Assessment of platelet reactivity with anti platelet agent (clopidogrel) after two drugs formulation PLAVIX® and PLAGERINE

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الخلاصة:

في دراسة مقطعية عرضية تضمنت 28 مريضا مصابا بعدم كفاءة الشرايين التاجية في مركز النجف لأمراض وجراحة القلب للفترة من تشرين الأول لغاية كانون الأول 2011. توزع المرضى إلى فئتين ، **فئة تستخدم عقار** plavix والفئة الثانية تستخدم عقار plagrine وتم قياس كفاءة تجمع الصفيحات الدموية لكيلا العينتين وتم تحليل النتائج بجهاز ال multiplate machine وتم تحليل النتائج إحصائيا باستخدام **برنامج** (spss version 19) وأظهرت النتائج انه لا يوجد فرق بين العقاريين بالنتيجة (**المساحة تحت المنحني** AUC) في كلا العينتين (plavix and plagrine) وكذلك أظهرت النتائج إن عوامل الخطورة (**الجنس ، السكر،الضغط** ,التدخين,الدهون) لم تؤثر على النتائج في كلا المجموعتين .

Abstract

Cardiovascular disease remains the main cause of mortality. Antiplatelet therapy is the main drug use in the management of coronary artery disease. Several million of people receivedcolpidogril, however the cost of the drug that might 3-4 dollars daily for the brand company sanofi .pharmacies start to sell cheaper generic from Indian origin .assessment of platelet function after two drugs(plavix and plagrine) by multiple electrode platelet aggregometry (MEA) shows no difference of both drugs on the multiplate activity,this is assessted by prospective cross sectional study included 28 patients randomized to receive either plavix or plagrine, there is no significant differences regarded the effects of some risk factors in outcome in both group plavix and plagrine.

Key words: Antiplatelet therapy, platelet activity, plavix, plagrine

INTRODUCTION:

Atherosclerosis is the reason behind coronary artery disease which is the leading cause of mortality and morbidity for human being worldwide[1].Platelets have been shown to play a central role in the pathogenesis of atherosclerosis[2].

clopidogerl is the second common most widely sold drug in the world[3] used in the management of CAD and stroke [4] .The main anti plattlet action of clopidogrel is theinopyridine class inhibit of ADP P2Y12 receptor responsible for aggregation [5].

Several millions of people received the drug daily . The brand companies sold more than 6 billion dollars in one year. However a lot of people could not offer the drug that might cost 3-4 dollars daily[6].

In 2006 many companies started to manufacture the drug generics out of the legal pharmaceutical patent from the brand manufacturer (plavix ® sanofi aventis,french).this led to many legal conflicts' and ended with proposed settlement[7].

Several methods used to analyze platelets function in the whole blood; One of this methods is multiple electrodes platelet aggregometry (MEA) which is easy and reproducible and sensitive method for measuring platelet aggregation and evaluation of anti platelet drugs especially clopidogrel [8].

Assessment of bioavailability of the anti platelet therapy (measured by the area under the curve) is crucial because it might predict stent thrombosis ([9] which is the true night mares for the interventionist.

The Iraqi pharmacies started to sell clopidogrel with different generics(plagerin, plavidosa …etc.) with great variable prices (Table 1)

