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Preoperative aspirin and heparin therapy does not increase perioperative blood loss and blood product requirements in coronary artery bypass graft surgery

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Abstract
Purpose. The effects of preoperative aspirin (ASA) and/or heparin therapy on perioperative blood loss and transfusion requirements were studied in patients undergoing primary coronary artery bypass graft (CABG) surgery using perioperative blood cell salvaging techniques.
Methods. The amounts of perioperative blood loss and transfusion requirements were recorded in four groups of patients, based on the preoperative medication: ASA group (51 patients), heparin group (33 patients), and ASA plus heparin group (38 patients), as well as a control group (49 patients who received neither of these medications).
Results. There were no significant differences among the four groups in cardiopulmonary bypass time, aortic cross clamp time, or the number of coronary artery grafts performed. Postoperative blood loss was highest in the ASA group, followed by the control, the ASA + heparin, and the heparin groups. Neither postoperative blood loss nor transfusion requirements showed significant differences among the four groups. Simultaneous administration of heparin with ASA also did not increase the blood loss or transfusion requirements.
Conclusion. Preoperatively administered aspirin and/or heparin did not significantly increase perioperative blood loss or the total amount of transfusion requirements. It is not necessary to delay elective CABG if blood cell salvaging techniques are used.

Key words: Aspirin, Heparin, Blood loss—surgical, Blood transfusion—autologous, Coronary artery bypass

Introduction

The antiplatelet and antithrombotic effects of aspirin (ASA) reduce the incidence of myocardial infarction without influencing the progression of the disease [1,2] and improve post-coronary artery bypass graft (CABG) graft patency [3]. An alternative to ASA for preventing myocardial infarction is continuous heparin infusion, which retards the coagulation rate, but this therapy requires patients to be hospitalized. Despite some adverse effects of ASA and heparin treatment during and after surgical procedures (such as increased bleeding, thrombocytopenia, gastric irritation or ulceration), there have been beneficial effects from the increasing use of these agents before surgery. Studies of the effects of preoperative ASA administration in patients undergoing CABG have been inconclusive, showing either increased blood loss [4–6,8,16] and transfusion requirements [5,6,8,16], and re-exploration for postoperative bleeding [6,8] or no increase in transfusion requirements [7,9] or postoperative blood loss [9,10].

This study was designed to assess the effects of preoperative ASA therapy on perioperative blood loss and allogeneic blood transfusion requirements in patients undergoing primary coronary bypass surgery when a blood cell salvaging technique was used perioperatively. Heparin also influences hemostasis via its fibrinolytic potential and possibly by activating platelets [11]. However, few studies have examined the effect of preoperative heparin given simultaneously with ASA on perioperative blood loss and allogeneic transfusion requirements. We therefore studied whether the continuous infusion of heparin in addition to ASA therapy increased perioperative blood loss and allogeneic transfusion requirements.

Methods

The institutional review board of the St. Louis University Hospital approved this project. Since this study was a retrospective analysis of medical records, written

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informed consent from the study patients was not required. The medical records of 177 consecutive patients who underwent a primary coronary artery bypass procedure at the St. Louis University Hospital were retrospectively reviewed. Patients who had a combined cardiac operation, heart transplantation, or previous cardiac operation were not entered in the study. All patients who had taken 325 mg of ASA daily within a week prior to surgery were included in the ASA group. Patients who were given a continuous heparin infusion, with partial thromboplastin time (PTT) at a therapeutic level (1.5–2 times normal) at the time of arrival in the operating room were included the heparin group. The ASA + heparin group consisted of patients who received both agents. The control group consisted of patients who received neither ASA nor heparin preoperatively. As no linear correlation between perioperative blood loss and bleeding time has previously been reported [5], and as bleeding time is highly dependent on technique [12,13], bleeding time is not a routine preoperative laboratory test at our institution. However, no patients in this study had clinical evidence of any coagulation disorder.

