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RESEARCH ARTICLE

IMPACT OF ANTIHYPERTENSIVE DRUGS ON C REACTIVE PROTEIN (HS-CRP) AND NEUTROPHIL LYMPHOCYTE RATIO (NLR)

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Abstract

Many studies showed the association between inflammation and Hypertension. Inflammatory markers may highlight the state of inflammation in hypertensive patients. This study aimed to investigate impact of antihypertensive drugs on high sensitive C-reactive protein (hsCRP) and neutrophil lymphocyte ratio (NLR). A comparative cross sectional study was conducted on 86 hypertensive patients attending cardiology outpatient clinic in Al-Gamhuoria Modern General Hospital, Aden, in the period from October to December 2023. Participants were divided into three groups: patients treated with mono-therapy from inhibitors of renin angiotensin aldosterone system (RAASI), patients treated with mono-therapy antihypertensive not acting on RAAS (NRAASI) and patients treed with combination of them (drug combination). Data on Age, Sex, BP level, BMI, duration of hypertension (HTN), family history of HTN, and medications used were collected. Blood samples for measuring HsCRP, neutrophils, lymphocytes were drawn. Descriptive statics and chi-square tests were used for data analysis. Almost equivalent distribution for males and females between groups, with a large proportion of the patients within each group laid in the age group 35-55 years. The median values of hypertension duration were 36, 48, and 54 months for RAASIs, NRAASIs and drug combination group, respectively. The target BP was obtained by 46.9% 45.5% and 50% of patients treated with RAASIs, NRAASIs and drug combination respectively. There was a statistically significant difference between SBP and DBP in patients with controlled BP and those with uncontrolled SBP levels and treated by different drug regimens (P=0.000 for each Bp level). There were significant differences between values of hs-CRP of patients with controlled (P=0.000) or uncontrolled (P=0.046) BP and treated with different modalities. The median differences in NLR between the groups were statistically significant; including groups of all patients P=.032, of patients having controlled BP P=0.014 as well as uncontrolled BP P=0.038. Comparing the uncontrolled of BP of the three groups we found the highest prevalence (9.3%)of patients with uncontrolled BP and had the lower level hsCRP (≤3mg /l) was in RAASIs group, while those with higher prevalence (11.6%) of uncontrolled BP and higher level of hs-CRP (>3mg/l) was in drug combination group. In conclusion, hypertensive patients treated with RAASI, NRAASI and drug combination and reached BP target showed significant reduction in hsCRP and NLR. Patients with uncontrolled BP treated with RAASIs revealed slightly lower hs-CRP than other groups. Careful selection of antihypertensive drugs may affect risks of CVD. This study recommends further prospective studies exploring the anti-inflammatory effect of antihypertensive drugs to ameliorate possible risks of cardiovascular disease.

Keywords: Hypertension, C-reactive protein, Inflammation, Blood pressure, Neutrophil.

Introduction

Hypertension is one of the record common chronic diseases, affects almost one billion of the world' population. (**ACC/AHA**) defines as systole blood pressure (SBP) ≥130mm Hg and diastolic blood pressure (DBP) and/or ≥80 mmHg [1].

HTN is divided into two major types: primary or essential and secondary HTN with more than 90% of persons with high BP have essential hypertension with

unknowing causes, or some genetic influences, and secondary HTN constitutes 5- 10% with vital known causes (**ACC/AHA**). HTN is not only the main cause of cardiovascular diseases (CVDs) morbidity and mortality [2], but also, the major risk factor for CVDs including heart failure, coronary artery disease, arterial fibrillation and stroke. [3]

Many studies have shown that inflammation is implicated in the development and maintenance of hypertension. Several mechanisms were suggested with immune cell populations involving in disease progression. [4,5] The vascular inflammatory process is reflected by increase number of inflammatory markers and there could be a link between HTN and atherosclerosis, which is the main basis of CVDs which is the important cause of mortality [6].

