Effect of clopidogrel on bleeding time: A comparison of different pharmaceutical forms

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الخلاصة:
في ظل انفتاح السوق العراقيه عموما والدوائيه خصوصا ودخول الادويه من مختلف المناشئ فوجد ما يعرف بالدواء الاصلي المنتج من شركات رصينه ويباع بسعر عالي جدا كما وجد الدواء الرخيص وهو منتج من شركات غير ذائعة الشهرة، ترى اي دواء نختار لمرضانا؟ وإذا كان الرخيص بنفس فاعلية الغالي لماذا يدفع الفرق وهو ليس بالفارق الهين خصوصا لمرضى عليهم تعاطيه لما تبقى من حياتهم. اشترط ان يكون الدواء منتج من قبل شركه مسجله بوزارة الصحه العراقيه.
أجريت هذه الدراسة ابتداء من الاول من كانون الثاني ٢٠١٠ وحتى الثلاثين من شباط ٢٠١١ واشتملت على ١٦١ مريضا (٩٢ رجل و٦٩ امراه) من مراجعي استشارية الأمراض الباطنيه ومراجعي استشارية أمراض القلب وقسطرة الشرايين في مستشفى الديوانيه التعليمي، حيث قسم المرضى الى ثلاثة مجاميع حسب الكلوبيدوكريل الذي يتعاطونه كما شكلت مجموعه رابعه من الذين لا يتعاطون اي مثبط للصفائح الزرقاء واعتبرت مجموعه ضابطه (كان تشكيل المجموعه الضابطه من اصعب المهام لندرة من لايتعاطون المثبطات وهم بنفس صفات المجاميع الأخرى) اجري فحص قياس سيولة الدم لكل المرضى وأظهرت النتائج ان لا فروق معنويه بين من يتعاطون الكلوبيدوكريل هايدروجين سلفيت الغالي والرخيص والكلوبيدوكريل بيسيليت من ناحية التاثير على سيولة الدم.

Abstract

The current study was designed to prove or disprove the superiority of the expensive clopidogrel HS over the cheap one & the clopidogrel besylate by comparing their effect on bleeding time among the users

Results:

The study revealed that there was no significant difference of bleeding time among patients using the expensive clopidogrel HS & those using the cheap one or those using clopidogrel besylate**.**

Conclusions:

The expensive drug not necessarily means that this drug is superior & probably we might have cheap but effective drug so the superiority of the expensive drug is not reality**.**

Keywords: Clopidogrel HS, expensive, cheap, clopidogrel besylate, bleeding time.

INTRODUCTION

Clopidogrel, a second-generation thienopyridine that inhibits platelet aggregation, is a mainstay, along with aspirin, in the management of patients with coronary artery disease, with acute coronary syndromes (ACS), and/or after percutaneous coronary interventions (PCI).

Clopidogrel is an inactive prodrug that requires hepatic bioactivation via several cytochrome P450 enzymes, including CYP2C19. The active metabolite irreversibly inhibits the platelet ADP receptor, P2Y12. [1, 2, 3,]

It is interesting to note that the effect of clopidogrel on platelet reactivity varies substantially among patients, and rates of ‘‘low’’, ‘‘hypo’’ or ‘‘non’’ responders to clopidogrel therapy up to 25% have been reported [4,5]

Clopidogrel and ticlopidine are licensed for the secondary prevention of vascular events in patients with established atherosclerotic disease (ischemic stroke, myocardial

infarction and peripheral vascular disease). Clopidogrel is an orally administered thienopyridine that selectively and irreversibly inhibits ADP-induced platelet aggregation [6] Clopidogrel is inactive invitro and requires in vivo oxidation by hepatic/ intestinal cytochrome (P450 isoenzymeunstable active metabolite of clopidogrel forms a disulfide bridge between a reactive thiol group and a cysteine residue of the P2Y12 platelet receptor.[7,8] clopidogrel available in Iraqi drug market in 2 forms either as clopidogrel

hydrogen sulfate (CHS) or clopidogrel besylate (CB) & the former one again available as very cheap pill costing not more than 2 $ for the 10 tablet to very expensive costing more than 50 $ for the 10 tablets . Which form you choose for your patients? & many patients ask such a question, again many patients cannot withstand paying such a high price for the remaining of their lives & again why they should pay such a very high price in the presence of the cheap one! This study was conducted to answer at least partially these questions by comparing the effect of these different pharmaceutical types of clopidogrel on bleeding time the mechanism that probably through which clopidogrel exerts its benefit.