All patients were anesthetized with a high-dose fentanyl-muscle relaxant-oxygen combination that was, in some patients, supplemented with volatile agents, as previously reported [14]. Cardiopulmonary bypass (CPB) was performed using a membrane oxygenator, and moderate hypothermia was maintained. Patients were systemically heparinized with a loading dose of 300 units of heparin/kg of body weight, and an additional amount of heparin was given to achieve an activated clotting time (ACT) of more than 480 s. After the termination of CPB, heparin was neutralized with protamine sulfate, given at a ratio of 1 mg of protamine to 100 units of residual heparin. Protamine was administered slowly through a central venous port of the pulmonary artery catheter. A further 25–50 mg of protamine was incrementally administered if the post-protamine ACT value was more than 120 s. Packed red blood cells (PRBC) were administered to maintain the hemoglobin level at more than 7 g/dl during CPB. Intraoperative blood cell salvage was performed using the Haemonetics Cell Saver System (Baxter Health Care, Irvine, CA, USA) from the time of skin incision until closure of chest. The remaining blood in the cardiopulmonary bypass circuit was also processed and retransfused in all patients. None of the patients received any pharmacological agents, such as aprotinin, aminocaproic acid, tranexamic acid, or desmopressin to support the coagulation process. In the postoperative period, mediastinal shed blood was collected by the Sorensen Receptal Autotransfusion System (Abbott Laboratories, North Chicago, IL, USA). The salvaged blood was sent to the blood bank for saline washing and concentration before it was retransfused. PRBC, platelets, and fresh frozen plasma (FFP) were transfused at the discretion of the attending surgeons or anesthesiologists. Analysis of variance (ANOVA) was used for continuous data to show differences among groups, and Student-Newman-Keuls or Duncan's test was used when appropriate. A P value < 0.05 was considered statistically significant. When categorical data were used (e.g., sex, emergency operation, any blood product requirements), results were expressed in terms of χ^2 critical values.

Results

ANOVA confirmed no significant differences in age, body surface area, number of vein grafts performed, duration of CPB, aortic cross clamp time, and length of postoperative hospitalization among groups. Correlation coefficients showed significant relationships between blood loss and emergency operation, CPB time, and the number of patients who received an internal mammary artery (IMA) graft. Multiple regression analysis showed differences in sex and emergency operation in the heparin group compared with controls. Significantly more patients in the control group than in the other groups received IMA grafts. Multiple regression analysis showed a significant correlation between volume of chest tube drainage and number of patients receiving IMA grafts in the control ($r = 0.29$; $P = 0.04$) and the ASA + heparin ($r = 0.30$; $P = 0.046$) groups. A significant inverse correlation was found between CPB time and blood loss ($r = -0.35$; $P = 0.047$) in the heparin group. There was no significant relationship between blood loss and emergency operations in any of the groups (Table 1 and 3).

Significant differences were observed in preoperative hematological indices; hemoglobin level was lower in the ASA + heparin and the heparin groups than in the ASA or the control groups. Hematocrit level was lower in the ASA + heparin group than in the ASA or the control groups and the platelet count was lower in the ASA + heparin group than in the control group. Although preoperative PTT and ACT were prolonged in heparinized patients, values obtained immediately after the patients arrived in the intensive care unit did not differ among groups. Hemoglobin levels and platelet counts were lower post-CPB in each group, but significant differences between pre- and postoperative values were not found among the groups (Table 2).

The blood transfusion requirements of the ASA, ASA + heparin, heparin, and control groups were 5.3 ± 4.9, 3.8 ± 4.4, 3.9 ± 3.5, and 3.5 ± 4.1 units, respectively. Only one patient (in the ASA group) received cryoprecipitate. Postoperative blood loss was greatest

Table 1. Perioperative characteristics of groups of patients receiving various preoperative treatments before undergoing CPB

