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OPCAB Therapy Survey: Off-Pump Clopidogrel, Aspirin or Both Therapy Survey

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ABSTRACT

Background: Standards for heparinization during off-pump coronary artery bypass (OPCAB) are lacking. Similarly, there are no established standards for antiplatelet therapy before or after OPCAB. The aim of this study was to determine current practices and standards for both antiplatelet and heparin therapy in OPCAB.

Methods: A postal, multiple-choice survey questionnaire was sent to 800 randomly chosen cardiothoracic surgeons in the United States and Canada. Responses were tabulated and analyzed.

Results: The overall response rate was 38% (304 surgeons). The respondents performed CABG in centers with an overall volume between 240 and 1,250 procedures per year (average 380 procedures per year). OPCAB procedures within the same institutions ranged from 20 and 375 cases per year. Sixteen percent (48) of the respondents routinely administer antiplatelet therapy preoperatively; of these, 18% (9) use clopidogrel (Plavix) and 65% (31) aspirin. Eighty-eight percent (267) of the respondents routinely administer antiplatelet therapy after OPCAB. Of these, 24% (65) use clopidogrel and 74% (197) aspirin. Anticoagulation protocols during OPCAB were more variable with 28% (85) administering full dose of heparin, 54% (164) administering half dose heparin, and 13% (40) administering 1/3 dose of heparin during construction of coronary anastomoses. Although 10% (30) maintain an activated clotting time (ACT) above 400 seconds, 70% (213) are content with an ACT above 300 seconds and less than 400 seconds, and 20% (61) responded as "other". The average blood shed postoperatively was 600 ml (range 300 ml and 1 liter). Forty percent (122) administer protamine at half dose, and 60% (182) administer a full dose.

Conclusion: Although the vast majority of surgeons use antiplatelet therapy postoperatively, a minority administer preoperative antiplatelet agents for OPCAB. The majority of surgeons use a half dose of heparin during OPCAB with ACT maintained above 300 seconds (> 80%). Prospective studies are necessary to determine the short and intermediate effects of antiplatelet therapy and heparinization doses in OPCAB surgery.

INTRODUCTION

Coronary artery bypass grafting (CABG) without cardiopulmonary bypass (CPB) has been introduced and popularized as an alternative to conventional myocardial revascularization in the treatment of coronary artery disease [Cohn 1998a, Cohn 1998b]. Although the long-term studies of beating heart coronary revascularization are in progress, the short and midterm efficacy and safety of CABG without CPB have been substantiated by numerous investigations [Subramanian 1997, Califiore 1998, Mack 1999, Cremer 2000]. Refinements in surgical techniques have been made to avoid hemodynamic compromise [Bergsland 1999], improve target vessels exposure, and achieve better mechanical epicardial stabilization [Soltoski 1999]. These advancements have substantially improved the safety and reliability with which distal coronary anastomoses can be made on the beating heart.

Although strict surgical protocols have been suggested to standardize the performance of OPCAB, no specific rules have been proposed for heparinization and platelet antiaggregation in OPCAB patients. On the basis of these considerations, several questions and concerns have arisen regarding the practice of antiplatelet therapy before and after OPCAB, and also the amount of heparinization required to perform these operations safely. The aim of the present study was to determine if, in the practice of the North American cardiac surgeons, 1) there is a uniform strategy for antiplatelet therapy before and after OPCAB, and 2) there is a standard for perioperative heparinization during OPCAB.

MATERIALS AND METHODS

In September 2000, a postal, multiple-choice survey questionnaire was sent to 800 randomly chosen cardiac surgeons practicing in the United States and Canada. The questionnaire was sent twice to maximize response rates and results were tabulated. Survey questions attempted to quantify the total num-

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Table 1. OPCAB survey submitted to 800 North American surgeons with a 38% response rate