Table 1: List of interchangeable brand or generic drugs

Unit description	**Price,USD**
Pladogrel (Indonesia)	
Pladogrel 75mg ×30s	$ 30.29
Plagril(myanmmar,peru)	
Plagril capsule/tablet/75mg(10unit)	$ 0.77
Plagril 75mg TAB/10	$ 0.71
Plagril 75mg ×2×7s	$ 0.71
75mg ×10s	
Plagrin(Bangladesh)	
Plahasan 75mg×1 blister×10 tablet	
Planor(turkey)	
Plaraz 75	
Platec(Indonesia)	
Platec 75mg ×3×10s	$ 27.23
Platfree(Myanmar)	
Platfree capsule/tablet/75mg(10units)	$ 1.12
Platfree 75mg TAB /10	$ 2.90
75mg ×10s	$ 2.90
Platfrin(india)	
Platfrin capsule/tablet/75mg(10units)	$ 1.20
Platfrin capsule/tablet/150mg(10units	$ 1.40
Platfrin 75 TAB/10	$ 1.20
Platfrin 150 TAB/10	$ 1.40
75mg ×10s	$ 1.20
150mg ×10s	$ 1.40
Platloc(india)	
75mg ×10s	$ 0.64
Platloc 75mg TAB/10	$ 0.64

AIM OF THE STUDY:

Aprospective cross sectional study to assess the platelet reactivity in response to clopidogrel after administration of two different drug formulation french brand and cheaper Indian generic. By applying MEA technique using multiplate® machine.

MATERIALS AND METHODS:

This study conducted in Al-Najaf cardiac center in Al-Sader teaching medical city from November 2011 till December 2011. The total number was 28 (21males, 7 females); 13 patients tested for plavix. Another 15 group tested for plagerine.

The two groups (plavix and plagerin) tested for platelet aggrregabilty and drug bioavailablity measured by the area under the curve versus time,target level (53-122) unit using multiple electrodes platelet aggregometry (MEA).

To ensure that both drugs reach the steady state level, samples collected after a duration of time -at least-more than 10 days following administration of the drugs.

The results were expressed as mean ± SD and analyzed by applying independent t-test. Significance variation was considered when ($p \leq 0.05$), α =0.05 using SPSS program version 19.

RESULTS:

There was no statistical difference between plavix group (11.000+-6.733) and plagerin group (5.234+-1.35) with p- value =0.299. (Table 2).

This results did not reach level of significance regarding the effect of risk factors (hypertension, diabetes and smoking) on the outcome neither in plavix group(Table 3), nor in plagerine group (Table 4).

There was linear relationship between isolated risk factors and AUC regarding BMI (Figure 1) and age (Figure 2).

We find the mean area under the curve among those using plavix group was more than that in plagerine group (Figur3) but this did not reach level of significance.

Table 2: Comparison of mean area of platelet aggregation (Unit) between patients on plavix and plagerine.

AUC	No.	Mean ± SD	St.error mean	p-value	95%confidence interval of the difference	
					Lower	Upper
plavix	13	11.000 ± 6.733	1.8674	0.299	- 2.2524	7.052
plagerine	15	5.234 ± 1.351	1.3515		- 2.373	7.173

Table 3: Mean area in unit between patients receiving plavix according to some risk factors:

Risk factor	No.	Mean area (u) of plavix ± S.E	p-value
Gender M F	 9 4	 10.660 ± 1.950 11.750 ± 4.714	0.802
Diabetes mellitus Yes No	 3 10	 13.670 ± 3.710 10.200 ± 2.190	0.450
Hypertension Yes No	 6 7	 12.667 ±2.530 9.570 ± 2.750	0.433
Smoking Yes No	 3 10	 7.660 ±1.760 12.000 ±2.314	0.350
Triglyceride Yes No	 **7** 6	 10.714 ± 2.588 11.333± 2.951	0.877

Table 4: Mean area in unit between patients receiving plagerine according to some risk factors:

Risk factor	No.	Mean area (u) of plavix ± S.E	p-value
Gender M F	 12 3	 8.667 ± 1.563 8.330 ± 3.179	0.926
Diabetes mellitus Yes No	 4 11	 10.000 ± 1.201 8.500 ± 1.447	0.793
Hypertension Yes No	 2 13	 6.000 ± 4.000 9.000 ± 1.467	0.471
Smoking Yes No	 2 13	 10.500 ± 1.500 8.307 ± 1.541	0.600
Triglyceride Yes No	 3 12	 5.000 ± 1.527 9.500 ± 1.559	0.193

