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Does Clopidogrel Reduce Major Adverse Cardiac Events in Patients Undergoing Non-Cardiac Vascular Surgery?

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Abstract

Aims: To determine the influence of Clopidogrel on major adverse cardiac events (MACE's) in patients undergoing non-cardiac vascular surgery. **Introduction:** Antiplatelet agents are regularly withdrawn prior to surgery due to concerns over bleeding risk, however there is some compelling retrospective data to suggest that while patients on antiplatelet agents do have higher rates of bleeding their overall prognosis is better off. **Methods:** We performed a prospective observational study on non-cardiac vascular surgery patients who had a successful non-cardiac related operation at the Royal Liverpool University Hospital. Baseline clinical parameters were systematically collected and in-hospital MACE's were recorded on post-op days 1 - 4. An average Eagle risk score was calculated for each group and statistical analysis using a statistical package for social sciences was used to determine significance. **Results:** 101 total patients were identified and 75 patients were deemed eligible for inclusion. 27 (36%) had peripheral arterial bypass surgery, 24 (32%) had an endovascular repair, 13 (17%) had carotid endarterectomy and 11 (15%) had open aneurysm repair. 14 (19%) of the recruited participants were taking clopidogrel prior to surgery. The mean Eagle risk score was 1.22 ± 0.93 in the non-clopidogrel arm and 0.92 ± 0.75 in the clopidogrel group. There was no significant difference in Eagle risk scores between the two groups. 13 (21%) of 61 patients not taking clopidogrel experienced MACE vs. 0 in those taking clopidogrel (P = 0.03). **Conclusion:** Our study suggests that clopidogrel reduces major adverse cardiac events in patients undergoing non-cardiac vascular surgery even in higher risk patients.

Subject Areas

Surgery & Surgical Specialties

Keywords

Clopidogrel, Major Adverse Cardiac Events, Post-Op Complications, Vascular Surgery

1. Introduction

Non-cardiac vascular surgery has undergone major recent advances that have improved the quality of life for patients and reduced the associated risks and complications. However, this type of surgery is associated with increased cardiovascular complications. Major Adverse Cardiac Events (MACE) such as unstable angina, myocardial infarction and cardiac death pose significant risks to patients [1] [2]. In non-vascular major surgery the percentage of patients having a cardiac event is approaching 7% [3] [4], however this is doubled to 13% in vascular surgical patients [2]. Those undergoing such procedures are likely to suffer from generalised arteriopathy [4] which may involve the coronary arteries and also tend to have more risk factors such as smoking, hypercholesterolemia and diabetes explaining this higher event rate in vascular than non-vascular surgical patients.

In the past a number of interventions have been studied to reduce this cardiac risk. Pre-operative investigations like exercise tolerance testing, myocardial perfusion scans, stress echocardiograms and cardiac catheterisation have been studied. Medical therapies have also been tried in an attempt to reduce cardiac complications. Beta-blockers have demonstrated some success in this regard, reducing peri-operative cardiac events in patients undergoing major surgery [5] [6]. However; controlled studies with nitrates, calcium-channel blockers, clonidine, or digoxin have all produced negative answers [7]-[11].

In the last decade there have been major advances in knowledge regarding the pathogenesis of atherosclerosis and acute coronary syndromes. The mechanism of acute coronary syndrome can now be explained by a process of plaque rupture [12]-[14] with subsequent thrombus formation leading to partial or complete arterial occlusion. The intra-coronary thrombus is composed of platelets and fibrin strands. Thrombin which is released by the vascular injury site plays an important role in platelet aggregation. It causes the platelets to release adenosine diphosphate (ADP), thromboxane A2, and serotonin which are potent stimulators of platelet aggregation. Because of their importance, most therapies for acute coronary syndromes focus on targeting platelets and thrombins. Aspirin is a cyclo-oxygenase inhibitor and therefore reduces platelet aggregation however its effectiveness is limited in the presence of thrombin and ADP induced platelet activity. Clopidogrel on the other hand acts by blocking the ADP receptors on the platelets, thereby reducing platelet aggregation. The CURE study (Clopidogrel in Unstable angina to prevent Recurrent Events) showed that combination of clopidogrel and aspirin anti-platelet therapy reduces ischemic events compared with aspirin therapy alone [15]. These findings are consistent with those of the CAPRIE study

(Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events), which showed superior reduction in ischemic events with clopidogrel therapy compared with aspirin, and which may be explained in part by aspirin resistance [16] [17].