Q-1:	How many CABGs/year are performed in your center?
Q-2:	How many OPCABs/year are performed in your cenetr?
Q-3:	For how many years you have been performing OPCAB?
Q-4:	Do you administer preoperative antiplatelets before OPCAB?
Q-5:	Which type of antiplatelet drug do you use?
Q-6:	Do you administer postoperative antiplatelets after OPCAB?
Q-7:	Which type of antiplatelet drug do you use?
Q-8:	For how long do you normally administer antiplatelet therapy after OPCAB?
Q-9:	Did you ever find anastomotic thrombi during OPCAB?
Q-10:	Have you noticed a higher incidence of deep venous thrombosis or pulmonay embolism after OPCAB?
Q-11:	How much heparin you administer during OPCAB?
Q-12:	Which ACT do you consider ideal during OPCAB?
Q-13:	Do you think that partial heparinization determines a lower incidence of perioperative bleeding?
Q-14:	How much protamine do you administer after OPCAB?
Q-15:	How much is your average intraoperative bleeding?
Q-16:	How much is your average postoperative bleeding?

ber of coronary procedures performed in the respondent's institution, the proportion performed as OPCAB procedures, and the number of years the respondent has practiced OPCAB. Several questions were formulated to determine whether preoperative, postoperative, or both preoperative and postoperative antiplatelet therapy is given to elective OPCAB patients, the types of common antiplatelet agents administered, and the duration of therapy thereof. In addition, several questions were formulated in order to identify the heparinization protocols during OPCAB, including heparin doses administered, ACT targets achieved, and reversal practices with protamine. The amount of shed blood during OPCAB and following the procedure were also collected in this survey analysis. The survey questions are listed in Table 1 (◎).

RESULTS

Of the 800 cardiac surgeons to whom the multiple-choice survey questionnaire was sent, 304 (38%) responded. The first question asked (Table 1, ◎) refers to the approximate number of CABG performed per year in the respondent's institution. The respondents performed CABG in centers that had an overall volume between 240 and 1,250 procedures per year (average 380 procedures per year) (Table 2, ◎). The second question related to the number of OPCAB cases performed in the respondent's institution. The number of OPCAB procedures within the same institutions ranged from 20 and 375 cases per year (average 74 OPCAB per year) (Table 2, ◎). The percent of CABG performed as OPCAB in these institutions ranged from 3% to 94%. The respondents indicated that they have been performing OPCAB for an average of 3.2 years (range 2 to 11 years). Questions 4 and 5 refer to the practice of preoperative antiplatelet therapy in OPCAB.

Table 2. OPCAB survey: results in 304 respondents

Q-1 # Cases/year	240-1250 (380)
Q-2 # OPCAB/year	20-375 (74)
Q-3 #years performing OPCAB	2-11 (3.2)
Q-4 Use Preop Antiplt Therapy	16% (48)
Q-6 Use Postop Antiplt Therapy	88% (267)
Q-9 Experienced Anastomotic Thrombosis	12% (36)
Q-10 Have normal incidence DVT or PE	98% (298)
Q-13 Partial heparin has _ bleeding	84% (255)
Q-14 Use full dose protamine	60% (182)
Q-15 Average Intraop Bleeding	200ml-1.5l (500ml)
Q-16 Average Postop Bleeding	300ml-1l (600ml)

Sixteen percent (48) of the respondents routinely administer antiplatelet therapy preoperatively (Table 2, ◎). Of those who administer preoperative antiplatelet therapy, 18% (9) administer clopidogrel alone, 65% (31) administer aspirin alone, and 15% (7) administer both clopidogrel and aspirin before elective OPCAB (Figure 1, ◎). The remaining 2% (1) use either dipyridamole or ticlodipine (Figure 1, ◎). These medications are continued until the morning of surgery. Questions 6, 7, and 8 are about postoperative antiplatelet therapy. Eighty-eight percent (267) (Table 2, ◎) of the respondents routinely administer antiplatelet therapy after OPCAB. Of these, 24% (65) administer clopidogrel postoperatively and 74% (197) aspirin (Figure 2, ◎). The remaining 2% (5) use a combination of the two medications (Figure 2, ◎). Clopidogrel therapy continued for four weeks in 38% (27), six weeks in 28% (19), one year in 10% (7), and indefinitely in 24% (17).