Patients & methods:

This retrospective study was conducted in Al-dewaniya teaching hospital from the 1st of January 2010 to the 30th 0f February 2011 all the patients are a visitor for either the cardiology & catheterization consultation unit or to the internist consultation unit. The patients classified according to the type of clopidogrel they do use into 3 groups,(those using the cheap clopidogrel hydrogen sulfate labeled as CCHS, those using the expensive clopidogrel hydrogen sulfate labeled as ECHS, those using expensive clopidogrel besylate labeled as ECB & because besylate available in expensive type only) ,the type of clopidogrel identified by direct visualization of the pill the patient may has, those who didn't accompanied by there medication were excluded from the study, the aim of the study was fully explained to the patients & if they agree a full history & clinical examination were done & recorded & then the patient send for bleeding time assessment. In this study a total of 161 patients, 69 females, 92 males, together with an other 50 patients (23 females, 27 males) not using any antiplateltes considered as a control group, so the patient divided ipatient receiving aspirin & other non steroidal anti-inflammatory drugs

1. Patients currently on warfarin.
2. patients on any type of clopidogrel within less than 5 days (clopidogrel peak action reached within 3-5 days)[9]

Bleeding time was done for every patient & because several methods were in use for the measurement of bleeding time in the lab. A lab. Personnel who was doing the test blindly, advised to use the standard method below.

Determination of bleeding time (Duck's method) [10]

The tip of the left ring finger (usual site)with usual aseptic precautions , we inflict a puncture wound ,it is of 3 mm depth & 0.5 cm length & without squeeze we notes the time of puncture & 1st appearance of blood & with filter paper gently blot the blood with out pressing or wiping the wound , repeat with a fresh piece of filter paper every 10 sec. tile no blood appear on the paper & then with counting of the filter papers which show the blot of blood on it & multiply the number by 10 sec., the bleeding time will be apparent.

Those patients with bleeding time less than one minute considered as non responders, those with bleeding time between 1-4 minutes considered as hypo responders.

Statistical analysis

Statistical analysis were done using SPSS computer software. All data are expressed as mean +SD unless otherwise stated. Paired T test was performed. Statistical significance was set at P-value > 0.05.

Results:

Patients were included retrospectively to the CCHS (n =62), the ECHS group (n = 50) , ECB group (n= 49) and to the control group(n = 50), there were no differences between the groups in terms of age, body mass index (BMI), gender distribution, ACE inhibitors, statins and b-blockers patients as compared to control patients. Laboratory data were also similar between the groups, Taken together the four groups demonstrated comparable characteristics (table-1-)

Table 1: clinical characteristics of the four study groups

	ECHS	**CCHS**	**ECB**	**CONT.**	**P value**
Age(yr)	60	60.67	58.2	60.2	Ns
Gender					
Female	20	27	22	23	
Male	30	35	27	27	
Medical history +RF[(a)]					
DM[(b)]	27	31	30	25	Ns
Systolic BP[(c))]	140	138	140	140	Ns
ACE inhibitor[(d)]	25	30	27	30	Ns
Beta –blockers	80	83	78	84	Ns
Ca^{++}channel blockers	7	10	9	8	Ns
Statin	90	95	97	30	0.001
Lab.data					
Platelets($x10^9$/L)	220	224	234	230	Ns
WBCC ($x10^9$/L	5000	5600	4800	5000	Ns
Hb(g/dl)	14	13.4	14	13.5	Ns
BMI(kg/m^2)	25	24.9	25	25	Ns

RF[(a)] = risk factorm **DM[(b)]**=diabetes mellitus, **BP[(c)]** = blood pressure, **ACE[(d)]** = angiotensin converting enzyme.

Table -2: bleeding time among different clopidogrel user groups :

Different clopedogrel users	**< 1 minute**	**1-4 minute**	**> 4 minute**	**TOTAL**
ECHS	3(6%)	3(6%)	44(88%)	50(100%)
CCHS	4 (6%)	5(8%)	53(85%)	62(100%)
ECB	2 (4%)	4(8%)	44(89%)	49(100%)
CONT.	6 (12%)	40(80%)	4(8%)	50(100%)

Among ECHS group 3 (6%) showing a bleeding time less than one minute & considered as non responder, 3 (6%) showing bleeding time between 1-4 minutes & considered as hypo responders, while among CCHS group 4 patients (6%) showing a bleeding time less than 1 minuet & considered as non responders & 5 patients showing bleeding time from 1-4 minuets & considered as hypo responders, while among ECB group 2 patients (4%) showing bleeding time less than 1 minuet & considered as non responders & 4 patients their bleeding time between 1-4 minuets & considered as hypo responders.

