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Frequent Change of Intra-group Drug Effect on the Blood Pressure Control and Adaptation of Therapy in Hypertensive Patients

Hipertansif Hastalarda Grup İçi Sık İlaç Değişiminin Kan Basıncı Kontrolüne ve Tedavi Uyumuna Etkisi

Müslüm Şahin[1], Serdar Demir[1], Süleyman Aktürk[2], Ali Fedakar[3], Gökhan Alıcı[1], Birol Özkan[1], Mehmet Vefik Yazıcıoğlu[1], Cantürk Çakalağaoğlu[3], Mustafa Yıldız[1], Ali Metin Esen[1], Mehmet Muhsin Türkmen[1]

[1] Department of Cardiology, Kosuyolu Heart Center, Kartal, Istanbul, Turkey
[1] *Kartal Koşuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, İstanbul, Türkiye*

[2] Department of Cardiology, Private Gebze Yuzyil Hospital, Kocaeli, Turkey
[2] *Özel Gebze Yüzyıl Hastanesi, Kardiyoloji Kliniği, Kocaeli, Türkiye*

[3] Department of Cardiovascular Surgery, Kosuyolu Heart Center, Kartal, Istanbul, Turkey
[3] *Kartal Koşuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Kalp Damar Cerrahisi Kliniği, İstanbul, Türkiye*

ABSTRACT

Introduction: *In this study, we investigated the effects of frequent and unnecessary change in medication to control of blood pressure. Also we investigated the role of the regular use of drugs in the treatment of hypertension.*

Patients and Methods: *Nine hundred hypertensive patients (509 males and 391 females; mean age 62.4 ± 12.1 years) were evaluated retrospectively. Only the patients taking anti-hypertensives for at least six months were included. Patients' records were examined in terms of anti-hypertensive treatment. Intra-group exchange and use of regularly in anti-hypertensive drugs were investigated. Effects of the change in blood pressure and patient compliance were investigated.*

Results: *When intra-group drug change was examined, rates of drug changes were as follows; angiotensin receptor blocker group, 62.3%; angiotensin converting enzyme group, 55.1%; beta-blockers group, 39.9%; calcium channel blocker group, 20.9%. While the ratio of non-compliance was 28.7% in the patient group with drug change, it was only 9.3% in the group without change in treatment. Average blood pressure difference was found 6.1 ± 7.6 mmHg and 7.6 ± 7.5 mmHg respectively ($p < 0.001$). The average number of drug usage with and without change of anti-hypertensive drug were 2.5 ± 0.87 and 2.2 ± 0.89 ($p < 0.001$) respectively.*

Conclusion: *In patients under angiotensin converting enzyme inhibitors and angiotensin receptor blocker treatments, intra-group change of medication is common. Frequent intra-group change of anti-hypertensive drugs has negative effects on blood pressure control.*

Key Words: *Hypertension; drug switching; patient compliance.*

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Yazışma Adresi/ Correspondence

Dr. Müslüm Şahin

Kartal Koşuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, Cevizli Kavşağı No: 2 34846 Cevizli, İstanbul-Türkiye

e-posta
sahinm78@yahoo.com

ÖZET

Giriş: *Bu çalışmada sık ve gereksiz ilaç değişiminin kan basıncı kontrolü üzerindeki etkisini araştırdık. Ayrıca, hipertansiyon tedavisinde düzenli ilaç kullanımının rolü çalışıldı.*

Hastalar ve Yöntem: *Dokuz yüz hipertansif hasta (509 erkek ve 391 kadın; yaş ortalaması 62.4 ± 12.1 yıl) geriye dönük olarak değerlendirildi. En az altı aydır antihipertansif ilaç alan hastalar çalışmaya dahil edildi. Hasta kayıtları antihipertansif tedavi yönünden incelendi. Grup içi değişim ve antihipertansif ilaçların düzenli kullanımı araştırıldı. Değişimin kan basıncı ve hasta uyumuna etkisi araştırıldı.*

Bulgular: *Grup içi ilaç değişim oranları; anjiyotensin reseptör bloker grubunda,%62.3; anjiyotensin dönüştürücü enzim grubunda,%55.1; beta-bloker grubunda,%39.9; kalsiyum kanal bloker grubunda,%20.9 olarak bulundu. Düzensiz ilaç kullanım oranı ilaç değişikliği olan hasta grubunda %28.7 iken, ilaç değişikliği olmayan hasta grubunda sadece %9.3 idi. Ortalama kan basıncı farkı sırasıyla 6.1 ± 7.6 mmHg ve 7.6 ± 7.5 mmHg idi (p < 0.001). Antihipertansif ilaç değişimi olan ve olmayan gruplarda kullanılan ortalama ilaç sayısı sırası ile 2.5 ± 0.87 ve 2.2 ± 0.89 idi (p < 0.001).*