Question 9 investigated the possibility of perioperative graft thrombosis during OPCAB. Twelve percent (36) of the respondents stated that they have had thrombosis of coronary grafts "unrelated" to technical imperfection during OPCAB (Table 2, ◎). Eighty-eight (268) percent have never experienced prothrombotic complications related to OPCAB. Similarly, the vast majority of respondents (98% = 298) did not report an increased incidence of deep venous thrombosis in patients following OPCAB, as compared to CABG performed with cardiopulmonary bypass (CPB) (Table 2, ◎).

Questions 11, 12, and 13 dealt with anticoagulation protocols with heparin. Anticoagulation protocols during OPCAB were more variable with 28% (85) of surgeons administering a full dose of heparin, 54% (164) of surgeons administering a half dose heparin, and 13% (40) of surgeons administering one-third of the full dose of heparin (Figure 3, ◎). Five percent (15) of the respondents administer variable doses of heparin during OPCAB. Although 10% (30) of the surgeons maintain an ACT above 400 seconds, 70% (213) are content with an ACT above 300 seconds and less than 400 seconds, and 20% (61) responded as "other" (Figure 4, ◎).

Question 13 deals with intraoperative bleeding during OPCAB. Eighty-four percent (255) believe that partial heparinization is associated with less intraoperative bleeding during OPCAB (Table 2, ◎), and 16% (49) believe that it does not affect the amount of intraoperative bleeding.

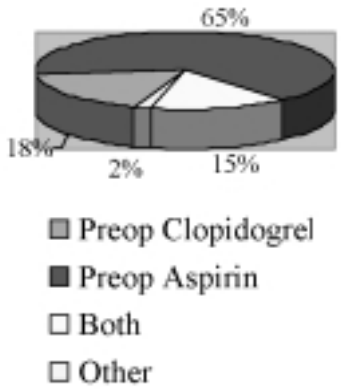

Figure 1. PreOPCAB antiplatelet therapy: clinical strategy in 48 respondent surgeons

Question 14 looks at reversal of heparin effect with protamine. Forty percent (122) of the surgeons administer protamine at half dose, and 60% (182) administer a full dose of protamine for reversal of heparin effect. A significant number of surgeons responded in the comments section that they do not have anticoagulation protocols for OPCAB, and that the heparinization schedule is individualized with a "shoot from the hip" approach.

Questions 15 and 16 deal with intraoperative and postoperative bleeding in OPCAB. The average intraoperative bleeding reported with OPCAB was 500 ml (range 200 ml and 1.5 liters), and the average blood shed postoperatively was 600 ml (range 300 ml and 1 liter).

COMMENT

During the past decade, the evolution of techniques of myocardial revascularization without CPB has resulted in the widespread popularization of this technique as a valid alternative to conventional coronary revascularization [Calafiore 1996, Mack 1997, Bergsland 1998]. Although these advancements have substantially improved the safety and reliability with which

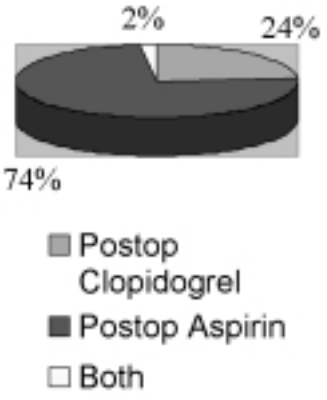

Figure 2. Post-OPCAB antiplatelet therapy: clinical strategy in 267 respondent surgeons