The role of Clopidogrel in reducing perioperative cardiac events in patients undergoing non-cardiac vascular surgery has not been assessed. We hypothesised that patients pre-operatively on clopidogrel would exhibit a lower risk of major adverse cardiac events (MACE) *i.e.*, acute coronary syndromes and myocardial infarctions, in the setting of non-cardiac vascular surgery.

2. Methods

2.1. Recruitment

The study is a prospective observational study, including patients who are scheduled for a major non-cardiac vascular surgery, including all types of bypass operations, aneurysm repair, both open and endovascular and carotid endarterectomy.

Patients were approached either at the time of agreeing to be listed in the vascular surgery clinics, or when they were admitted electively. Alternatively, those who present as emergencies and require in-patient surgery were seen on the ward and invited to participate. A patient information pack was provided, and once this had been read and the individual had decided to participate, written consent was obtained.

2.2. Ethics

This paper received ethical approval from the Royal Liverpool and Broadgreen University Hospital.

All workings in this paper were carried out in accordance with the WMA declarations of Helsinki.

2.3. Informed Consent

All patients provided informed written consent for their participation in this study.

2.4. Exclusion Criteria

Patients were excluded if:

- Unable to give or unwilling to give informed consent,
- Clinical evidence of an acute infection at the time of pre-operative assessment,
- Had known acute coronary syndrome within the preceding 3 months.

2.5. Endpoints

The endpoint of the study was the occurrence of an intermediate or high risk acute coronary syndrome peri-operatively. This was determined by a rise in the serum cardiac troponin ($T \geq 0.06$ ng/ml). Cardiac troponins are recognised to be highly sensitive and specific biochemical markers for myocardial necrosis and predict

increased risk of mortality and re-infarction in patients presenting with acute coronary syndrome (ACS) [18] [19]. It is appreciated that it remains debated what cut-off value of troponin should be used to define a clinically important MI. This study used a recognised cut off value of troponin T of ≥ 0.06 given previous work has shown this parameter to be associated with a significantly adverse prognosis [20]-[22]. It is also considered that where troponin levels may not always be pathological a change in the post-operative ECG, with the development of new pathological q waves or T wave inversion in two or more consecutive leads was also accepted as an end point. These changes were reviewed by two separate observers, and agreement was required for ECG criteria to be accepted as an endpoint. In this study, stroke was also defined as a major adverse cardiac event.

2.6. Data Collection

Preoperative data was collected within seven days of the intended date of operation. The collected clinical variables were determined by the parameters measured in the Eagle vascular surgical risk index [23], *i.e.* q waves on the ECG, a history of angina, history of ventricular ectopy requiring treatment, diabetes mellitus or age greater than 70. Medical history including the drugs history and currently prescribed medications were recorded from the patient notes and a breakdown of these can be seen in **Table 1**. A further assessment was made within 48 hours of surgery to determine that there was no sign of a clinically apparent acute infection, in accordance with the exclusion criteria. Blood samples were collected pre-operatively to ensure that the troponin T was normal, as a raised level would indicate a recent ACS and thus lead to exclusion of the patient. Similarly pre-operative baseline ECG was performed to assess for ECG changes complying with primary end point analysis.

Table 1. The drugs history and currently prescribed medications were recorded.

