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Evaluation ofAaspirin, Clopidogrel or Their Combination In Hypertensive Patients

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الخلاصة:

الغرض من هذه الدراسة هو تقييم تأثير الأسبرين, كلوبيدوكريل أو مركبهما على عوامل مختلفة لدى مرضى ارتفاع ضغط الدم.

التصاق, تنشيط وتكتل الصفيحات الدموية هي ركيزة في تكوين الخثرة الدموية الذي يلي تمزيق الخثرة الدهنية ويسبب المتلازمات التاجية الحادة.

أسبرين, كلوبيدوكريل يمارسان تأثيرهما ضد الصفيحات الدموية عن طريق منع أنتاج ثرومبكسان أ 2 وممرات تكتل الصفيحات الدموية المستحثة بالادينوسين داي فوسفيت, على التوالي.

هذه الدراسة صممت لتقييم التأثير المحتمل للأسبرين وكلوبيدوكريل أعطيت أما كل على حدة أو في مركب لدى مرضى ارتفاع ضغط الدم الأساسي على ضغط الدم و عوامل أخرى إضافة إلى تأثيرهم على شكل الدهون باستعمال دراسة سريريه عشوائية, مضاعفة, مستترة وانتقالية.

هذه الدراسة تتضمن 78 مرضى ارتفاع ضغط الدم استلموا أسبرين 100ملغم, كلوبيدوكريل 75ملغم أو مركبهما(75ملغم أسبرين و 75ملغم كلوبيدوكريل) قبل بدء البرنامج العشوائي.

ضغط الدم الانقباضي والانبساطي, معدل النبض, معدل التنفس وضغط تشبع الأوكسجين سجلت كل أسبوع بينما مستوى البروتين الدهني واطئ الكثافة,البروتين الدهني عالي الكثافة وإحصاء الصفيحات الدموية سجلت كل شهر.

انخفاض مؤثر في ضغط الدم الانقباضي والانبساطي قد سجل في كل مجاميع العلاج(الاحتمالية أقل من 0,05), لكن بالنسبة لمعدل النبض كان هناك انخفاض مؤثر في مجموعة الأسبرين ومجموعة المركب, لكن في مجموعة الكلوبيدوكريل كان هناك زيادة مؤثرة, كذلك لاحظنا نقصان مؤثر في معدل التنفس مع الأسبرين وكلوبيدوكريل, لكن هذا النقص كان غائب مع المركب, مستوى البروتين الدهني واطئ الكثافة أزداد بشكل مؤثر خلال العلاج مع الأسبرين أو كلوبيدوكريل بينما مركبهما لم يظهر تغييرات مؤثرة, البروتين الدهني عالي الكثافة أزداد بشكل مؤثر خلال العلاج مع الأسبرين أو المركب بينما كلوبيدوكريل لم يظهر تغييرات مؤثرة.

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اسـتنتجنا أن الأسـبرين, كلوبيـدوكريل أو مركبهمـا كـانوا فعـالين فـي تخفـيض ضـغط الـدم الانقباضـي والانبساطي لدى مرضى ارتفاع ضغط الدم.

ثانيـا", فـي الأشـخاص ألسـريعي التـأثر, المركـب أفضـل مـن الأسـبرين و كلوبيـدوكريل حيـث لا تغييـرات لوحظت مع المركب على معدل التنفس.

أخيرا", بالنسبة إلى حدود هذه الدراسة, لم يكن هناك تأثير مؤثر للأسبرين, كلوبيدوكريل أو مركبهما على شكل الدهون وإحصاء الصفيحات الدموية.

Abstract:

The objective of this study is to evaluate the effect of aspirin, clopidogrel or their combination on different parameters in hypertensive patients.

Platelets adhesion, activation, and aggregation are central to thrombus formation, which follows atherosclerotic plaque disruption and causes acute coronary syndromes. Aspirin and clopidogrel exert their antiplatelet effects by inhibiting thromboxane A2 production and adenosine diphosphate–induced platelet aggregation pathways, respectively. This study was designed to evaluate the possible effects of aspirin and clopidogrel given either alone or in combination in patients with essential hypertension on blood pressure and other parameters in addition to lipid profile using a randomized double blind, crossover clinical study.

The study includes 78 hypertensive patients received aspirin 100mg, clopidogrel 75mg or their combination (75mg aspirin &75mg clopidogrel) prior randomization schedule. Systolic, diastolic blood pressure, pulse rate, respiratory rate and SPO_2 were recorded at weekly intervals while, serum levels of LDL-C, HDL-C and platelets count were recorded at monthly intervals.

Significant decline in SBP, DBP in all treatment groups ($p<0.05$) was recorded, but for pulse rate, there was significant decrease in aspirin group and combination group while for clopidogrel group there was significant increase,

also we noticed significant decrease in respiratory rate with aspirin and clopidogrel but this decrease was absent with combination, LDL-C levels were significantly increased during treatment with aspirin or clopidogrel, while their combination did not show significant changes, HDL-C levels were significantly increased during treatment with aspirin or combination, while clopidogrel did not show significant changes.