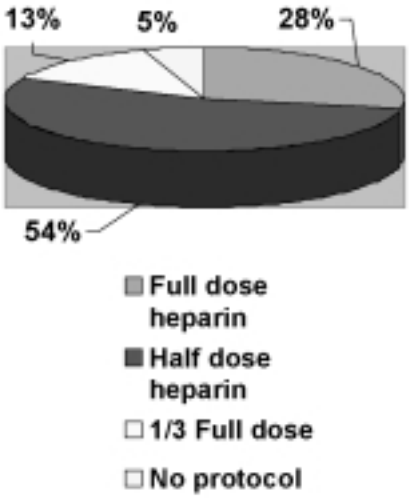

Figure 3. OPCAB heparinization protocols in 304 surgeons

OPCAB can be performed routinely, the effects and indications for antiplatelet therapy and heparinization in OPCAB patients remain unknown. Several questions and concerns may arise as to the practice of antiplatelet therapy before and after OPCAB, and also the amount of heparinization required to perform these operations safely. The aim of the present study was to determine if (1) there is a uniform practice for antiplatelet therapy before and after OPCAB, and (2) a standard for heparinization during OPCAB. The data shown in our survey, along with numerous studies and investigations on techniques of off-pump myocardial revascularization recently published in the literature [Mack 1997, Cohn 1998a, Cohn 1998b, Bergsland 1998], clearly demonstrate an increasing interest of cardiac surgeons in the OPCAB procedure. Nevertheless, the practice pattern of cardiac surgeons in regards to antiplatelet therapy and heparinization for OPCAB is highly variable and standard protocols have not yet been developed.

Unlike conventional surgery on CPB, OPCAB surgery does not trigger the systemic inflammatory response but surgical tissue trauma remains a constant between the two techniques. The preserved hemostasis achieved by using the OPCAB tech-

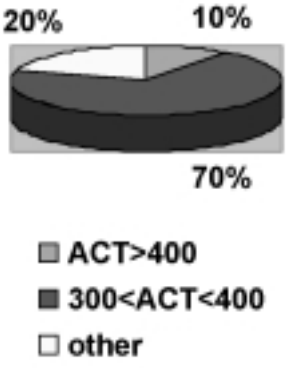

Figure 4. ACT protocols during OPCAB in 304 respondent surgeons

nique may lead to a procoagulant state, as already reported for major general surgery procedures. On the contrary, whenever hemostasis is impaired, i.e., in the conventional CABG on CPB, the chances of microvascular thrombosis are reduced. As a consequence the risk of anastomotic thrombosis unrelated to technical mistakes should be greater in OPCAB patients.

In our experience anastomotic thrombosis has been diagnosed in more occasions during OPCAB [D'Ancona 2000]. Intraoperative graft flow measurements are very useful in diagnosing anastomotic thrombosis. Surgeons who do not use any method of graft patency verification are not aware of their patency rates and cannot prevent intracoronary thrombosis that may occur during OPCAB as a consequence of insufficient anticoagulation. Other authors [Mariani 1999] have reported cases of intracoronary thrombosis and episodes of pulmonary embolism in OPCAB.

In a recent prospective study, Mariani et al. [Mariani 1999] have tested the procoagulant activity in a series of 22 patients undergoing off-pump CABG. Prothrombin F1-2, factor VII, and fibrinolysis degradation products were sampled to test the coagulation activity. Platelet activation was tested by sampling b-thromboglobulin and von Willebrand factor. Blood samples were taken at different intervals during the operation and after 24 hours. Procoagulant activity, represented by prothrombin F1-2, increased significantly only 24 hours after surgery. A depletion of coagulation factors in the extrinsic pathway was indicated by a significant decrease of factor VII 24 hours after surgery. Fibrinolysis was also activated as indicated by an increase in the level of degradation products at postoperative day one. A significant increase of von Willebrand factor was also noticed at day one. However, b-thromboglobulin and platelets count remained unchanged. This study clearly shows that the procoagulant activity of OPCAB is significant mainly 24 hours after surgery and is somewhat independent of platelets activation. Unfortunately this study lacks a control group of patients operated on-CPB. However similar results have been proposed for patients operated on-CPB in which a procoagulant state with increased prothrombin fragments 1-2, decreased factor VII, and delayed fibrinolysis have been documented [Boislair 1993]. On the basis of these observations, we have recently started to use a more aggressive protocol for heparinization and antiplatelet therapy in OPCAB patients [Bergsland 2000].

Heparinization: We use to fully heparinize our OPCAB patients, keeping an ACT between 400 and 500 seconds. The ideal target is 400 seconds and ACT levels are rechecked frequently during the procedure. A more aggressive anticoagulation is also justified by the fact that, in patients with heparin resistant thrombin activity, intravascular thrombosis is more likely to occur whenever the ACT remains below 300 seconds after the administration of heparin [Oltrona 1996, Petaja 1996, Violaris 1996]. We have found that intraoperative bleeding is acceptable if accurate surgical hemostasis is performed before giving heparin. We immediately filter and recirculate the shed blood to maintain adequate intracardiac filling pressures during the different maneuvers of elevation and rotation of the heart [Bergsland 2000].