	ASA ($n = 51$)	ASA + Heparin ($n = 44$)	Heparin ($n = 33$)	Control ($n = 49$)
Age (years)	64.5 ± 9.2	63.7 ± 10.4	67.1 ± 9.1	61.7 ± 11.4
Male/Female	38/13	34/10	20/13*	36/13
BSA (m^2)	1.96 ± 0.20	1.94 ± 0.20	1.88 ± 0.22	1.96 ± 0.22
Elective/Emergency	48/3	39/5	24/9**	45/4
No. of vein grafts	2.2 ± 1.2	2.5 ± 0.9	2.3 ± 1.0	2.2 ± 0.8
IMA (%)[a]	64.7	47.7***	45.4***	77.5
CPB time (min)	123 ± 36.7	130.7 ± 41.3	124.2 ± 38.1	139.7 ± 53.8
Aortic clamp time (min)	74 ± 23.3	74.3 ± 26.1	66.4 ± 22.5	81.3 ± 27.4
Postop. hosp. (days)	8.7 ± 1.3	10.5 ± 9.6	8.9 ± 6.3	8.8 ± 3.9

*Significant difference compared with all other groups ($P < 0.05$); **Significant difference compared with all other groups ($P < 0.05$); ***Significant differences compared with ASA and control groups ($P < 0.05$).
Numeric data values are expressed as means ± SD.
n, Number of patients studied; ASA, aspirin; BSA, body surface area; CPB, cardiopulmonary bypass; IMA, internal mammary artery; Postop. hosp, length of postoperative hospitalization.
[a] number of patients receiving internal mammary artery graft.

Table 2. Perioperative hematological indices

	ASA ($n = 51$)	ASA + Heparin ($n = 44$)	Heparin ($n = 33$)	Control ($n = 49$)
Preop. Hb (g/dl)	13.6 ± 1.4	12.6 ± 1.7[1]*	12.8 ± 1.7[1]*	13.6 ± 1.4
Hct (%)	40.2 ± 3.9	37.2 ± 4.6[2]*	38.1 ± 4.7	40.2 ± 4.1
Platelets ($\times 10^3$)	253.0 ± 77.0	240.6 ± 74.0[3]*	247.1 ± 61.5	285.7 ± 84.2
PT (s)	12.1 ± 0.7	12.4 ± 0.7	12.9 ± 1.1	12.3 ± 0.9
PTT (s)	26.9 ± 9.0	71.2 ± 39.5[4]*	74.3 ± 40.3[4]*	25.3 ± 4.1
ACT (s)	152.9 ± 43.8	185.6 ± 48.2[5]*	211.3 ± 90.9[5]*	150.4 ± 48.0
Intraop. ACT (s)	637.7 ± 137.9	575.3 ± 153.3	556.4 ± 142.4	671 ± 157.8
Postop. Hb (g/dl)	10.7 ± 1.6	10.6 ± 1.4	11.1 ± 1.4	10.9 ± 1.2
Hct (%)	31.7 ± 4.7	31.2 ± 3.8	32.7 ± 3.9	32.1 ± 3.7
Platelets ($\times 10^3$)	149.9 ± 51.5	161.6 ± 62.8	148.7 ± 48.7	177.7 ± 60.5
PT (s)	15.7 ± 1.6	14.9 ± 1.4	14.9 ± 1.5	15.5 ± 1.4
PTT (s)	31.5 ± 8.0	30.6 ± 7.0	30.8 ± 8.3	28.9 ± 6.1

[1]* $P < 0.05$ *vs* ASA and control; [2]* $P < 0.05$ *vs* ASA and control; [3]* $P < 0.05$ *vs* control; [4]* $P < 0.05$ *vs* ASA and control; [5]* $P < 0.05$ *vs* ASA and control.
Values are expressed as means ± SD.
n, Number of patients studied; ACT, activated clotting time; ASA, aspirin; Hb, hemoglobin; Hct, hematocrit; Intraop. ACT, ACT during bypass; Preop, preoperative results; Postop, results of the first postoperative blood sample in the intensive care unit; PT, prothrombin time; PTT, partial thromboplastin time.

in the ASA group (1499 ± 958 ml), followed by the control (1260 ± 704 ml), ASA + heparin (1154 ± 692 ml), and heparin (1083 ± 525 ml) groups. Despite these findings, neither postoperative blood loss nor the total amount of transfusion requirements showed significant differences among the four groups (Table 3). However, the number of patients who were not transfused in the control group was significantly greater than that in the other three groups (Fig. 1).