The causal relation between hypertension and inflammation lies in that both can alter the function of endothelial cells leading to reduction of nitric oxide (NO) availability, vascular stiffness and loss of elasticity which culminates with blood pressure elevation and remodeling of CV tissue. [7,8] suggested that IFNα is a link between inflammation and renin angiotensin aldosterone system (RAAS), the main player in hypertension development. Inhibition of this system may ameliorate cytokines and reduces inflammatory markers in favor less organ injury [9]

THN is prevalent in developed and developing countries. In the USA, the prevalence of HTN among overall residents ages ≥ 20years was 45.4%. [10], [11]

Hispanic –Americans made 44.7%.[12] and the rest for non-Hispanic people. Hypertension also increases in Chinese people to 46.4% [10], [11]. On the other hand, in developing countries, the prevalence of HTN is by 28.5%, where the prevalence among women was less than that in men. [13] In Yemen, a study has shown that the prevalence of HTN among rural residents was more than urban, where prevalence of HTN in urban constitutes 7.5% and in rural 7.8%. [14]

Several studies have demonstrated that inflammatory markers behave not only as markers but also as mediators of hypertension and its consequences. [15] and development of CV events. [16]

Crp is the well-established inflammatory marker for CVD. It is produced in the liver through induction process by the pro-inflammatory cytokine interleukin (IL)-1 and others. Hscrp shows strongest association with hypertension. Several clinical trials demonstrated increase plasma levels of CRP in hypertensive patients. [17] Studies suggest an association between CRP and cardiovascular disease and complications [18]. It functions biologically in different areas of inflammation and host responses, including the complement pathway, apoptosis, phagocytosis, NO release, and cytokine production. [19]

A growing evidence proposes association between blood cells measured in cell blood count (CBC) differentiation such as platelets, white blood cells, neutrophils and lymphocytes and hypertension. [20] Even though, well-known risk factors for CVD are in use, additional biomarkers are necessary for the unresolved cardiac cases. Increasing research points to inflammatory markers since inflammation is linked to the development of cad including HTN. Inflammatory cells such as lymphocytes, eosinophils, and neutrophils have been implicated in CVD [21]. Neutrophils secret inflammatory mediators causing vascular wall damage implicated in progress of HTN. On the contrary, lymphocyte regulate the inflammatory response and thus play a role against atherosclerosis [22]. Consequently, the neutrophil to lymphocyte ratio (NLR) has been suggested as an inflammatory biomarker, a risk predictor for CVD and an effective predictor of hypertension [23]. Nevertheless, the impact of NLR on CVD still require further investigations for certainty.

Recent studies showed the importance of leukocyte count for the productivity of NLR for CVD development [24]. In the last decade, NLR has been emerged as a direct and reliable indicator of the inflammatory status, used to predict prognosis and survival in patients with coronary artery disease and been recognized as an effective predictor of hypertension [23]. Neutrophils can lead to the release of reactive oxygen species, which contribute to oxidative stress [25]. That is linked to complications of CVD. An isolated rise in neutrophil count accompanied with high NLR has been reported in several conditions, including acute stroke [26], myocardial infarction [27] and atherosclerosis [28]. Moreover, elevated WBC count, especially neutrophil count, was significantly associated with an increased risk of developing hypertension among Japanese men and women, that provides evidence for the role of inflammation in the development of hypertension. [29]

There are different pharmacological approaches to the management of HTN including diuretics, beta-blockers, calcium channel blockers, and renin–angiotensin inhibitors. Each of the classes of medications have their own indication [30]. Angiotensin-converting enzyme inhibitors (ACEIs) and Angiotensin receptor blocker (ARBs) are especially important because they can affect immune system induced by angiotensin II indirectly. [31] The study aimed to investigate the impact of antihypertensive drugs on inflammatory markers, hs CRP and NLR.

Methodology

Study design and setting

This comparative institution based cross-sectional study was carried out at the cardiology outpatient clinic in Al-Gamhuoria Modern General Hospital, Aden, in the period from October to December 2023.

Inclusion criteria

Known hypertensive patient treated with antihypertensive drug for more than six months, aged 30 years and above of both sexes and accepted to participate in the study was enrolled.

Exclusion criteria

Patients with comorbid such as cardiovascular diseases, liver and kidney disease or any inflammatory disorders, immune disorders, acute or chronic infection, malignancy who using anti-inflammatory drugs including NSAIDs and corticosteroids or taking antibiotics, pregnancy and lactating mothers and those who refuse to participate were excluded.

Sampling

Convenient sampling method was applied to enroll patients attending clinics according to eligibility.

