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BLEEDING POST CORONARY ARTERY BYPASS SURGERY
Clopidogrel - Cure or Culprit ?

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ABSTRACT • BACKGROUND : Clopidogrel, in addition to aspirin, has become a common treatment of acute coronary syndrome and for stent thrombosis prevention, when given before percutaneous transluminal coronary angioplasty. However, some patients turn out to have surgical coronary artery disease and are sent for coronary artery bypass grafting (CABG) where the irreversible effect of aspirin and clopidogrel on platelet function becomes a concern. This study was conducted to evaluate the role of preoperative use of clopidogrel in bleeding complications after CABG.

MATERIAL AND METHODS : A total of 462 patients who underwent CABG between 2001 and 2003 were studied as a retrospective cohort. Comparison was made between patients who had taken clopidogrel within 7 days of surgery (n = 162), and those who were not exposed to clopidogrel (n = 300). Chest tube output and bleeding index (a modified TIMI criteria), were the primary outcomes measured.

RESULTS : Our data showed that patients taking clopidogrel within 7 days of surgery have a higher bleeding index than those who were not exposed to the drug (p = 0.024). Similarly, chest tube output was significantly higher in those who were exposed to clopidogrel within 7 days compared to those not taking clopidogrel (p = 0.01). To further dissect this relationship, we divided our population into three categories. We found that patients taking clopidogrel within 3 days prior to CABG (immediate exposure) have a higher bleeding index and TIMI major bleeding than either patients taking the drug between 3 and 7 days (recent exposure) or patients not exposed to clopidogrel at all (p = 0.009 and 0.03 respectively for inter-groups comparison). The same was true for chest tube output (p = 0.05 and 0.01 respectively).

CONCLUSION : Clopidogrel increased the risk of post-CABG bleeding if taken within three days prior to surgery but not if taken before that.

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Haydar AA, Abchee AB, El-Hajj II, Hujairi NMA, Tfaili AS, Hatoum T, Quateen A, Bakri R, Afzali B, Goldsmith DJA. Saignement post-chirurgie cardiaque : Clopidogrel - Responsable ou innocent ? J Méd Lib 2006 ; 54 (1) : 11-16.

RÉSUMÉ • OBJECTIF : Le clopidogrel associé à l'aspirine est devenu le traitement de choix du syndrome coronarien aigu et pour la prévention de la thrombose des stents lorsqu'il est administré avant l'angioplastie coronaire transluminale percutanée. Mais cette association devient problématique lorsque les patients doivent subir un pontage aorto-coronarien à cause de l'effet irréversible de l'aspirine et du clopidogrel sur la fonction plaquettaire. L'objectif de cette étude vise à évaluer le risque d'hémorragie postopératoire en cas de prise de clopidogrel en période préopératoire.

MATÉRIEL ET MÉTHODES : Une étude rétrospective a été menée chez 462 patients ayant subi un pontage aorto-coronarien entre 2001 et 2003. Une comparaison a été faite entre les patients ayant reçu le clopidogrel dans un délai de 7 jours avant la chirurgie (n = 162) et les patients n'ayant pas reçu le clopidogrel (n = 300). Le but primaire était la mesure du débit du drain thoracique et l'estimation de l'index de saignement (critères modifiés de TIMI).

RÉSULTATS : Les résultats primaires ont montré un index de saignement et un débit du drain thoracique supérieurs dans le groupe de patients ayant reçu le médicament (p = 0,024 et p = 0,01 respectivement). Pour plus de précision, la population étudiée a été répartie en 3 groupes : ceux ayant reçu l'antiagrégation plaquettaire 3 jours avant l'opération, ceux l'ayant reçu entre le 3e et le 7e jour avant l'opération et ceux n'ayant pas reçu de traitement. Les résultats ont montré un index de saignement, et un débit par drain thoracique plus élevés dans le premier groupe comparé aux autres groupes, avec une valeur de p significative.

CONCLUSION : Le clopidogrel augmente le risque de saignement post-chirurgie cardiaque lorsqu'il est administré dans les 3 jours précédant la chirurgie.