	Previous coronary artery disease	Previous MI	Previous CABG	PVD	Diabetes	Hypertension	High cholesterol
Not on clopidogrel	17	9	6	11	21	29	24
On clopidogrel	3	6	2	5	4	9	13
Total	20	15	8	16	25	38	37

MI: Myocardial Infarction, CABG: Coronary Artery Bypass Graft, PVD: Peripheral Vascular Disease.

Post-operatively blood samples for troponin-T were taken on day-2 and day-4 and an ECG was performed after day-2. Patients who were discharged before collection of the first sample of troponin-T were excluded and those who were discharged before day 4 in whom no endpoint had been noted were assigned to the no-endpoint group.

3. Statistical Analysis

Statistical analysis was performed using SPSS software. The Chi square test was used for non-parametric testing and p values were expressed using Fisher's exact test. Eagle risk scores were analysed by using t-test and presented as mean ± S.E.M. A p-value of < 0.05 was statistically significant.

4. Results

In total 101 candidates were identified for assessment and off those, 75 were deemed eligible for participation. These participants were then subdivided into two groups, those who were known to be taking clopidogrel prior to surgery and those who were not on clopidogrel prior. 14 patients were identified to be taking regular clopidogrel prior to surgery.

75 patients fulfilled the inclusion criteria. Out of those 27 (36%) had peripheral arterial bypass surgery, 24 (32%) had endovascular repair, 13 (17%) had carotid endarterectomy and 11 (15%) underwent open aortic abdominal aneurysm (AAA) repair. Of the 75 eligible participants, 14 were taking clopidogrel prior to surgery.

13 major adverse cardiac events (MACE's) were noted. These include 1 individual who had a stroke, 5 who had isolated raised troponin, 3 who had isolated ECG changes and 4 who had both raised troponin and ECG changes. Of the 13 MACEs recorded, 0 participants were noted to be on clopidogrel prior to surgery ($p = 0.03$). Out of the 13 MACE's identified the majority occurred in patients undergoing AAA repair [4 of 11 patients (45.4%) in open repair and 6 of 24 patients (20.8%) in EVAR repair]. 3 MACE's were noted post bypass operation and 0 were recorded post endarterectomy (Figure 1(a) & Figure 1(b)).