Sample size

The cardiology clinic at Al-Gamhouria General Modern Hospital receives 1200 patients from different districts in Aden Governorate who complain of various CV conditions during 2022, out of them almost 30 hypertensive patients without cardiovascular diseases and 70 with CVD monthly. There were 90 hypertensive patients, represent the study population, during the study period (3 months). Based on these data, the sample size of 72 was calculated by Steven K Thompson equation (Thompson, 2012) [32]. Adding 20% for dropping out, the final sample size will be 86 patients.

$$n = \frac{N \times p(1-p)}{\left[\left[N-1 \times \left(d^2 \div z^2\right)\right] + p(1-p)\right]}$$

N: population study=90
Z: score corresponding to the level indication (0.95) and equal (1.96)
d: Standard Error equal (0.05)
P: Property availability and neutral and equal (0.34) derived from previous study [15]
= 90x0.34(1-0.34)/89x0.0006507705+0.2244
= 20.196/0.282318575= 71.536= 72
Sample size will be 72+20%=86 patients.

Data collection

The data was collected after obtaining verbal informed consent from each participant during the clinic visit from 8:30 to11:30 a.m. in Al-Gamhuoria Modern General Hospital. The researcher interviewed the patient using a structured questionnaire including demographic (sex, age, family history of hypertension, duration of hypertension), habits (chewing khat, cigarette smoking), medical (diabetes, drugs used). The blood sample was drawn from a peripheral vein by making a venipuncture using a sterile 10 ml needle, pull 5ml of blood after placed rubber band called tourniquet on upper arm of each participant, and immediately transfer into two plain tubes.

Participants were divided into three groups: patients treated with mono-therapy from inhibitors of renin angiotensin aldosterone system (RAASI), patients treated with mono-therapy antihypertensive not acting on RAAS (Non-RAASI) and patients treated with combination of them (drug combination).

Investigation

The drawn blood was divided into two parts. 2ml of collected blood was put in a tube containing K3EDTA for analyzing by CBC hematology analyzer Sysmex Japan, instrument as mentioned by [33]. The rest 3ml of collected blood was kept in Gel tube (Gel & clot activator) for 1hour, then centrifuged at 3000 rpm for 10 min to separate serum in (thermo centrifuge). 2 ml of serum will measure on Cobas c311using alatex particle-enhanced immunoturbidimetric assay following the manufacturer's instructions Roche Hitachi. Germany) for analysis. [34]

Blood pressure was measured by mercury sphygmomanometer using appropriate cuff size on right arm after the participant has been seated for at least 5 minutes in the seated position. The average of the last two reading was taken.

Definition of variables

Blood pressure

BP was classified according to (**ACC/AHA 2017**) [1]. Guidelines for the management of arterial hypertension as target controlled (<130/80 mmHg) and uncontrolled (≥130/80 mm Hg) blood pressure.

High sensitive C-reactive protein (hsCRP)

hsCRP was classified generally as low risk (<1.0mg/L), moderate risk (1.0-3.0mg/L) and high risk (> 3.0 mg/ L) [35]. For the purpose of the study, we used also Wan et al. classification of hsCRP as low risk (≤ 3mg/L) and high risk (>3mg/L) for CVD [36].

Body mass index

BMI was classified as underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obese (≥ 30 kg/m^2). [37]

Neutrophil to lymphocyte ratio (NLR)

NLR was calculated by dividing the total neutrophil count on the total lymphocyte count. [38]

Statistical analysis

Data were checked then entered the Statistical Package for Social Sciences (SPSS) software version 25 (IBM Corp, Armonk, NY, USA). Descriptive statistics was calculated by using mean and standard deviation for quantitative variables such as age, BP levels, BMI, while frequencies and percentages were used for qualitative variables, including demographics, hsCRP categories, and groups of BP, BMI. Association between two categorical variables and nominal data was made using the Chi-square. ANOVA test was used to compare between means of three groups for normal distribution quantitative data. Kruskal-Wallis was performed for non-parametric data. *P* value less than 0.05 was considered statistically significant.

Ethical consideration

Ethical approval was granted by the Research Ethics Committee of the Faculty of Medicine and Health Sciences, University of Aden (REC-160 -2023). The study was conducted after obtaining verbal informed consent from each participant. Each study participant was given adequate information about the objectives of the study, the content of the questionnaire, as well as the confidentiality of the information.

Results

In the present study, the total number of hypertensive patients recruited was 86, with equal distribution for males and females (43freuency for each which made 50% for males and females) patients. Table 1 shows the distribution of hypertensive patients according to antihypertensive drug classes utilized by the patients and target BP. Thirty-two (37.2%) patients were treated with RAAS inhibitors, 22 (25.6%) with non-NRAAS inhibitors and 32 (37.2%) patients with drug combination. According to ACC/AHA 2017, the target Bp (<130/80 mmHg) was obtained by 46.9% 45.5% and 50% of patients treated with RAASIs, NRAASIs and drug combination respectively.