Sonuç: *Anjiyotensin dönüştürücü enzim inhibitörleri ve anjiyotensin reseptör bloker tedavisi altındaki hastalarda grup içi ilaç değişimi yaygındır. Antihipertansif ilaçların grup içi sık değişimi kan basıncı kontrolünü olumsuz etkiler.*

Anahtar Kelimeler: *Hipertansiyon, sık ilaç değişimi, hasta uyumu.*

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INTRODUCTION

Hypertension is the most important preventable cause of mortality in the world. Overall 26.4% (95% CI 26.0-26.8%) of the adult population in 2000 had hypertension and that was expected to increase to 29.2% by 2025[1]. A previous study revealed that the prevalence of hypertension was 33.7% in Turkey[2]. Hypertension is a costly disease because it often requires multi-drug therapy, long-term treatment, and some antihypertensive drugs are expensive[3]. If all the objectives in clinical guidelines on the treatment of hypertensive patients are achieved, 46.000 deaths per year can be prevented. However, a lot of studies showed that blood pressure control rates remained poor in the majority of patients with hypertension. The low blood pressure control rate is usually due to inadequate effective treatment, frequent change of medication and lack of patient compliance. In this study, we investigated the effects of frequent and unnecessary intra-group drug change on patients' compliance and blood pressure control in hypertensive patients.

PATIENTS and METHODS

The study protocol was approved by the local ethics committee. Patients were identified retrospectively from hospital records. 900 consecutive hypertensive patients who applied to Kartal Kosuyolu Education and Research Hospital Cardiology Outpatient Clinic between January 2010 and March 2011 were included. The data were obtained from outpatient clinic records, the pharmacy system records and patients during the outpatient clinic application. Patients were previously diagnosed with hypertension and had been using anti-hypertensive drugs for at least six months. Patients without high blood pressure history but using blood pressure lowering drugs for the treatment of cardiovascular diseases were not evaluated as hypertensive and not included in the study. Patients who have coronary artery disease, congestive heart failure, chronic renal failure, and patients whose prescriptions were changed by other health institutions were excluded from the study. Information of medication changes were obtained from records of the pharmacy system. Drug change was defined as a change in an anti-hypertensive drug with another drug from the same group with a different active component for at least one time. Changes of drug during the period of the study were noted.

Anti-hypertensive drugs was classified as angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), beta-blockers (BB), calcium channel blockers (CCB), diuretics and others. A change in medication between different groups or the addition of new drugs in the absence of adequate blood pressure control was not accepted as a change and these patients were excluded. Patients using combined anti-hypertensive drug were also excluded. Short term (days) or long term (months) discontinuation of drug was determined as irregular anti-hypertensive drug usage.

Causes for the change in medication were grouped as inadequate blood pressure control, side effects of medications, dislike the drug and I do not know, or physician

preference. Systolic and diastolic blood pressure values of the first and last of the examination were recorded from outpatient clinic records. Mean arterial blood pressure values were obtained by the formula diastolic blood pressure + pulse pressure/3 and the average differences in blood pressure (mean arterial blood pressure in the first examination -final examination) were calculated. Patients were grouped according to the change of medication. The patient groups which had a change in drug (n= 446) and without a change (n= 454) were compared in terms of the average blood pressure difference and the number of medications used.

Follow-up

Patients were followed up retrospectively for a minimum of six months and maximum of 21 months (mean 16 months).

Statistical Analysis

Data were analysed using SPSS software for Windows 13.0 (SPSS Inc, Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation, while categorical variables were expressed as percentage. A p value of < 0.05 was considered as statistically significant. During the evaluation of the data, Student's t-test was used for comparison of two groups for normally distributed parameters. Mann-Whitney U test was used for group-based comparisons of parameters without normal distribution. Chi-square test was used for comparison of qualitative data. We evaluated that the relationship between patient groups with and without change in blood pressure medication and the average difference blood pressure and number of drugs with the Mann-Whitney U test. Drug changes effect on the number of drugs and regular drug use was assessed by chi-square test. The effect of causes of drug change on the average difference of blood pressure were evaluated with Kruskal-Wallis H test.