We concluded that aspirin, clopidogrel or their combination were effective in decreasing SBP & DBP in hypertensive patients.

Secondly, in susceptible individual, combination is better than aspirin and clopidogrel, since no changes observed with combination on respiratory rate.

Finally, according to the limits of this study, there was no significant effect of aspirin, clopidogrel or their combination on lipid profile and platelets count.

Key words: Aspirin, clopidogrel, hypertensive patients.

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Introduction:

Several antiplatelet agents with different mechanisms of action are currently available for secondary prevention of ischemic stroke[1].When used as a single agent, the efficacy of antiplatelet therapy is modest. Aspirin is the best-studied and most widely used antiplatelet agent for stroke prevention [2]; however, it provides only an approximately 15% relative risk reduction for secondary prevention of stroke or other major vascular events[3]. The greatest benefit from aspirin was observed in older patients, patients with known CAD, and patients with impaired exercise capacity[4]. Clopidogrel, a thienopyridine derivative that inhibits platelet aggregation, has been widely studied in the treatment of patients at risk for cardiovascular events [5]. It inhibits platelet aggregation by selectively inhibiting the binding of the adenosine 5'-diphosphate molecule to the $P2Y_{12}$ receptor on the platelet surface[6]. This property of clopidogrel leads to inhibition of platelet activation and aggregation, thereby making it an important agent in the prevention of thrombotic complications especially in acute vascular ischemic events[7]. Hypertension is one of the major cardiovascular risk factors, independently of age, sex, or race [8]. Arterial blood pressures, both systolic and diastolic, are correlated with the incidence of coronary heart disease and stroke. As the risk increases continuously within the pressure ranges, the risk in individuals with borderline hypertension is somewhat higher than that of normotensive individuals[9]. The present study was designed to evaluate the possible effects of aspirin, clopidogrel or their combination on blood pressure pulse rate and other parameters in addition to lipid profile using a randomized double blind, crossover clinical study.

Materials and Methods:

Seventy eight out patients with essential hypertension attending the department of internal medicine, Al-karama Hospital; were selected to participate in this study. The criteria for eligibility included patients with mean age of (63.1+/– 7 years); 53% were female. Patients with renal and hepatic impairment, pregnant women, or those who were taking oral contraceptives were excluded from the study. All patients gave their written informed consent for their participation in the study which complies with the institutional ethics for clinical studies. Before inclusion into the study, regular measurement of blood pressure was carried out at weekly intervals for four weeks. All information about each patient was recorded in case sheet. All patients were studied on their usual diet and no dietary advice was given. All patients were received the same treatment for hypertension.

After blood pressure measurement, patients were divided into the following groups according to specific treatment regimen as follows:

* Group I- 26 patients with essential hypertension, they were received 100mg of aspirin tablet once daily and lasted for three months.

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* Group II- 26 patients with essential hypertension, they were received 75 mg clopidogrel once daily and lasted for 3 months.
* Group III- 26 patients with essential hypertension, they were received a combination of (75 mg aspirin and 75 mg clopidogrel) tablet and lasted for 3 months.

Blood pressure, pulse rate, SPO_2, respiratory rate, temperature was measured by EAGLE 1000 patient monitor and Chison 600 J. These parameters were determined according to the reading obtained from the patient monitor.
HDL-C levels, was measured using specific kits (Biolabo SA-France) and LDL-C was obtained by equation depending on the level of HDL-C.

Patients were asked if they had been any change in their presenting symptoms or development of new symptoms at each follow up visit.

Statistical evaluation was performed using ANOVA, differences were considered significant with $P<0.05$.

Results:

A description of patients according to some clinical and laboratory parameters is given in tables (1, 2)

Treatment with aspirin provided a significant reduction ($p<0.05$) of both systolic, diastolic blood pressures, and significant reduction of pulse rate compared to their levels before starting the treatment as shown in table-1. Moreover, treatment with 100mg aspirin tablet showed significant decrease in respiratory rate ($P<0.05$). While HDL-C & LDL-C levels were significantly increased ($P<0.05$) compared to their levels before starting the treatment, as shown in table-2.

Treatment with clopidogrel 75mg also provided a significant reduction of systolic, diastolic blood pressure, but provided a significant increase in pulse rate compared to their levels before starting the treatment and significant decrease in respiratory rate ($p<0.05$)as shown in table-1; while LDL-C level was significantly increased ($p<0.05$) as shown in table-2.

Treatment with combination provided significant reduction of systolic, diastolic blood pressure and pulse rate compared to their levels before starting the treatment.($p<0.05$), with no significant effect seen concerning respiratory rate as shown in table-1. Moreover, HDL-C level was significantly increased ($p<0.05$), as shown in table-2.