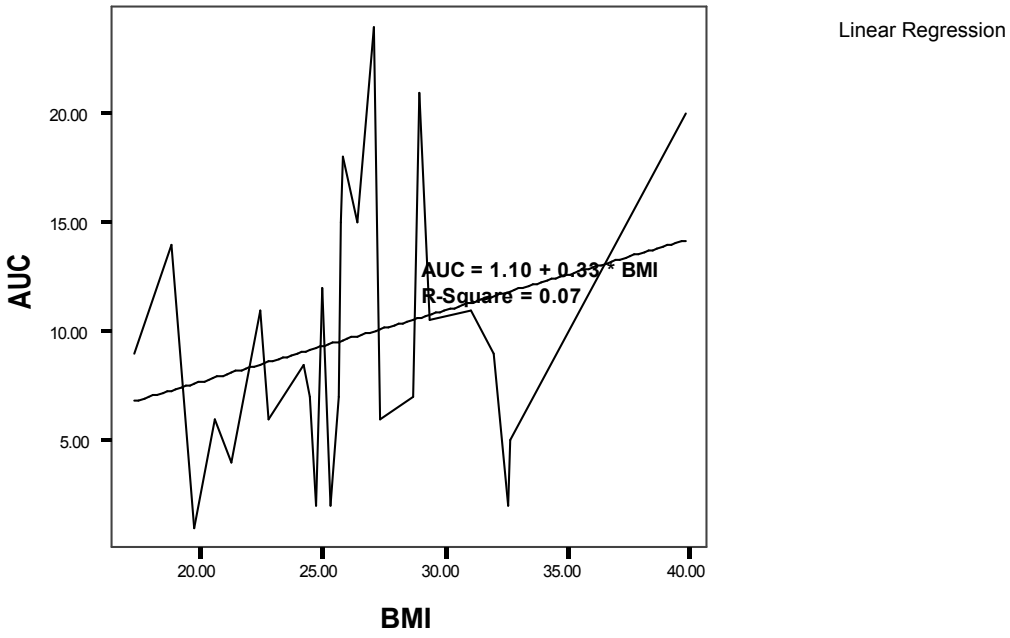


Figure 1: linear regression relationship between body mass index(BMI) and area under the curve (AUC) in unit.