INTRODUCTION

The use of combination anti-platelet therapy in cardiac patients is increasing yearly [1]. The CURE study established the usefulness of combination therapy of clopidogrel and aspirin in preventing recurrent events described as acute myocardial infarction, stroke, and cardiovascular death in patients presenting with unstable angina [2]. Another indication for the use of combina-

ABBREVIATION LIST

CABG	↔	Coronary artery bypass graft	CCU	↔	Coronary care unit
PTCA	↔	Percutaneous transluminal coronary angioplasty	ARF	↔	Acute renal failure
PC	↔	Packed cells	MI	↔	Myocardial infarction
CHF	↔	Congestive heart failure	PT	↔	Prothrombin time
CSU	↔	Cardiac surgery unit	CPB	↔	Cardiopulmonary bypass

tion anti-platelet therapy is coronary artery stenting [3]. The use of multiple drugs acting at different points in the platelet-inhibition cascade is however not free of complications. The potentially serious complication noted with the addition of clopidogrel in the CURE trial was an increased risk of bleeding [2]. The absolute rate of major bleeding increased by 3.5%, nearly half of which defined as "life-threatening" or major bleeding according to TIMI criteria [4-5].

As the use of clopidogrel has gained further popularity and indications in coronary artery disease patients, running a placebo-controlled trial to look at the safety of this drug in terms of bleeding is difficult. In our study, we examined whether the pre-coronary artery bypass grafting (CABG) use of clopidrogel and aspirin increases the risk of postoperative bleeding by looking (either prospectively or retrospectively) at a cohort of patients who are taking the drug, and we monitored the outcome and bleeding parameters (chest tube output, and "bleeding index"). Reviewing the literature, few small studies have attempted to address this issue [6-8].

MATERIAL AND METHODS

Patients

A retrospective observational cohort study was conducted at the American University of Beirut Medical Center (AUBMC). Medical records of patients who underwent CABG between June 2001 and December 2003 were reviewed. All the patients had their CABG done at the same center (AUBMC) and by either one of two surgeons, with a well defined protocol for surgery, anesthesia, time to extubation, cardiac surgery unit stay, postoperative use of inotropes, anticoagulation, and antiplatelets, as well as electrolytes replacement. All patients had RBC cell saver technique intra-operatively and in the early period postoperatively. All patients underwent conventional CABG not including valvular surgery or emergency or redo CABG.

Excluded patients were those who had received oral anticoagulation, thrombolysis within 24 hrs, or glycoprotein IIB/IIIA within 12 hrs of CABG.

A total of 462 patients were left for final inclusion into the study. Of these 462 patients, 162 patients received clopidogrel within one week prior to surgery (82 patients within 3 days [Group A, immediate exposure] and 80 between 3 and 7 days of the CABG [Group B, recent exposure]). The remaining 300 patients were not exposed to clopidogrel (Group C).

Data collection

From the medical records, all the preoperative patients' characteristics including co-morbidities, medications, blood chemistry, fibrinogen, and previously proven or suspected predictors of bleeding, were recorded (Table I). The postoperative course of the patients was monitored for duration of stay, arrhythmias, recurrent ischemia (defined as recurrent chest pain, new electrocardiogram (ECG) changes, or elevation in cardiac enzymes), renal insufficiency (defined as more than 50% increase in baseline creatinine), and electrolytes imbalance. Cardiac surgery unit (CSU) stay was calculated and any critical coronary care unit (CCU) stay was added to it. A CSU stay ≥ 36 hrs was considered as prolonged. Postoperative intubation lasting ≥ 12 hrs or intravenous (IV) of inotropes use for ≥ 36 hrs were also considered to have prolonged hospital stay. Systolic dysfunction was diagnosed if the patient's echocardiographic ejection fraction was less than 40%. All blood components including packed red blood cells (PC), fresh frozen plasma (FFP), and platelets given postoperatively were recorded from the medical records irrespective of the time of transfusion (transfusion threshold was hemoglobin < 9 g/dl). Preoperative/postoperative hemoglobin (Hgb) and hemoglobin at discharge were also noted. Chest tube output was recorded as well.

Endpoints

Primary endpoints

1. Chest tube output.
2. Bleeding index. It assesses the drop in hemoglobin and accounts the need for transfusions.
   The bleeding index is defined as :
   Bleeding index = (Pre-op. Hgb) – (Hgb at discharge) + PC transfused (U), where 1 unit of PC is considered equivalent to 1 g/dl change in Hgb.

The bleeding index was compared in the three groups of patients exposed to clopidogrel. A bleeding index more than 5 g/dl was considered as major bleeding according to TIMI criteria [5].

Secondary endpoints

Secondary endpoints included clinical outcomes. These were arrhythmias (atrial fibrillation/flutter or sustained ventricular tachycardia), acute myocardial infarction (AMI), acute renal failure (ARF), cerebrovascular accident (CVA) whether ischemic or hemorrhagic, prolonged CSU/hospital stay, recurrent ischemia, prolonged mechanical ventilation, need for re-exploration for bleeding control, mortality, gastrointestinal bleeding and macroscopic hematuria.