RESULTS

509 (57%) males and 391 (43%) females were included in the study, and the mean age was 62.4 ± 12.1 years (Table 1). While 173 (19.2%) patients were using one anti-hypertensive drug, 320 (35.5%) patients two, 326 (37.3%) patients three and 77 (8.5%) patients were using four or more anti-hypertensive drugs. The average number of anti-hypertensive drugs used was 2.36 ± 0.89. Irregular drug usage rate was 19% in the study group.

When the intra-group drug changes were analyzed in a year; the number of mean change in a year was 1.65 ± 2.47. In ARB users, the switch to another ARB which had a different active ingredient was 62.3%. 74.2% of them changed once, 18.7% of them twice and 7.1% of them three or more times. The switch rate from an ACEi to another ACEi was 55.1%. 71.9% of them changed once, 21.6% percent twice, and 6.5% three or more times. The rate of intra-group drug change in BB and CCB was 39.4% and 20.9% respectively.

Table 1. Demographic characteristics of the patients (n= 900)

Male/female, %	57/43
Age, years	62.4 ± 12.1
Mean blood pressure in the first consultation, mmHg	111.9 ± 10.8
Mean blood pressure of the last consultation, mmHg	105 ± 9.5
Mean difference, mmHg	6.9 ± 7.6
The average number of anti-hypertensive drugs	2.36 ± 0.89
The average number of change	1.65 ± 2.47
Beta-Blocker usage, %	61.6
Diuretic usage, %	61.2
Angiotensin receptor blocker usage, %	52.2
Angiotensin converting enzyme inhibitor usage, %	30.6
Calcium channel blockers usage, %	27.8
ACEi + ARB usage, %	1.4
Other anti-hypertensive drugs, %	3
OAD usage, %	28.4
Insulin usage, %	9.7
OAD + insulin usage, %	6.8
Fibrate usage, %	4
Statin usage, %	27.2

Data are presented as mean ± standard deviation and percentages.
ACEi: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker, OAD: Oral anti-diabetic.

The most frequent reasons for medication changes were physician preference/I do not know (43%), and inadequate blood pressure control (33.8%) (Table 2). The mean blood pressure differences according to the causes of change were not significantly different between the groups (Table 3, p= 0353). Table 4 shows the relationship between the reasons of change and the number of drugs used. According to the number of drugs used, there is no statistical difference between the causes of change

Table 2. Distribution of reasons for medication changes

Reasons of change (n= 446)	%
Physician preference/I do not know (192)	43.0
Dislike of medication (60)	13.4
Side effects (43)	9.6
Inadequate blood pressure control (151)	33.8

Table 3. The relationship between the causes of change and average blood pressure difference

Reasons of change (n= 446)	Av. blood pressure difference (mmHg)	p
Physician preference/I do not know (192)	6.45 ± 7.47 mmHg	0.353
Dislike of medication (60)	5.08 ± 7.27 mmHg	
Side effects (43)	7.67 ± 7.74 mmHg	
Inadequate blood pressure control (151)	5.84 ± 8.02 mmHg	

Av: Average, ± : Standard deviation.

(p= 0.440). Irregular drug usage with drug change was 28.7% and without change was 9.3%. The mean blood pressures at initial presentation in patients with and without drug change were 113.2 ± 11.3 mmHg and 110.6 ± 10.9 mmHg respectively while the average blood pressure difference was found 6.1 ± 7.6 mmHg and 7.6 ± 7.5 mmHg respectively (p ≤ 0.001). The average number of drugs used with and without change of anti-hypertensive drugs were 2.5 ± 0.87 and 2.2 ± 0.89 (p < 0.001) respectively (Table 5). The number of anti-hypertensive drugs in the patient groups with regular and irregular usage of drugs was found as 2.2 ± 0.86 and 2.7 ± 0.9 respectively (p < 0.001).

DISCUSSION

In this study, we investigated the effect of intra-group drug change in medication in hypertensive patients. Intra-group changes were more common in ACEi and ARB medication group. Our results revealed that the blood pressure control rate was poor in patients with intra-group in medication. The number of drugs and irregular drug use was also higher in patients with drug change. In addition, the findings of our study showed that the change in medication was often due to the preference of the physician.

Serious complications of hypertension usually occur after many years. Arterial hypertension may lead to myocardial infarction, stroke, kidney failure, heart failure and death from by a variety of cardiovascular disease. The effective control of blood pressure reduces these risks[4,5]. However, a lot of studies showed that blood pressure control rates remained poor in the majority of patients with hypertension. Hypertension control rates ranged from 5.4 to 58% in 51 studies done in 31 countries[6]. Many factors play role in ensuring the effective control of blood pressure. Some of these factors are patient com-

Table 4. The relationship between the reasons of change and the number of drugs used

	The number of drugs (n, %)		
The reasons of change (n= 446)	1 drug	2 drugs	3 or more
Physician preference/I do not know (192)	30 (%15.6)	63 (%32.8)	99 (%51)
Dislike of medication (60)	10 (%16.7)	24 (%40.0)	26 (%43.6)
Side effects (43)	7 (%16.3)	13 (%30.2)	23 (%53.5)
Inadequate blood pressure control (151)	16 (%16.6)	45 (%29.8)	90 (%59.6)

According to the number of drugs used, there is no statistical difference between the causes of change (p> 0.05).