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		Aspirin	Clopidogrel	Combination
Systolic BP	**Baseline**	167.185 ± 2.111 a	162.115 ± 6.486a	141.346 ± 4.075b
	After	122.815 ± 0.823 * a % changes -26.54	122.731 ± 1.174 * a % changes -24.29	123.462 ± 2.65 * a % -12.65
Diastolic BP	**Baseline**	91.00 ± 1.868 a	87.846 ± 1.838 a,b	85.00 ± 1.98 b
	After	77.148 ± 1.312 *a % -15.22	77.038 ± 0.747 * a % -12.30	78.654 ± 0.962 * a % -7.47
Pulse rate	**Baseline**	85.00 ± 1.905 a	76.846 ± 2.167 b	83.346 ± 1.395 a
	After	76.63 ± 0.949 * a % -9.85	78.231 ± 1.349 * a % 1.8	81.615 ± 1.107 * b % -2.08
Respiratory rate	**Baseline**	11.037 ± 0.305 a	10.385 ± 0.188 b	11.269 ± 0.175 a
	After	9.593 ± 0.136 * a % -13.08	9.654 ± 0.24 * a % -7.04	11.192 ± 0.188 b % -0.68
Temp	**Baseline**	37.026 ± 0.026 a	36.985 ± 0.025 a	34.881 ± 1.793 a
	After	37.019 ± 0.027 a	36.981 ± 0.025 a	36.50 ± 0.398a
SPO_2	**Baseline**	91.37 ± 0.299 a	92.269 ± 0.382 b	88.923 ± 3.301 a,b
	After	93.407 ± 0.426 *a % 2.23	93.577 ± 0.497 * a % 1.42	95.115 ± 0.61 * b % 6.96

Table-1: Effect of aspirin, clopidogrel and their combination on hemodynamic parameters before and after 3 months of treatment.

* $P<0.05$ with respect to baseline value.Non-identical superscripts (a,b) among groups represent significant difference, $P<0.05$.

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		Aspirin	Clopidogrel	Combination
HDL	**Baseline**	34.615 ± 0.787 a	37.077 ± 1.103 b	44.66 ± 3.265 c
	After	39.038 ± 0.599 * a % 12.78	37.00 ± 0.81 b % -0.21	52.00 ± 2.817* a % 16.43
LDL	**Baseline**	103.538 ± 3.682 a	98.923 ± 1.448 a	93.208 ± 2.232 b
	After	113.038 ± 2.316 * a % 9.18	106.385 ± 1.716 * b % 7.54	85.792 ± 2.075 c % -8.45
Platelets	**Baseline**	205.538 ± 4.396 a	203.846 ± 3.756 a	197.875 ± 6.946 a
	After	209.923 ± 3.728 a % 2.13	228.077 ± 9.077 * b % 11.89	193.083 ± 3.812 c % -2.42

Table-2: Effect of aspirin, clopidogrel and their combination on lipid profile and platelets count.

* P<0.05 with respect to baseline value.

Non-identical superscripts (a,b,c) among groups represent significant difference, P<0.05.

Discussion:

Elevated blood pressures increase heart workload and progression of unhealthy tissue growth (atheroma) that develops within the walls of arteries. The higher the pressure, the more stress that is present and the more atheroma tend to progress and the heart muscle tends to thicken, enlarge and become weaker over time[10]. Persistent hypertension is one of the risk factors for strokes, heart attacks, heart failure and arterial aneurysms, and is the leading cause of chronic renal failure[11]. Even moderate elevation of arterial pressure leads to shortened life expectancy. At severely high pressures, mean arterial pressures 50% or more above average, a person can expect to live no more than a few years unless appropriately treated[12]. There are many physical factors that influence arterial pressure. Each of these may in turn be influenced by physiological factors, such as diet, exercise, disease, drugs or alcohol, obesity, excess weight and so-forth. One of these physical factors is: Viscosity, or thickness of the fluid. If the blood gets thicker, the result is an increase in arterial pressure. It had been thought that aspirin and related "blood thinner" drugs decreased the viscosity of blood, but studies found[13] that they act by reducing the tendency of the blood to clot instead, this explain the significant

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changes observed in SBP& DBP with aspirin, clopidogrel and their combination.

Concerning the significant decrease occurs in respiratory rate with aspirin, this was related to a deficiency in bronchodilator prostaglandins; prostaglandin inhibition may make arachidonic acid produce more leukotrienes with bronchoconstrictor activity [14]. This topic has been reviewed (SEDA The current theory of the mechanism relates to the inhibition of cyclo-oxygenases[15] allowing the bronchoconstrictor PGF2 to predominate in susceptible individuals. In spite of the effect observed on serum level of LDL-C & HDL-C was significant for aspirin, clopidogrel or combination either decreases or increase, can not consider within the normal range.

We concluded that, aspirin, clopidogrel and their combination were effective in decreasing blood pressure in patients with hypertension and this compatible with other study [16]. Secondly, Aspirin can cause pulmonary edema, particularly in the elderly, especially if they are or have been heavy smokers[17], so combination is better in such susceptible individuals, since no changes observed with combination on respiratory rate. Finally, according to the limits of this study, there was no significant effect of aspirin, clopidogrel & their combination on lipid profile & platelets count.

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