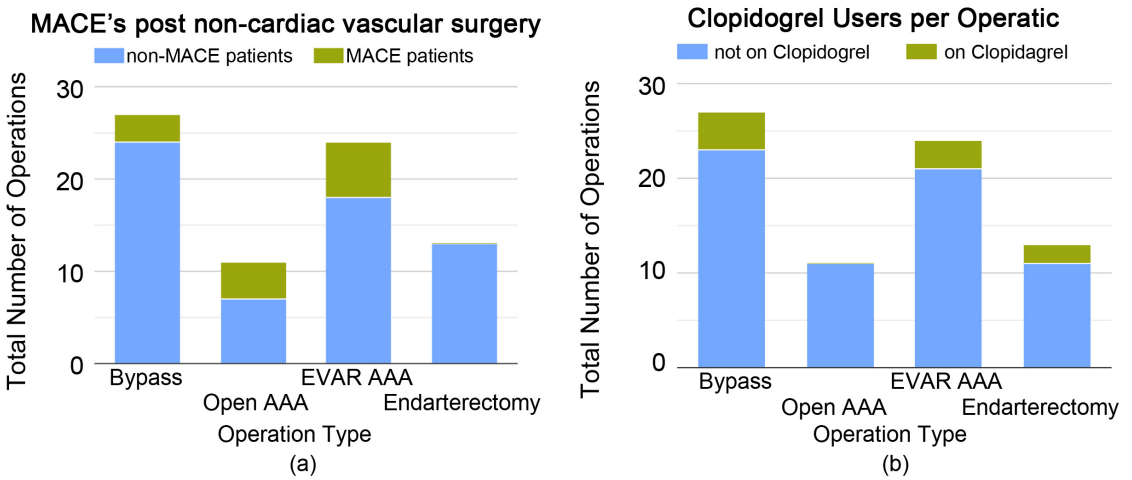

Figure 1. (a): A total of 75 operations were included for study. 27 bypass operations, 11 open AAA repairs, 24 EVAR repairs and 13 carotid endarterectomies. A total of 13 post operative MACE's were recorded: 3 post bypass, 4 post AAA repair & 6 post EVAR repair. There were no recorded MACE's post endarterectomy. (b): A total of 75 operations were included for study. 27 bypass operations, 11 open AAA repairs, 24 EVAR repairs and 13 carotid endarterectomies. 14 participants were recorded to be on clopidogrel pre operation, 4 scheduled for bypass operations, 3 scheduled for EVAR & 7 scheduled for endarterectomy. There were no clopidogrel users scheduled for open AAA repair.

When assessing Eagle Risk Criteria; 45 patients met one identifiable criterion, 11 had two or more identified criteria and 19 met no Eagle risk criteria. In the clopidogrel group 67% of patients had one or more Eagle risk criteria. The mean Eagle risk score was 1.22 ± 0.93 in the non-clopidogrel group while the clopidogrel group had a mean Eagle Risk Criteria of 0.92 ± 0.75 ($p = 0.3$). Patients with one or more Eagle risk criteria experienced more cardiac events than those who didn't have any criteria (30.4% vs. 11.1%, $p = 0.05$).

5. Discussion

The major finding of this study was that despite a similar risk profile to those not on clopidogrel, patients on clopidogrel had significantly fewer post-operative MACE'S than those who were not. 0 MACE's were recorded in patients taking clopidogrel. These findings were noted despite stopping the clopidogrel perioperatively [24]. Perioperative major cardiac events are common in patients undergoing non-cardiac surgery and myocardial infarction is considered to be the commonest cause of death in post-operative patients [25] [26]. These cardiac complications are a major problem for surgeons and physicians as they continue to occur despite pre-operative investigations and appropriate medical therapies and have become a major concern during the post-operative period [27]. Our study demonstrated the same elevated peri-operative cardiac risk in vascular surgical patients that has been reported in several studies [23] [28]-[33].

The assessment of potential vascular surgical patients has changed dramatically over the years. The task force of the American College of Cardiology and the American Heart Association has published guidelines for the pre-operative evaluation of such patients and according to these guidelines, those who have risk factors such as myocardial infarction, congestive cardiac failure and diabetes mellitus should undergo non-invasive cardiac evaluation before surgery [20]. Despite this, the rate of post-operative MACE's remains high at up to 13% [2] and thus further strategies are required to attempt to reduce this burden of risk.

Eagle and his colleagues [34] identified five clinical indicators (age > 70, angina, Q waves on the ECG, diabetes, treated ventricular ectopias) that predicted post-operative cardiac events in non-cardiac vascular surgery. Clinical scoring systems are important and can help in predicting the risk of perioperative MACE. The Eagle scoring system is one of the available evaluation methods [34]; others include the Goldman and Detsky indices, which were developed for risk evaluation in general surgery and predict the risk of coronary events between 0.4% and 56% [1] [26] [35], depending on the type of surgery and the clinical profile of the patient. These have the advantage of being easy to use, as they employ easily determinable clinical parameters, but they tend to define intermediate groups with widely divergent risk estimates and also may underestimate the chance of perioperative MACE in vascular surgery patients [28]. In our study we have demonstrated that patients who had one or more Eagle risk criteria had an increased risk of major adverse cardiac events compared to those who did not have any risk

criteria. The mean Eagle risk scores were not statistically significantly different between the clopidogrel and non-clopidogrel groups. The type of vascular surgery is also important and in this study patients who underwent AAA repair, either open or EVAR experienced more MACE's. We also noted that the number of patients taking clopidogrel in this group was smaller than patients undergoing peripheral arterial and carotid surgery. There was no statistically significant major bleeding noted in either group.