Discussion

ASA induces platelet dysfunction and irreversibly acetylates cyclooxygenase, inhibiting arachidonic acid metabolism, and, as a consequence, thromboxane A2, which is the mediator of platelet aggregation. Platelet function is suppressed for the duration of platelet's life span. The anticoagulant effect of heparin is mediated through its interaction with antithrombin III, which inactivates thrombin, factor Xa, and factor IXa, and inhibits the coagulation process [15]. The CPB procedure itself induces hemostatic dysfunction. During CPB, platelet aggregation abnormalities increased and the total platelet count decreased, but none of these findings were correlated with the volume of chest tube drainage [17]. The correlation between CPB time and postoperative bleeding was mainly due to an impairment of platelet function induced by CPB [18]. In this study, we found no significant difference in CPB time among the four groups examined (Table 1). However, in the heparin group there was an inverse correlation

Table 3. Intra- and postoperative blood loss and homologous transfusion requirements

	ASA (n = 51)	ASA + Heparin (n = 44)	Heparin (n = 33)	Control (n = 49)
Intraoperative salvaged blood (ml)	788 ± 323	666 ± 256	725 ± 324	667 ± 315
Chest tube drainage (ml)	1499 ± 958	1154 ± 692	1082 ± 525	1260 ± 704
PRBC (U)	3.4 ± 1.8	2.5 ± 2.6	2.3 ± 1.85	2.0 ± 1.9
FFP (U)	2.8 ± 2.2	0.8 ± 1.4	1.1 ± 1.8	1.2 ± 2.0
Platelets (No. of patients who received)	14	13	9	10
Cryo (No. of patients who received)	1	0	0	0
Total blood products received (U)	5.3 ± 4.9	3.8 ± 4.4	3.9 ± 3.5	3.5 ± 4.2

There were no statistically significant differences in any of these variables among groups.
Numeric data are expressed as means ± SD.
n, Number of patients studied; Cryo, cryoprecipitate; FFP, fresh frozen plasma; PRBC, packed red blood cells; U, units.

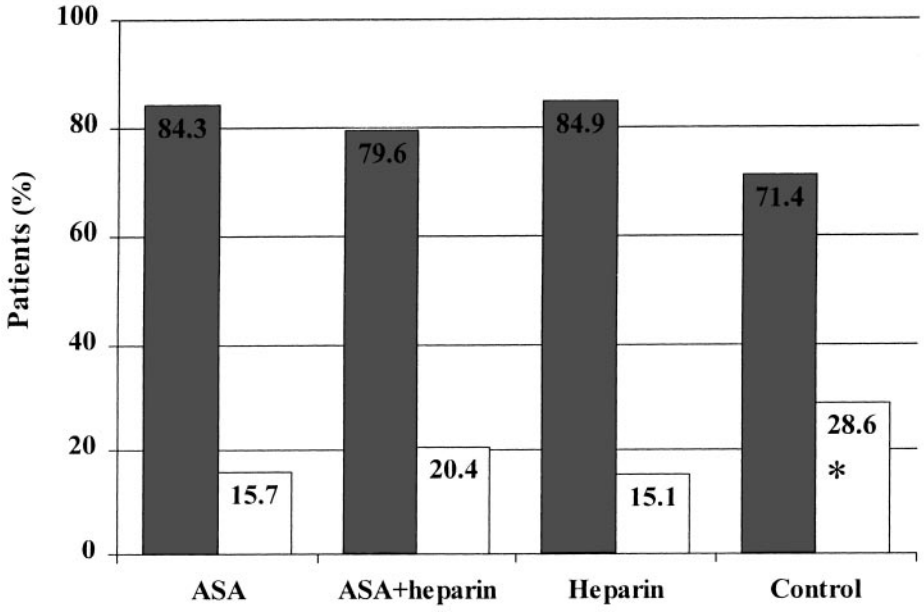

Fig. 1. Percentage of patients who required any allogeneic blood products in the perioperative period. Significantly more patients (* $P < 0.05$) were not transfused in the control group than in the other groups. *Gray bars*, Transfused patients; *white bars*, non-transfused patients

between CPB time and blood loss, although the correlation coefficient was only −0.35. Significantly fewer patients received IMA grafts in the heparin groups compared with the non-heparin groups. IMA grafting is reported to increase blood loss [14]. We believe, that IMA grafting plays a significant role in the negative correlation between blood loss and CBP time, although we were not able to determine the extent of the role IMA grafting played in the correlation observed in this study.