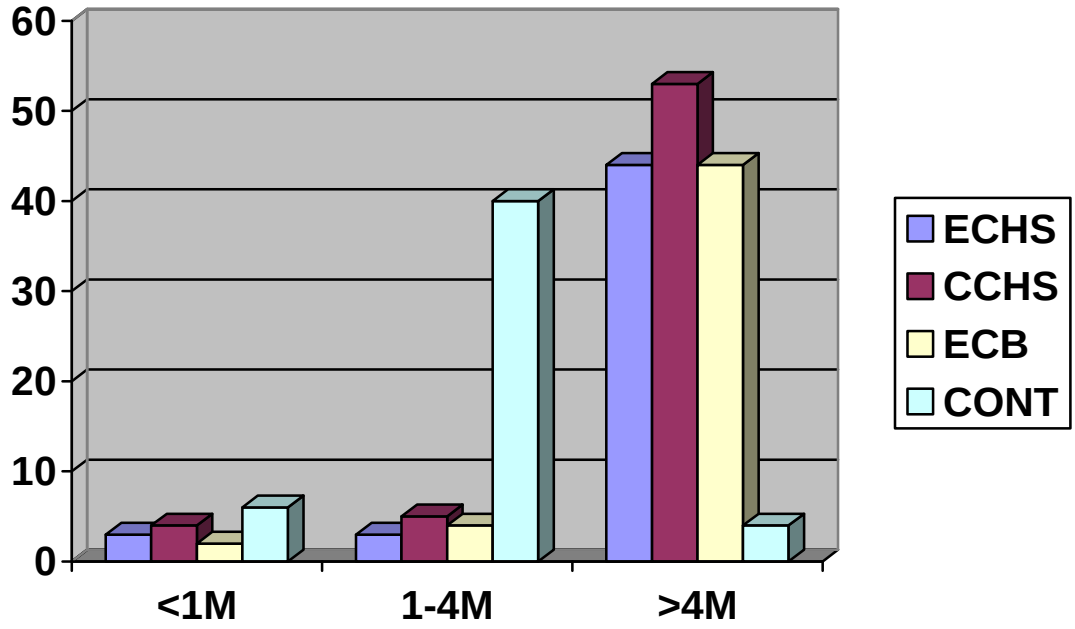

Figure -1: bleeding time differences among users of different Clopidogrel types.

ECHS : expensive clopidogrel hydrogen sulfate users
CCHS : cheap clopidogrel hydrogen sulfate users
ECB : expensive clopidogrel besylate users
CONT : control group

DISCUSSION

In this study the effect of clopidogrel hydrogen sulfate in its both type the cheap or the expensive type & clopidogrel besylate on bleeding time nearly similar,(no significant difference), where 12% among those using the expensive clopidogrel HS showing a bleeding time less than 4 minuets & considered as hypo & non responders, while among CCHS users 14% showing a bleeding time less than 4 minuets & considered as hypo & non responders, this nearly the same among those using the besylate where 12% showing bleeding time less than 4 minuets. These results probably correlate well with the well known fact that 15-20% of the population showing some resistance to the platelets inhibitory effect of clopidogrel[4,5], the condition probably responsible for those encounter a therapeutic failure & its serious consequences[11] One type of salt of medication does not necessarily have the same clinical effect as does another salt. For example, it has been shown that different metoprolol salts provide different clinical effects. The two formulas of metoprolol succinate and metoprolol tartrate lead to different results in terms of risk reduction in the therapy of chronic heart failure. Studies favor metoprolol succinate whereas metoprolol tartrate seems to be less effective in reducing mortality (MERIT-HF, COMET trials)[12,13] . in this study there is no significant difference in bleeding time whether the patients used the cheap or the expensive clopidogrel hydrogen sulfate & even clopidogrel besylate which recently produced to overcome the variability of response among the users[8], again this drug

fails to achieve such aim where 12% of those using this drug showing bleeding time less than 4 minutes & considered as non or hypo responders so there is no significant similar & the expensive drugs probably not necessarily the better drugs.

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