Platelets have a well-established role in atherosclerosis and arterial thrombosis [12]. As discussed before platelets are important in the formation of a thrombus that can cause total or sub-total occlusion of the coronary arterial tree. Clopidogrel acts by inactivating platelet ADP receptor in a dose-dependent manner and is found to be more effective in reducing thrombotic events in patients with symptomatic atherosclerotic disease in a large, randomized clinical trial with a similar safety profile as aspirin [16] [18]. Clopidogrel also prolongs bleeding time approximately twofold [36] [37]. The prolonged bleeding time can return to normal after ten days of therapy being stopped. This represents the life span of platelets which is also approximately ten days. The mechanisms explained earlier may be the reason that clopidogrel showed benefit in reducing the cardiac risks in vascular surgical patients in this study. This effect of clopidogrel has not been assessed in the past and to the best of our knowledge our study is the first to identify the benefit of clopidogrel.

It is now clear that peri-operative cardiac events have multifactorial aetiology. During the peri-operative period the levels of catecholamines are high giving rise to a high sympathetic drive. Beta-blockers decrease sympathetic activation thus producing negative inotropic and chronotropic effects, resulting in a subsequent decrease in myocardial oxygen demand. Beta-blockers have also been shown to decrease the incidence of peri-operative complications in patients undergoing non cardiac surgery and this beneficial effect of beta-blockers has been demonstrated in intermediate and high-risk patients undergoing non cardiac surgery [5] [6] [38]. Therefore, the preoperative and peri-operative use of beta-blockade in patients undergoing non cardiac surgery has become the standard of care. There are some limitations in the use of beta-blockers such as severe airway disease and severe left ventricular dysfunction and especially in patients with severe vascular disease their use may be very restricted. This study is unable to demonstrate a lower rate of cardiac complications in patients receiving beta-blockers at the time of surgery. Possible explanations for this may be the smaller number of patients in the study (only 18 patients were on beta blockers), secondly patients with known coronary artery disease are more likely to be on beta-blockade therapy, as it is the standard of care in this group and hence, the beneficial effect of beta-blockers might be offset by the higher likelihood for complications in this subgroup and thirdly, we were not aware of the duration of time that the patients had been placed on beta-blockers.

Statins have properties of plaque stabilization and may prevent cardiac events.

There are a few studies [39]-[41] which showed some promising results in favour of statins in reducing coronary events, however the numbers of events in these studies were few and therefore further studies are required to confirm these effects. Given the limited current evidence, the effectiveness of peri-operative use of statins remains uncertain. This controversial beneficial effect of statins in reducing coronary events in surgical patients which was reported earlier was not demonstrated in our study.

There were some limitations to our study firstly, the cut-off value of troponin-T used in our study was 0.06 ng/ml although in some studies the level of 0.03 ng/ml has been associated with increased risk of myocardial damage in predicting long term survival [42]. However, the cut off value of 0.06 has shown to be significantly associated with adverse prognosis [20]-[22]. Secondly, our study was not designed to fully evaluate the complications like bleeding that can be associated with clopidogrel therapy. The total number of patients in the study was relatively small, as was the group taking clopidogrel but despite this a statistically significant benefit for those on clopidogrel was demonstrated, which could not be explained on the basis of their risk profile, as 67% of patients on clopidogrel had at least one Eagle risk criteria and as discussed earlier there were more MACE if patients had one or more than one risk criteria.

In conclusion, we report that clopidogrel can reduce the number of major adverse cardiac events preoperatively in patients undergoing major noncardiac vascular surgery despite stopping it peri-operatively. This effect of clopidogrel was also noted in higher risk patients. Other medicines, particularly beta-blockers did not influence the outcome. These results suggest the need for a randomised, controlled trial to confirm our findings.

Declarations

The authors declare no conflicts of interest.

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