Perioperative blood loss and transfusion requirements did not increase even when heparin was administered simultaneously with ASA in the preoperative period. Reich et al. [7], Rawitscher et al. [9], and Torosian et al. [10] reported similar results. In other studies, preoperative ASA administration was reported to increase postoperative bleeding [4–6,8,16] and blood transfusion requirements [5,6,8,16], and even the incidence of re-exploration for excessive bleeding [6,8] in patients undergoing elective CABG. The different results reported by these studies may be explained in terms of whether any cell salvaging techniques, such as autologous transfusion or hemodilution were used. Hemodilution was reported to be one determinant that decreased transfusion requirements in cardiac surgery [14]. None of the studies reporting increased transfusion requirements used any blood cell salvaging techniques [5,6,8]. On the other hand, either a cell saver or both a cell saver and intraoperative hemodilution were used in the present study and in other studies [7,9] which reported no increase in transfusion requirements. The number of patients studied may influence the statistical

power of analysis; however, the daily dose of ASA was not a factor that influenced differences among the studies [4].

In the present study, we compared the use of the total amount of products transfused, as well as the individual products (PRBC, FFP, and platelets) among the four groups examined and found any differences to be nonsignificant (Table 3). However, the number of patients in the control group who were not transfused during their hospitalization was greater than that in the other three groups (Fig.1). This is not necessarily a new finding. Sethi et al. [6] reported that patients in their ASA group received more blood products (PRBC, platelets, cryoprecipitate, and FFP) than did the patients in the non-ASA group, but there was no difference in the percentage of patients (6.5% *vs* 7%) who received blood products. The higher hemoglobin and hematocrit were positive factors for the decreased transfusion requirements, while, on the other hand, IMA was a negative factor [14]. In the present study, the preoperative hemoglobin/hematocrit ratios, male/female ratios, elective/emergency ratios, and the percentage of patients receiving IMA grafts in the control group were different from these parameters in the other groups. Various factors have been reported as significant for perioperative blood salvage [14]. Whether any one, or combinations of these factors, played a role in the lower number of patients who received transfusion in the control group could not be determined from the results of our study.

In the ASA + heparin group there was neither a synergistic effect on the perioperative blood loss and transfusion requirements, nor a difference in blood loss and transfusion requirements from other groups. This is not an unexpected finding, since the biological half-life of intravenously administered heparin ranges from 60 to 150 min [15], and ACT during and after CPB in the ASA + heparin group was maintained at the same level as in the other three groups. Postoperatively, we observed an increase in the volume of chest tube drainage in the ASA group, as previously reported [4,5]. Reich et al. [7] also reported that the volume of shed blood increased significantly in their ASA group, but allogeneic transfusion requirements were not increased when a blood cell salvaging technique was utilized and strict transfusion criteria were used to avoid transfusion.

The clinical implications of our study are: (1) that it is not justified to delay elective primary coronary surgery for the purpose of discontinuing aspirin, if blood cell salvaging techniques are utilized perioperatively, and (2) that patients would not be exposed to an increased risk of myocardial ischemia by delaying the surgery.

In conclusion, as the present study was retrospective, and the study patients were not randomized to ASA versus heparin, there are limitations to the conclusions we can draw. However, the results indicate that: (1) aspirin and/or heparin therapy did not increase perioperative blood loss and allogeneic transfusion requirements, (2) the volume of blood loss per se was not the major factor for determining transfusion requirements when blood cell salvaging techniques were used meticulously in all patients perioperatively, (3) preoperative infusion of heparin in addition to ASA therapy did not increase perioperative blood loss and allogeneic transfusion requirements compared with ASA or heparin alone and (4) as preoperative anticoagulant therapy with ASA and/or heparin does not affect perioperative blood loss when blood cell salvaging techniques are used, the therapy does not need to be discontinued prior to surgery.

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