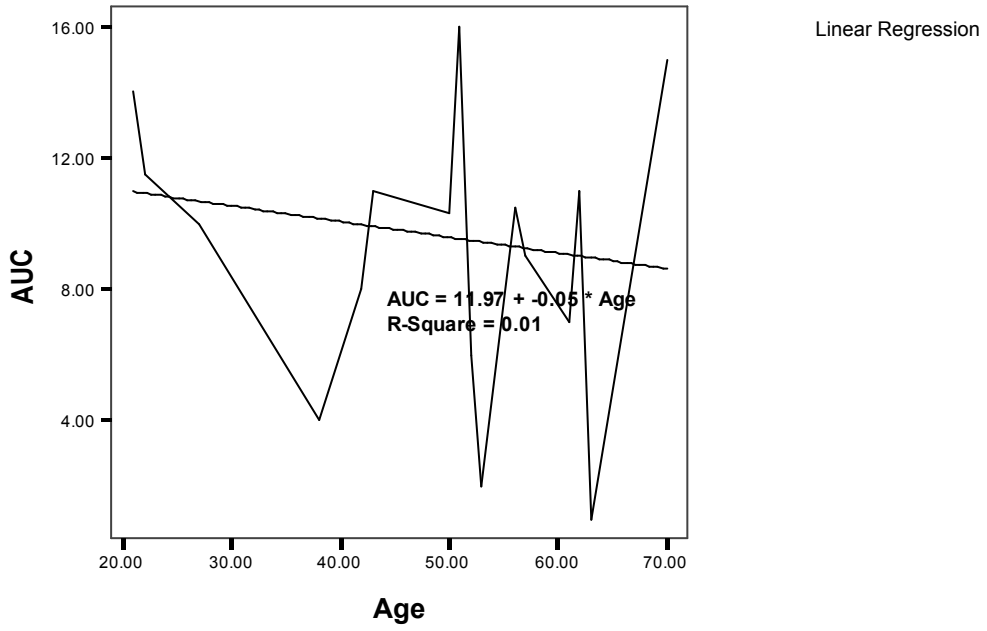
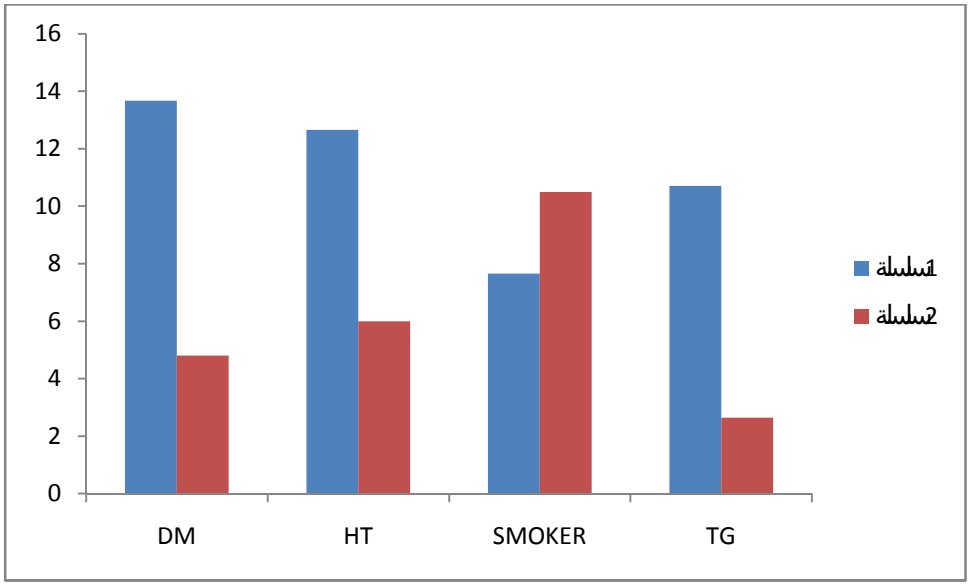


Figure 2: linear regression relationship between age and area under the curve (AUC) in unit.



Series 1: plavix

Series 2: plagreine

Figure 3: mean area of platelet aggregation in unit between patient receiving plavix and plagreine in relation to risk factor.

DISCUSSION:

Blood sample of 28 patients with ischemic heart disease were included for estimated the platelet aggregability after two different brands of drug (plavix and plagrine); tested by using the multiple electrode platelet aggregometry (MEA), the results demonstrated no statistical differences between plavix group (mean ± SD) was (11.00 ± 6.733) with P- value equal to 0.299 as in(Table 2).

Regarding isolated factors (gender, diabetes, hypertension, and smoking), sex had no effect on the mean area under the curve.

The curve in plavix arm, which is consistent with cure trial [(10)], this also occurred in the plagrine side.

Diabetes is accompanied by platelete function disorders hyporesponsiveness to clopidogril [(11).].

However this is consistent with our study (13.67 ± 3.710) versus (10.00 ± 2.190) in plavix group and (10.00 ± 1.201) versus (8.500 ± 1.447) in patients with plagrine group.

Both drugs formulation gave good level regarding bioavailabity of the antiplatlet therapy, which represent presence of clopidogrel active ingredient that gave adequate test result regarding platelet inhibition.

Also our result showed the mild deference regarding area under the curve(AUC), which was little higher in plavix group, which is not reach level of significance.

CONCLUSION:

Plagerine is as effective as plavix regarding the anti plattlet effect and can be used as alternative and cheaper therapy for pericutanus coronary intervention (PCI) and other indications for antiplatlet.

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