Table1. Distribution of hypertensive patients by drug classes utilized and BP target

	RAAS Inhibitors n=32 (37.2%) No %	NRAAS Inhibitors n=22 (25.6%) No %	Drug combination n=32 (37.2%) No %
Controlled BP	15 46.9	10 45.5	16 50
Uncontrolled BP	17 53.1	12 54.5	16 50

RAAS: renin angiotensin aldosterone Inhibitor, NRAAS, non-renin angiotensin aldosterone inhibitor.

According to table 2, 56.3% of RAASIs group were males, while 59.1% of NRAASIs group were females. Moreover, the results point to a large proportion of the patients within each group lies in the age group 35-55 years. In addition, the median values for duration of hypertension were 36, 48, and 54 months for RAASIs, NRAASIs and drug combination group, respectively. Almost half of patients in each group had no family history of hypertension.

Table 2. Distribution of hypertensive patients by sex, age, family history, and duration of hypertension

Parameter	RAAS Is n=32 No (%)	RAAS Is n=22 No (%)	Drug combinatio n n=32 No (%)
Sex			
Male	18 (56.3)	9 (40.9)	16 (50)
Female	14 (43.8)	13 (59.1)	16 (50)
Age group			
<35 years	3 (9.4)	2 (9.1)	4 (12.5)
35-55 years	16 (50.0)	16 (72.7)	17 (53.1)
≥56	13 (40.6)	4 (18.2)	11 (34.4)
Age mean ± SD yrs.	**57.6±8.72**	**55.6±5.70**	**56.7±8.79**
FH of HTN			
Yes	16 (50.0)	9 (40.9)	15 (46.9)
No	16 (50.0)	13(59.1)	17 (53.1)
Duration of HTN in months			
Median IQR	**36 (36)**	**48 (84)**	**54 (33)**

Note: %related to the column of the study patients; FH of HTN: Family history of hypertension

Regarding drugs utilized by the participants, Table 3 illustrates antihypertensive drugs and others for combined conditions. Patients in RAASIs and NRAASIs used only one drug, while those in drug combination utilized two drugs one of them belongs to inhibitors of RAAS. Frequent comorbid drugs are oral hypoglycemic and statins.

Table 3. Drugs utilized by hypertensive patients among groups

RAASIs	NRAASIs	Drug combination
Antihypertensive drugs		
Lisinopril 5,10mg Losartan 50,100 mg Candisartan 8mg Enalapril 5,10mg	Amlodipine 5-10 Bisoprolol 2.5 5mg	Losartan 50mg Lisinopril 5,10mg Enalapril 5,10mg Hydrochlorothiazide12.5 Bisoprolol 2.5,5mg Amlodipine 5,10mg
Others		
Aspirin 75mg Statin 10,20mg Metformin 500mg Glibenclamide 5mg Glimpril 2,3mgmg Sitagliptin 50mg	Metformin 500mg Aspirin 75mg Statin10,20mg Sitagliptin 50mg	Aspirin75mg Metformin 500mg Statin 10,20mg Glimpril 2,3mg Sitagliptin 50mg Glinbenclamide 5mg

RAASi: renin angiotensin aldosterone inhibitor, NRAASi: non renin angiotensin aldosterone inhibitor.

There was a statistically significant difference between SBP and DBP in patients with controlled BP and those with uncontrolled SBP levels and treated by different drug regimens (P=0.000 for each blood level). The highest levels for uncontrolled SBP (149.4±13.28 mmHg) were for patients in drug combination group,

while the lowest levels of uncontrolled SBP (140.5±4.97 mmHg) were for those patients treated with NRAASIs, Table 4.

Table 4. SBP and DBP of hypertensive patients treated with RAASIs, NRAASIs and combination group with controlled and uncontrolled BP

Parameter	RAAS Inhibitors	NRAAS Inhibitors	Drug Combination	*P*
Controlled SBP (mmHg)	123.6±5.57	122.7±4.45	123.9±6.38	.000*
Controlled DBP (mmHg)	79.0±2.71	78.0±3.88	76.7±4.84	.000*
Uncontrolled SBP (mmHg)	147.2±9.09	140.5±4.97	149.4±13.28	.000*
Uncontrolled DBP (mmHg)	86.0±11.14	80.5±5.98	88.4±11.93	.000*

SBP: Systolic blood pressure; DBP: Diastolic blood pressure *ANOVA test.