Table 5. Comparison of the groups

	Have a drug change	Not having a drug change	p
The average blood pressure difference	6.19 ± 7.68	7.68 ± 7.54	< 0.001
The number of drugs used	2.5 ± 0.87	2.21 ± 0.89	< 0.001
Regular drug usage	%71.3	%90.7	< 0.001
Irregular drug usage	%28.7	%9.3	

Data are presented as mean ± standard deviation and percentages.

pliance and regular drug use[7]. According to our study findings, frequent change of medication reduced the effective blood pressure control of patients. In the same way, frequent intra- group drug change affected patients' compliance.

The distribution of the most recently used drugs was ARB, 52.2%, ACEi 30.6%, BB 61.6%, diuretics 61.2%, calcium channel blockers 27.8%., and others 3% . Also combination therapy with ACE inhibitors and ARBs was used by 1.4% in our study. This combination is generally not preferred in hypertension. It may be preferred due to additional diseases such as diabetes mellitus. Because previous study showed that both agents improve insulin sensitivity by increasing NO generation, also may prevent diabetic nephropathy[8,9]. Seventh Report of the Joint National Committee (JNC 7) guide strongly emphasized that diuretics, used in combination, increased the activities of other anti-hypertensive drugs and helped achieve the target blood pressure[10]. In our study, the high rates of diuretic use (61.2%) showed that this proposal was has largely been taken into account in treatment. Medicines containing the same substance produced by different companies can be changed frequently. In our study, we compared patients with and without intra-group drug change.

The rate of decrease in mean arterial blood pressure was found to be less in patients with drug change that without drug change. Again, it was found that drug use was more irregular and the number of anti-hypertensive drugs was higher in the group with drug change. According to our results, frequent and unnecessary drug change increased irregular drug use and reduced the rate of effective blood pressure control.

Inadequate blood pressure control and drug-induced side effects constitute the most important reasons for changing medication[4]. In this study, the causes of change were ranked as the following; physician preference or I do not know (43%), inadequate blood pressure control (33.8%), dislike of medication (13.4%) and side effects (9.6%). In a study by Mohammadi et al. determined that most physicians prescribed medications without an explanation to patients[11]. In our study, physician preference / I do not know are expressed as the most common cause. Active participation of patients in the planning process of the treatment is known to increase the success of blood pressure control. However, according to our study findings, a significant portion of patients does not know the cause of change in medicine.

The relationship between the causes of change and average blood pressure difference and the average number of medications used was studied but there was no significant difference. However the change in medicine affected the average blood pressure difference and the number of drugs used. Physicians not only play a critical role in the success of treatment but also determine the cost of treatment. Fischer et al. in their study showed prescription of anti-hypertensive drugs in accordance with guidelines may save as much as 1.2 billion dollars across the country[12]. In our study, the change to another agent from the same group was 62.3% for ARB, 55.1% for ACEi, 39.9% for BB group and 20.9% for calcium channel blockers group within one year of study. It is known that ARB usage was significantly increased in the world and Turkey and it was reported to be even higher than ACEi[13,14]. The prices of ARB and ACEi were higher than BB and calcium channel blockers. Intra-group drug changes were seen higher with expensive drugs such as ACEi and ARB. In a previous study, free samples provided by company were shown to be partly responsible for these changes[15]. Similarly, other studies emphasized that physician's relationship with the company closely affects drug choice[16].

Limitations of the Study

Our study is a retrospective study and hence the some clinical information and records may be inaccurate. Another limitation is the single center study. Last limitation, a direct cost analysis was not done in our study. But the groups were compared according to number of drugs used. Because of the increasing number of drugs in creases the cost of treatment.

CONCLUSION

Intra-group drug change was seen higher in ACEi and ARB groups which usually have similar effectiveness and side effects. The usage of ARB, an expensive group, was found high. According to our study, frequent and unnecessary drug change caused less effective blood pressure control. It also increased the number of drugs used and interfered with the patient's compliance. We also assumed that the cost also became higher with the increased number of drugs.

CONFLICT of INTEREST

None declared.

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