Investig Med 2016; 64:1102-1108.
10. Lodovici M, Bigagli E, Tarantini F, Di Serio C and Raimondi L: Losartan reduces oxidative damage to renal DNA and conserves plasma antioxidant capacity in diabetic rats. Exp Biol Med (Maywood) 2015; 240:1500-1504.
11. Mourad AA, Heeba GH, Taye A and El-Moselhy MA: Comparative study between atorvastatin and losartan on high fat diet-induced type 2 diabetes mellitus in rats. Fundam Clin Pharmacol 2013; 27:489-497.
12. Chang SW, Gong Y, McDonough CW, Langaee TY, Nasiri Kenari N, Beitelshees AL, Gums JG, Chapman AB, Turner ST, Johnson JA and Cooper-DeHoff RM: Melatonin Pathway and Atenolol-Related Glucose Dysregulation: Is There a Correlation? Clin Transl Sci 2016; 9:114-122.
13. Kalyuzhin VV, Teplyakov AT, Pushnikova EY, Bespalova LD, Kalyuzhina EV and Kolesnikov RN: Comparative evaluation of the impact of four-week therapy with amlodipine and atenolol on quality of life and blood lipid composition in patients with coronary heart disease associated with metabolic syndrome. Ter Arkh 2013; 85: 68-72.
14. Punda A, Polić S, Rumboldt Z, Bagatin J, Marković V and Lukin A: Effects of atenolol and propranolol on platelet aggregation in moderate essential hypertension: randomized crossover trial. Croat Med J 2005; 46: 219-224.
15. Yang K, Tao L, Mahara G, Yan Y, Cao K, Liu X, Chen S, Xu Q, Liu L, Wang C, Huang F, Zhang J, Yan A, Ping Z and Guo X: An association of platelet indices with blood pressure in Beijing adults: Applying quadratic inference function for a longitudinal study. Medicine (Baltimore) 2016; 95:e4964.
16. Borowitz JL and Isom GE: Nicotine and Type 2 Diabetes. Toxicological Sciences 2008; 103:225–227.
17. Furuhashi M, Mita T, Moniwa N, Hoshina K, Ishimura S, Fuseya T, Watanabe Y, Yoshida H, Shimamoto K and Miura T: Angiotensin II receptor blockers decrease serum concentration of fatty acid-binding protein 4 in patients with hypertension. Hypertens Res 2015; 38: 252-259.
18. Ueno N and Satou Y: The enhanced effect of atenolol on hypertension in metabolic syndrome. Metab Syndr Relat Disord 2011; 9:369-373.
19. Di Nicolantonio JJ, Fares H, Niazi AK, Chatterjee S, D' Ascenzo F, Cerrato E, Biondi-Zoccai G, Lavie CJ, Bell DS and O'Keefe JH: β- Blockers in hypertension, diabetes, heart failure and acute myocardial infarction: a review of the literature. Open Heart 2015; 2:e000230.
20. Ding DD, Wang W, Cui ZG and Wang HY: Changes of platelet α-particle membrane protein, platelet activating factor and platelet parameters in patients with hyperuricemia. Zhongguo Shi Yan Xue Ye Xue Za Zhi 2012; 20:394-397.
21. Buch A, Kaur S, Nair R and Jain A: Platelet volume indices as predictive biomarkers for diabetic complications in Type 2 diabetic patients. J Lab Physicians 2017;9:84-88

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