Protamine administration: At the end of the procedure, we partially (50%) reverse the heparin effect with protamine. If the diathesis is acceptable, we do not administer any protamine.

Perioperative and postoperative bleeding: Bleeding is significantly reduced in OPCAB patients [Puskas 1998, Lancey 2000, Nader 2000] together with the total number of blood transfusions [Yokoyama 2000]. The results of our study show an average postoperative bleeding of 600 ml as reported by the surgeons interviewed. Our findings on more than 1,200 patients operated off-CPB are comparable.

Antiplatelet therapy: If the directions for intraoperative heparinization are still very empirical, the indications for preoperative and postoperative antiplatelet therapy are even more undetermined. Only 16% out of 304 respondents are routinely administering antiplatelet therapy preoperatively. The preferred medication is aspirin (80%). We are routinely using preoperative aspirin; in all our OPCAB patients 325 mg of aspirin are given till the day of surgery. Secondary prevention with antiplatelets has proven to be very effective in patients that have undergone CABG [Makkar 1998, Topol 2000]. In our survey, 88% of the respondents are routinely using antiplatelets after OPCAB. The majority of them (74%) prefer aspirin. The Antiplatelet Trialists' Collaboration demonstrated a significant benefit of aspirin over placebo in maintaining graft patency [Antiplatelets' Trialists Collaboration 1994]. Despite the benefits of aspirin, a large recurrence rate is present after conventional CABG [Bhatt 2000].

The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study was a multicenter randomized trial including 19,185 patients and comparing the effects of an ADP receptor antagonist (clopidogrel) versus aspirin. The trial showed superiority of clopidogrel in reducing recurrent ischemic events with fewer bleeding complications. In 1,480 patients with previous history of cardiac surgery, the effects of long term therapy with clopidogrel were even more evident and clopidogrel resulted in a reduction in vascular death, myocardial infarction, stroke, or re-hospitalization with a 31.2% relative risk reduction (95% CI, 15.8 to 43.8; P=0.0003) [Bhatt 2001].

Since June 2000, we have started an aggressive secondary prevention with clopidogrel after OPCAB. A 75-mg dose is given the night of surgery and is continued for at least one month after the operation. In the majority of patients, clopidogrel is associated with aspirin at doses of 325 mg per day. Current research is focusing on the possible additive effect of aspirin and clopidogrel in preventing recurrent cardiac events [Harker 1998]. The Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) and the Clopidogrel for Reduction of Events During Observation (CREDO) trials will randomize more than 10,000 patients to determine if combined therapy with clopidogrel and aspirin represents the future of antiplatelet management. In our analysis, only 24% of the respondents are currently using clopidogrel for secondary prevention after OPCAB. Most of the surgeons are possibly concerned about the possible side effects of this drug. In reality, clopidogrel is as equally well tolerated as aspirin [CAPRIE Steering Committee 1996]. Furthermore, there is evidence that 10-40% of patients have inadequate antiplatelet response to aspirin developing resistance after one week of therapy [Barnathan 1987, Cohen 1997]. Of more concern, there appears to be an association between concomitant aspirin and ACE inhibitor use and increased mortality [Peterson 2000].

CONCLUSION

The feasibility of OPCAB has been proven and standard surgical techniques have been proposed to ease the construction of coronary anastomoses on the beating heart. The differences between OPCAB and traditional CABG on CPB go well beyond the pure surgical technique. Different strategies should be kept in perspective for an appropriate pharmacological management of the OPCAB patients. Particular attention should be directed to the preoperative, perioperative, and postoperative treatment of the OPCAB candidates. Adequate levels of anticoagulation and aggressive platelet antiaggregation should be considered to prevent the procoagulant activity of these patients. Inadequate pharmacological management could compromise graft patency rate and determine unjustified criticism towards this revolutionary technique.

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