The median values of hs-CRP of the three groups showed non-significant difference (*P*=0.104), with the lowest value observed in patients treated with drug combination, and the highest for NRAASIs group, Table 5. On the other hand, there were significant differences between values of hs-CRP of patients with controlled *(P*=0.000) or uncontrolled *(P*=0.046) BP and treated with different modalities, Table 4. In addition, the results showed that the median values of hs-CRP of patients having good controlled BP lied within the category for hs-CRP (≤3 mg/l) with the lowest value for patients utilized drug combination. While patients with uncontrolled BP showed hs-CRP levels (> 3 mg/l) and the highest value for patients with utilized drug combination. Moreover, patients with UCBP and treated with RAASIs revealed the lowest value of hs-CRP (4 mg/l) than the other groups, Table 5.

We found relatively high neutrophil count and relative low lymphocyte count among groups with the highest neutrophil and lowest lymphocyte in drug combination group. The difference between groups were significant (P < 0.05). The median differences in NLR between the groups were statistically significant; including groups of all patients *P*=.032, of patients having controlled BP *P*=0.014 as well as uncontrolled BP *P*=0.038, Table 5.

Comparing the uncontrolled of BP of the three groups we found the highest prevalence (9.3%) of patients with uncontrolled BP and had the lower level hsCRP (≤3mg /l) was in RAASIs group, while those higher prevalence (11.6%) also with uncontrolled BP and higher level of hs-CRP (>3mg/l) was in drug combination group, Table 6.

Table 6. Relationship of hs-CRP levels among patients treated with RAASIs, NRAAS inhibitors and drug combination. (n=86)

	hs-CRP ≤3 mg/l Low risk No (%)	hs-CRP > 3 mg/l High risk No (%)	X2 P-value
RAAS Inhibitors n=32			
Uncontrolled (17)	8 (9.3)	9 (10.5)	0.723
Controlled (15)	8 (9.3)	7 (8.1)	
NRAAS Inhibitors n=22			
Uncontrolled (10)	3 (3.5)	7 (8.1)	0.184
Controlled (12)	7 (8.1)	5 (5.8)	
Drug combination n=32			
Uncontrolled (16)	6 (7.0)	10 (11.6)	0.001
Controlled (16)	15 (17.4)	1 (1.2)	

Chi-square test

Table 5. Inflammatory markers in hypertensive, controlled and uncontrolled patients treated with RAAS, NRAAS inhibitors and drug combination

	RAAS inhibitors n=32	NRAAS inhibitors n=22	Drug combination n=32	*P*
hs-CRP mg/l med+ IQR	3.1(4)	3.8(6.9)	2.0(3.4)	.104+
Neutrophil % mean±SD	46.1±11.63	40.8±6.81	47.7±10.94	.054*
Lymphocyte % mean±SD	42.1±11.37	46.2±6.49	40.1±10.04	.085*
NLR med +IQR	1.1(.92)	0.9(.34)	1.2(.72)	**.032+**
Controlled BP				
hs-CRP mg/l med+ IQR	3 (4.5)	2.5(6.7)	1(1.3)	**0.000+**
Neutrophil % mean±SD	42.6±12.25	38.1±7.48	45.9±7.10	**0.022***
Lymphocyte % mean±SD	46.6±12.39	48.0±6.38	41.4±6.46	**0.023***
NLR med +IQR	0.9(.63)	0.8(.37)	1.1(.54)	**0.014+**
Uncontrolled BP				
hs-CRP mg/l med+ IQR	4(3.4)	4(7.7)	4.3(4.5)	**0.046+**
Neutrophil % mean±SD	49.1±10.48	44.0±4.39	49.5±13.78	**0.050***
Lymphocyte % mean±SD	38.2±9.02	44.2±6.32	38.9±12.78	**0.038***
NLR med +IQR	1.3(.89)	0.9(.29)	1.3(1.37)	**0.038+**

*ANOVA test, +Kruskalwallis test, median+interquartile for non-normal distribution, mean ±SD for normal distribution data.