TABLE I
BASELINE CHARACTERISTICS OF THE PATIENTS

	Group A N = 82	**Group B** N = 80	**Group C** N = 300	**p-value**
AGE (years)	64.5 ± 9.2	60.2 ± 11.1	63.0 ± 9.7	0.102
CREATININE (mg/dl)	1.06 ± 0.25	1.3 ± 0.9	1.1 ± 0.6	0.088
PLATELETS	238.8 ± 37.7	221.1 ± 60.3	250.5 ± 83.2	0.072
BMI (kg/m^2)	28.6 ± 3.8	28.7 ± 4.3	28.5 ± 4.1	0.775
GENDER (female)	13.4%	27.8%	20.9%	0.196
HYPERTENSION	47.8%	48.6%	45%	0.853
DM	32.8%	35.1%	35%	0.944
CVA	6.0%	8.1%	2.2%	0.054
SMOKERS	61.2%	59.5%	56.8%	0.782
CRF	22.4%	27%	16.5%	0.182
CHF	22.4%	20.6%	22.8%	0.967
APROTININ INTAKE	65.7%	56.8%	51.9%	0.109
ASA within 7 days	79.1%	86.5%	77.0%	0.402
BYPASS TIME (min)	52.3 ± 16.7	58.1 ± 34.7	60.7 ± 26.4	0.059
PRE-OP INR	0.9 ± 0.2	0.9 ± 0.1	0.9 ± 0.1	0.816
PRE-OP FIBRINOGEN	4.6 ± 1.4	4.4 ± 1.2	6.1 ± 1.9	0.909
PRE-OP Hgb (g/dl)	13.7 ± 1.2	12.9 ± 1.8	13.3 ± 1.6	0.11

Group A : exposure to clopidogrel within 3 days of surgery **Group B** : exposure to clopidogrel between 3 and 7 days of surgery.
Group C : no exposure to clopidogrel in the week preceding surgery.
BMI : body mass index **DM** : diabetes mellitus **CVA** : cerebrovascular accident **CRF** : chronic renal failure
CHF : congestive heart failure **ASA** : acetylsalicylic acid **INR** : international normalized ratio

Statistical analysis

Data were entered and analyzed using statistical package for social sciences (SPSS) v. 11. Kruskall Wallis and Mann-Whitney tests were used to compare non-parametric means. One-way Anova and Student t tests were used for comparison of parametric means. $P < 0.05$ was considered as statistically significant.

RESULTS

The mean chest tube output in patients taking clopidogrel within 7 days (n = 162) was 599.7 ml while it was 503.6 ml in those not exposed to the drug (p = 0.01). The mean bleeding index in patients taking clopidogrel within 7 days and those not exposed to clopidogrel were significantly different (p = 0.024). As we had a sufficiently large number of patients exposed to clopidogrel, we divided our patients into three groups. Group A, patients exposed to clopidogrel within 3 days prior to CABG (n = 82), group B, patients exposed to clopidogrel between 3 and 7 days prior to CABG (n = 80), and group C, patients not exposed to clopidogrel (n = 300).

The baseline characteristics of patients are shown in table I. The three groups were comparable in age, sex, and BMI. Baseline prothrombin time (PT), fibrinogen, preoperative hemoglobin, creatinine, cardiopulmonary bypass (CPB) time, intra-operative use of aprotinin, and use of aspirin in the week preceding the operation were also comparable between the three groups (Table I). Diabetes mellitus (DM), chronic renal failure (CRF), congestive heart failure (CHF), history of cerebrovascular accident (CVA), and history of smoking were equally distributed.

Our data showed that group A (people taking clopidogrel within 3 days prior to CABG) have a higher bleeding index than either group B or C (p = 0.009 for inter-groups comparison, p = 0.002 for groups A and C comparison, and p = 0.045 for groups A and B comparison) and chest tube output (p = 0.05 for groups A and C, and p = 0.01 for groups A and B) (Table II). However, patients taking clopidogrel between 3 and 7 days prior to CABG (Group B) had a bleeding index and chest tube output comparable to patients not exposed to clopidogrel (Group C) (p = 0.905 and 0.54 respectively).

To dissect these results in view of the AHA/ACC guidelines, we compared the chest tube output in patients taking clopidogrel between 3 and 5 days (N = 38, mean = 501 ml) and those exposed to the drug between 5 and 7 days (N = 42, mean = 589 ml), p = 0.507. The same applies when we compared bleeding index between the first subgroup (mean = 4.35 g/dl) and the second subgroup (mean = 4.43 g/dl), p = 0.151.