Discussion

The present study examined the impact of long use of antihypertensive drugs on the inflammatory markers hsCRP and NLR among hypertensive patients who were treated by taking drugs for more than six months with different treatment modalities according to the guideline by ACC/AHA [1]. The study recruited 86 known hypertensive patients attending cardiac outpatients' clinic at Al-Gamhouria Modern General hospital. The study sample was divided into three groups, those using inhibitors of RAAS, NRASS and drug combination for the purpose of comparison. The study revealed that almost equivalent percentages of participants in each group obtained the optimal BP target (controlled) according to the guideline by ACC/AHA with serum levels of hsCRP less than that reached in uncontrolled participants of the same groups. This result agrees with studies reported association between CRP and risk of development hypertension [16], found association between increase tertiles of WBC count with increased risk ratios of HTN in the full cohort, and among women and men. [39]

The study involved 86 participants with accidental equal proportion (43, 50%) of males and females. This result is in line with Alhamami et al, study from Iraq where had 51 men, 50women [40] The mean age of all participants was 56.8±8.04years which is consistence with the mean age (58.2±16.7) reported by Chotruangnapa et al. [41]. Patients did not have comorbid except 23.3% had DM and 26.7% dyslipidemia. Chotruangnapa et al study from Thailand supports our result in which 23.3% were DM, but dyslipidemia was high (58.7%) [41]. Seventy five percent of the patients were in age group 35-55years. This result disagrees with Enawgaw etal study where 48.9% of the participants were in age group 35-55 years. In addition, duration of disease in the same study was 3.47±2.8 years which is in line with the found median duration of HTN was 48 (33-60) months[42].

The mean age of the patients in groups was almost equivalent as well as most of the patients in each group laid in age group of 35-55 years. In addition, almost half of the participants in each group did not have family history of hypertension and had a duration of hypertension range between 30and 54 months (less than five years). Therefore, all mentioned findings altogether point to limited differences between the groups and may strengthen the outcomes.

Mao et al in their study proved that the number of subjects who received cardiovascular benefits directly from antihypertensive drugs was not significantly large. In addition, they demonstrated that a SBP range of 130-140 mmHg may increase the risk CVD [43]. Our study showed statistically significant differences in mean SBP and DBP of poorly controlled patients between treatment groups. The mean values of SBP were above 140 mm Hg, which may indicate lower benefits of hypertension treatment and increase possible future risk of CVD. This is in line with what mentioned by Mao et al. But in contrary to Mao et al, the study identified also a significant proportion of patients reached a goal SBP less than 130 mm Hg suggesting a possible benefit of antihypertensives in lowering CVD that was accompanied with reduction in hsCRP levels. This finding agrees with Awad et al., Marinier et al, and Mahmood and Abdu Al-Kader, who mentioned antihypertensive lisinopril reduce hsCRP. [44,45,46]

The drugs utilized by the patients were lisinopril, enalapril, losartan and candisartan in RAAS group as single drug for each patient, out of them lisinopril, enalapril and losartan were found to be the main components of drug combination to bisoprolol or amlodipine. Palmas studied the association between antihypertensive drug classes and CRP levels among participants with treated hypertension by calcium channel blockers, beta-blockers, diuretics, and ACE inhibitors, or ARBs. They found that serum CRP levels were lower among participants taking beta-blocker than among those not taking beta-blocker (2.13 *v* 2.54 mg/L, $P < 0.002$). In line with Palmas result, beta-blockers (Bisoprolol in drug combination) might be implicated in the lowest serum CRP level of controlled patients treated with drug combination compared to other groups in the present study. Moreover, a meta-analysis supported evidence for the effectiveness of ACEIs and ARBs on CRP in which ACEIs had a beneficial lowering effect on CRP [47] while ARBs showed effectiveness as a class only regarding reduction of CRP [44] In addition, Marinier et al. support our result in which two drug therapy was significantly associated with increased BP control [45] Given that the present of beta-blocker in addition to RAASI in drug combination group could be involved as the reason for the lowest level of CRP levels of controlled BP among the groups. Also, combination drugs has been reported more effective than mono-therapy as mentioned in Savoia and Schiffrin review; Life style modification and pharmacological healing involvement to control BP proposed to decrease vascular inflammation in hypertensive patients, and achveiment of CVD reduction better outcomes in RCTs. (48)

Comparing the uncontrolled patients of the three groups, the study found a higher prevalence of uncontrolled patients treated with RAASIs showing a lower level hsCRP (≤3mg /l), in spite, SBP was above 140 mm Hg. This surprising finding may suggest the lower probability of occurrences of cardiovascular complications in these patients with poorly controlled BP. The study concluded that RAASIs might have beneficial effect on delaying CV complications even with higher SBP, which can be investigated further in large samples.

On other hand, the prevalence of uncontrolled patients treated with drug combination was higher (11.6%) within the category of hs-CRP >3mg/l. This finding suggests that uncontrolled patients utilizing drug combination and had higher levels of hsCRP might be prone to future CV complications. This agrees with Suliman et al study who reported β-blockers and combination therapy showed positive CRP value more than patients treated with ACEI group [49]; also Palmas study stated that patients taking diuretics had higher unadjusted CRP levels than those not taking diuretics [47], Ridker *et al* study showed that valsartan reduce hsCRP more than combined (valsartan +Hydrochlorothiazide) irrespective to blood pressure reduction in stage 2 HTN. [50]

Alhamami et al from Iraq found a positive CRP test in a significant patients with high BP and longer duration of hypertension where they attributed this to the state of atherosclerosis and the associated inflammatory process as CRP is an inflammatory marker.[40]. The present study found the levels hs-CRP of BP well controlled patients were less than those levels of uncontrolled BP and lied within the hs-CRP category (≤3 mg/l) with the lowest value [1(1.3)] for patients used drug combination. The reduction in CRP levels among controlled patients is supported by a study done in Aden diabetic center that the use of enalepril for 6 weeks in newly diagnosed diabetic hypertensive patients with higher crp levels reduced significantly this marker [46]

Horne et al, investigated predictive ability of WBC including neutrophil and lymphocyte for risk of death from CVD or myocardial infarction (MI). They proved that high neutrophil count or low lymphocyte count are powerful predictors for CVD, and elevated N/L ratio is the most powerful predictor [51].Likewise,Tian N.,et al study in African American observed an important correlation between regulation of BP, development of hypertension, and highest neutrophil and lowest lymphocyte [52] Given our results of RAASIs group, the high neutrophil and low lymphocyte count of patients with uncontrolled BP agree with that reported by Horne et al. Moreover, the higher NLR (1.3) compared to NLR (0.9) of those patients with target goal BP in the same group may propose them to risk of CVD. On contrary, patients in this group having controlled BP showed low neutrophil and high lymphocyte with lower NLR. This supports the fact that RAASIs ameliorate inflammation, including inflammatory markers and retard progression of hypertension related complications [18]

Extraordinarily, we found that neutrophil count was high among patients having controlled BP or uncontrolled BP treated with drug combination as well as lymphocyte count was low in both arms. The raise neutrophil count and decline in lymphocyte count among patients with controlled BP may reflect the continuing inflammation irrespective to controlled BP. On the other hand, patients with poor BP control and a raise in neutrophil count might subject to risk of CVD.

In case of patients used mono-therapy in NRAASIs group, they showed a lower neutrophil count in controlled or uncontrolled BP subjects and the lowest NLR between groups which may be supported by Toba H *et al*. who reported amlodipine prevented communication of inflammatory mediators. [53]

Limitation

This study had several limitations. First, the study design was cross-sectional, which limits the ability to establish causality and determine temporal relationships. Second, the study was conducted at a single center, which may affect the generalizability of the findings. Third, due to financial difficulties and higher expense of the tests, glucose concentration, and lipid profile could not be measured. Finally, the study sample size was relatively small reflecting the proportion of patients with hypertension without CVD attending the cardiac outpatients clinic. Despite these limitations, the study may be pioneered on inflammation and inflammatory markers among hypertensive patients in Yemen.

In conclusion, hypertensive patients treated with RAASI, NRAASI and drug combination and reached BP target showed significant reduction in hsCRP and NLR. Patients with uncontrolled BP treated with RAASIs revealed slightly lower hs-CRP than other groups. Careful selection of antihypertensive drugs may affect risks of CVD. This study recommends further prospective studies exploring the anti-inflammatory effect of antihypertensive drugs to ameliorate possible risks of cardiovascular disease.