Taking bleeding index ≥ 5 g/dl as indicator of major bleeding according to TIMI criteria [5], we found that patients with immediate exposure to clopidogrel (Group A)

had higher incidence of major bleeding (56.7%) than either patients with recent exposure (Group B) (38.2%) or patients with no exposure to clopidogrel (Group C) (39.6%), p = 0.03 for inter-means comparison, p = 0.009 for group A and C comparison, and p = 0.875 for group B and C comparison (Table II).

There were no differences in the number of platelet units transfused among the three groups (p = 0.139) nor in the number of FFP units transfused (p = 0.656).

The three groups were similar in terms of postoperative complications (ARF, MI, arrhythmia, mechanical ventilation, and renal failure) and CSU stay. No difference in the rate of re-exploration for control of bleeding was noted among the three groups (Table II). In addition there was no difference in the rate of other major or minor postoperative bleeding variables like gastrointestinal or hematuria (data not shown).

DISCUSSION

As the indications for clopidogrel expand, the use of aggressive antiplatelet therapy is seen in a larger number of patients who then require urgent CABG. Clopidogrel is now given in addition to aspirin as the standard of care for the prevention of stent thrombosis and for ST elevation (TIMI 28 clarity trial and COMMIT/CCS-2 trial) and non ST-elevation acute coronary syndrome [2-3]. However, giving a combination of highly potent irreversible antiplatelet agents is not free of complications, and bleeding is the most important one [4].

Clopidogrel is an inhibitor of adenosine diphosphate (ADP) induced platelet aggregation, acting by direct inhibition of ADP, binding to its receptor. Following an oral dose of ^{14}C-labeled clopidogrel in humans, approximately 50% was excreted in the urine and approximately 46% in the feces in the 5 days after dosing. As the elimination half-life of the main circulating metabolite was 8 hours after single and repeated administration, we decided to study whether clopidogrel is safe if given up to three days prior to surgery [9].

In this study, in addition to the conventional chest tube output which conformed with the published data, we tried to look at a new variable that takes into consideration both the drop in hemoglobin calculated at time of discharge, and we added to this the number of packed red cells units (PCU) given to the patients, to finally reach a number we called "bleeding index". This bleeding index is inferred from TIMI bleeding criteria [5]. All the trials in the literature that studied the effect of clopidogrel on bleeding post CABG looked at either the blood

TABLE II
PRIMARY AND SECONDARY OUTCOMES

	Group A N = 82	**Group B** N = 80	**Group C** N = 300	**p-value**
Chest tube output	659.1 ± 44.8	540.4 ± 29.2	503.6 ± 23.8	0.05*
				0.01▼
				0.54♦
"Bleeding index" (g/dl)	5.42 ± 2.22	4.39 ± 1.81	4.49 ± 2.05	0.009*
				0.002▼
				0.905♦
Platelets units used	0.13 ± 0.13	0.26 ± 0.26	0.03 ± 0.02	0.139
FFP units used	0.1 ± 0.08	0	0.06 ± 0.02	0.565
Bleeding index more than 5 g/dl	56.7%	38.2%	39.6%	0.03*
				0.009▼
				0.875♦
Arrhythmia	19.4%	16.7%	15.9%	0.303
AMI	1.5%	0%	1.1%	0.776
CVA	1.5%	0%	0.5%	0.588
ARF	9.0%	8.6%	5.4%	0.448
Prolonged mechanical ventilation	7.5%	8.6%	5.5%	0.665
Prolonged CSU stay	7.6%	11.1%	4.2%	0.141
Prolonged inotrope use	9.1%	19.0%	7.7%	0.501
Recurrent ischemia	1.5%	0%	2.4%	0.798
Re-exploration	1.5%	2.8%	1.6%	0.869

Group A : exposure to clopidogrel within 3 days of surgery **Group B** : exposure to clopidogrel between 3 and 7 days of surgery.
Group C : no exposure to clopidogrel in the week preceding surgery. * Inter-groups comparison ▼ Groups A and C comparison
♦ Groups B and C comparison **FFP** : fresh frozen plasma **AMI** : acute myocardial infarction
CVA : cerebrovascular accident **ARF** : acute renal failure **CSU** : cardiac surgery unit

product transfusions [6-8], the chest tube output [6-7], or at the re-exploration rate [6]. Relying on these data the American College of Cardiology (ACC)/American Heart Association (AHA) recommended in their guidelines in 2002 that clopidogrel should be stopped at least 5 days and preferably 7 days prior to CABG [10-11].

Our data showed that as per the AHA recommendations clopidogrel taken one week prior to CABG increases the risk of postoperative bleeding. However when we categorized our patients into immediate (within 3 days) and recent (between 3 and 7 days) clopidogrel exposure, we found two different effects. The chest tube output and bleeding index increased in patients with "immediate" exposure to clopidogrel but not in those with "recent" exposure prior to surgery.

The mean bleeding index in patients taking clopidogrel within three days was 5.42 g/dl versus 4.4 g/dl in those taking the drug before three days and those not taking the drug. In addition the incidence of major bleeding according to TIMI bleeding criteria was higher in the immediate exposure group (i.e. group A) (56.7%) than in the recent/no exposure groups (i.e. groups B and C) (39.6%) ($p = 0.03$) (Table II). This high bleeding index (more than 5 g/dl) is major or life-threatening bleeding according to TIMI bleeding criteria [5].

We did not find any positive secondary outcome in our study (Table II). There was no increase in re-exploration rate in patients taking clopidogrel in our cohort although this finding was reported by Yende et al. [6].

Our data is one step ahead from most of the data presented in the literature, as we did not only compare the risk of bleeding in patients taking clopidogrel versus those not taking it [12], but we tried to find out the time-relation between clopidogrel and bleeding post CABG. Our data is in harmony with that of Ascione et al. [13], who found that clopidogrel, given within 48 hours prior to CABG increased the risk of blood transfusions. However, our larger database did not show an increase in mortality. Our results were similar to those of Chu et al. [14] who found that clopidogrel given within 4 days of surgery increases the risk of bleeding.

Our data has several advantages. First, it comes from a large patient cohort, from a single center with two cardiothoracic surgeons following a standardized CABG protocol. Second, our modified TIMI bleeding criteria or "bleeding index" backed up by the increased chest tube output, made us more confident that our results are valid and reproducible. In fact, if these findings were to be reproduced in a larger population, they may implicate a change in the guidelines for using clopidogrel prior to cardiac surgery.

CONCLUSION

Our results showed that clopidogrel is associated with an increased risk of bleeding in patients undergoing CABG, only if given in the three days preceding surgery, but not if given before that.

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النزف التالي لجراحة الشرايين الإكليليّة بتحويلة: كلوبيدوغريل. معالجة أو مدعى عليه؟

موجز: الموضوع – أصبح الكلوبيدوغريل بالإشتراك مع الاسبرين العلاج المختار للمتلازمة الإكليليّة الحادّة وللوقاية من جلطات عندما يعطى قبل رأب العرق الإكليلي جلدياً عبر اللمعة. هذا الإشتراك يسبّب مشكلة إذا كان المريض سيخضع لتجسير أبهري إكليلي بسبب التأثير اللاعكوس للإسبرين والكلوبيدوغريل على وظيفة الصفيحات. غاية هذه الدراسة هي لتقييم خطر النزف التالي للجراحة في حال تناول الكلوبيدوغريل قبل العمليّة.
المرضى والطرق – دراسة إسترجاعيّة عند ٤٦٢ مريضاً أجري لهم تجسير أبهري إكليلي بين ٢٠٠١ – ٢٠٠٣. تمّت المقارنة بين المرضى الذين أُعطوا كلوبيدوغريل خلال ٧ أيام قبل العمليّة (١٦٢) والذين لم يُعطوا كلوبيدوغريل (٣٠٠). الهدف الأول هو الصبيب الدموي من المنزح الصدري وتقييم مشعر النزف (معايير متحوّلة TIMI).
النتائج – أظهرت النتائج الأوليّة أنّ مشعر النزف وصبيب المنزح الصدري هو أعلى في فئة المرضى الذين أعطوا العلاج (إحتمال ٠,٠٢٤ واحتمال ٠,٠١ تباعاً). ولتدقيق أكثر فإنّ المرضى الذين أجريت عليهم الدراسة وضعوا في ٣ فئات:
١ – الذين تناولوا مضادّ التكتّل للصفيحات ٣ أيام قبل الجراحة.
٢ – الذين تناولوا العلاج بين اليومين الثالث والسابع قبل الجراحة.
٣ – الذين لم يتناولوا العلاج.
أظهرت النتائج أنّ مشعر النزف وصبيب المنزح الصدري هو أعلى في الفئة الأولى نسبة للفئتين التاليتين مع قيمة احتمال واضحة.
الخلاصة – الكلوبيدوغريل يزيد من خطر النزف التالي لجراحة القلب إذا أعطي ٣ أيام قبل العمليّة.