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مقالة بحثية

تأثير الأدوية الخافضة للضغط على علامات الالتهاب والبروتين التفاعلي C عالي الحساسية (hsCRP) ونسبة الخلايا الليمفاوية العدلة (NLR)

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المُلخّص

أظهرت العديد من الدراسات العلاقة بين الالتهاب وارتفاع ضغط الدم. وقد تسلط الضوء علامات الالتهاب على حالة الالتهاب عند مرضى ارتفاع ضغط الدم. تهدف هذه الدراسة إلى التحقق من تأثير الأدوية الخافضة للضغط على علامات الالتهاب والبروتين التفاعلي C عالي الحساسية (hsCRP) ونسبة الخلايا الليمفاوية العدلة. أجريت دراسة مقطعية مقارنة على 86 مريضا يعانون من ارتفاع ضغط الدم ويترددون على العيادة الخارجية لأمراض القلب في مستشفى الجمهورية العام الحديث، عدن، في الفترة من أكتوبر إلى ديسمبر 2023. تم تقسيم المشاركين إلى ثلاث مجموعات: المرضى الذين عولجوا بالعلاج الأحادي من مثبطات نظام ألدوستيرون أنجيوتنسين الرينين (RAASI)، والمرضى الذين عولجوا بخافضات ضغط الدم أحادية العلاج التي لا تعمل على نظام الرينين (NRAASI) والمرضى الذين تم علاجهم بمزيج منهم (مجموعة التركيبة الدوائية). تم جمع بيانات عن العمر والجنس ومستوى ضغط الدم ومؤشر كتلة الجسم ومدة ارتفاع ضغط الدم (HTN) والتاريخ العائلي للضغط والأدوية المستخدمة. تم سحب عينات الدم لقياس HsCRP، العدلات، الخلايا الليمفاوية. تم استخدام الإحصاء الوصفي واختبارات مربع كاي لتحليل البيانات. توزيع متساو تقريبا للذكور والإناث بين المجموعات، مع نسبة كبيرة من المرضى داخل كل مجموعة وضعت في الفئة العمرية 35-55 سنة. كانت القيم المتوسطة لمدة ارتفاع ضغط الدم 36 و 48 و 54 شهرا ل RAASIs و NRAASIs ومجموعة تركيبة الأدوية، على التوالي. تم الحصول على ضغط الدم المستهدف المنضبط بنسبة 46.9% 45.5% و 50% من المرضى الذين عولجوا ب RAASIs و NRAASIs ومزيج الأدوية على التوالي. كان هناك فرق ذو دلالة إحصائية بين SBP و DBP في المرضى الذين يعانون من ضغط الدم الخاضع للرقابة وكذلك أولئك الذين لديهم مستويات SBP غير المنضبطة وعولجوا بأنظمة دوائية مختلفة (P = 0.000 لكل مستوى BP). كانت هناك فروق ذات دلالة إحصائية بين قيم hs-CRP للمرضى الذين يعانون من ضغط الدم الخاضع للرقابة (P = 0.000) أو غير المنضبط (P = 0.046) والذين عولجوا بأنظمة مختلفة. كان متوسط الاختلافات في NLR بين المجموعات ذات دلالة إحصائية. بما في ذلك مجموعات من جميع المرضى .032 = P، من المرضى الذين لديهم ضغط منضبط 0.014 = P وكذلك الضغط الغير منضبط 0.038 = P. بمقارنة ضغط الدم غير المنضبط للمجموعات الثلاث، وجدنا أن أعلى معدل انتشار (9.3%) للمرضى الذين يعانون من ضغط الدم غير المنضبط وكان لديهم مستوى أقل من hsCRP (≤3mg / l) كان في مجموعة RAASIs، في حين أن أولئك الذين لديهم معدل انتشار أعلى (11.6%) لضغط الدم غير المنضبط ومستوى أعلى من hs-CRP (>3mg / l) كان في مجموعة تركيبة الأدوية. في الختام، أظهروا مرضى ارتفاع ضغط الدم الذين عولجوا ب RAASI و NRAASI ومزيج الأدوية ووصلوا إلى ضغط دم منضبط انخفاضا كبيرا في hsCRP و NLR .كشف المرضى الذين يعانون من ضغط الدم غير المنضبط الذين عولجوا ب RAASIs عن انخفاض طفيف في-hs CRPمقارنة بالمجموعات الأخرى. قد يؤثر الاختيار الدقيق للأدوية الخافضة للضغط على مخاطر الإصابة بالأمراض القلبية الوعائية. توصي هذه الدراسة بإجراء المزيد من الدراسات المستقبلية لاستكشاف التأثير المضاد للالتهابات للأدوية الخافضة للضغط لتخفيف المخاطر المحتملة لأمراض القلب والأوعية الدموية.

الكلمات المفتاحية: ارتفاع ضغط الدم، البروتين التفاعلي C، التهاب، ضغط الدم، العدلات.

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