# The Effect of Preoperative Aspirin and/or Heparin Therapy on Coagulation and Postoperative Blood Loss after Coronary Artery Bypass Surgery

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**ABSTRACT**

**Objective:** *To assess the effects of preoperative aspirin and/or intravenous heparin therapy on perioperative coagulation tests and postoperative blood loss for 24-hour after coronary artery bypass surgery.*

**Methods:** *Multiple conventional coagulation tests, activated clotting time, thrombelastograph, skin bleeding time and platelet aggregation were performed before induction of anaesthesia, following protamine administration and after skin closure in 45 patients.*

**Results:** *There was no significant difference in either coagulation tests or postoperative blood loss (median of 860 mL with a range of 275 to 2800 mL, versus 833 ml with a range of 500-1380 mL) between the aspirin and no-aspirin patients. Preoperative heparin therapy affected most coagulation tests (e.g. international normalised ratio, activated partial thromboplastin time, thrombin clotting time, prothrombin time, activated clotting time and coagulation time of thrombelastography) before anaesthesia. The effects disappeared following protamine administration and after skin closure. Post operative blood loss was not significantly increased for the heparin group compared with the no-heparin group (median of 850 mL with a range of 700-1400 mL, versus 856 mL with a range of 275-2800 mL, respectively). Similar results were seen in patients receiving preoperative co-administration of aspirin and heparin compared with patients receiving aspirin alone. There was no suppression of platelet activity in patients receiving preoperative heparin or co-administration of aspirin and heparin. However, such suppression was found in patients receiving aspirin only.*

**Conclusion:** *This study suggests that preoperative aspirin ingestion and intravenous heparin therapy should be administered as indicated and that concerns about the risk of postoperative bleeding should not lead to modification or cessation of such therapy.* (**Critical Care and Resuscitation 1999; 1: 130-139**)

**Key words:** Coronary artery bypass, aspirin, heparin, coagulation tests, postoperative blood loss

The induction of coagulation abnormalities and postoperative bleeding is a major concern in cardiac surgery. Platelet dysfunction and systemic hyper-fibrinolysis induced by cardiopulmonary bypass (CPB) are important causes of excessive postoperative bleeding.[1-3] Preoperative pharmacological therapies, such as anticoagulation and/or antiplatelet agents may affect coagulation status and, thereby, increase postoperative bleeding. Some patients with unstable angina receive intravenous heparin therapy prior to

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coronary artery bypass (CABG) surgery. However, limited data are available regarding the effects of preoperative heparin therapy on perioperative coagulation and blood loss after CABG surgery, even though heparin infusion is a commonly used therapeutic approach. There are conflicting reports of the effect of preoperative heparin therapy. Some studies show increased bleeding after cardiac surgery[4] and others show no increase.[5,6] The high dose of heparin administered prior to CBP has been reported to increase postoperative bleeding.[7,8]

Aspirin is the most commonly prescribed antiplatelet drug in cardiac patients and it may aggravate platelet dysfunction and increase blood loss during and following CPB.[9-11] However, many studies have failed to demonstrate that preoperative low dose aspirin ingestion has any effect on postoperative blood loss.[12-14] Furthermore, there are concerns over the combined effects of antiplatelet and anticoagulation agents, such as aspirin and heparin before surgery. Co-administration of aspirin and heparin was reported to significantly prolong the template bleeding time[15] and increase the risk of bleeding.[16]

Conventional coagulation tests (CCT) and activated clotting time (ACT) are employed clinically to monitor anti-coagulation therapy. Thrombelastography (TEG) has been proposed as a useful monitor of coagulopathy in cardiac surgery[17,18] and skin bleeding time (SBT) and platelet aggregation (PLT AGG) have been used as measures of platelet function. All of these tests can be used to monitor the effect of aspirin or heparin on coagulation and platelet function.

We conducted a prospective study in patients undergoing primary CABG, monitoring the peri-operative coagulation effects of aspirin or heparin using CCT, ACT, TEG, SBT and PLT AGG, and seeking to identify; 1) whether preoperative treatment with aspirin or heparin induces coagulation abnormalities; 2) whether the abnormalities were associated with an increase in the amount of postoperative blood loss, and; 3) whether preoperative co-administration of aspirin and heparin has an effect on postoperative blood loss.

## METHODS

Forty five patients undergoing primary CABG were studied following approval of the protocol by the Hospital Ethics Committee and after informed consent was obtained. Exclusion criteria included abnormal liver function tests, serum creatinine greater than 0.15 mmol/L and a history of clotting abnormalities or bleeding diathesis.

All patients received standardised anaesthesia, surgery and CPB. Preoperative medications included oral diazepam and intramuscular papaveretum and hyoscine. After the insertion of peripheral venous, arterial and pulmonary artery catheters, anaesthesia was induced and maintained with fentanyl, low dose diazepam or midazolam, pancuronium and isoflurane or halothane. A roller pump (Cobe, Lakewood, CO 80215, USA) with a 40 μm arterial filter and membrane oxygenator (DIDECO, D703) was used for CPB. Pump prime consisted of 1000 ml of lactate Ringer's solution and 500 ml of polygeline (Haemaccel, Hoechst, Germany) with 10000 units of heparin. Moderate hypothermia (28°C - 30°C) was induced and the cardiac index was maintained at 2.4 L/min/m² throughout CPB. Heparin was administered to maintain an ACT of more than 480 seconds during CPB. Myocardial protection was induced with blood cardioplegia. The remaining volume in the CPB machine after discontinuation of CPB was drained and reinfused. Postoperatively patients were managed according to a standard protocol by intensive care staff who were blinded from the study.

Blood samples for all tests were drawn from a heparin-free radial arterial line at three time points in the operation theatre: 1) before induction of anaesthesia, 2) 10 minutes after protamine administration, and 3) after skin closure. SBT was performed only before anaesthesia and after skin closure.

The conventional coagulation tests which were performed included international normalised ratio for prothrombin (INR), activated partial thromboplastin time (aPTT), thrombin clotting time (TCT), pro-thrombin time (PT), platelet factor 3 ($PF_3$), fibrinogen concentration, and platelet count. Platelet aggregation studies were performed using the aggregation agonists adenosine diphosphate (ADP) at a concentration of 4 μmol/L, epinephrine (50 μmol/L) and ristocetin (1.5 μg/L) (Chronolog Corp. Aggro-meter). A dedicated haematology scientist performed all these tests as well as the SBT. ACT was measured using the Hemachron 400. TEG (Thrombelastography D, Haemoscope, Skokie, IL) was performed according to standard technique.[19] Measured variables included reaction time (r), coagulation time (r + k), clot formation rate ($\alpha$), maximum amplitude (MA) and whole blood clot lysis index (WBCLI).

Data analysis included a comparison of the amount of postoperative blood loss (assessed from the volume of blood collected from mediastinal, pleural and pericardial drains) in the first 24 hours postoperatively, CCT, ACT, TEG, SBT, and PLT AGG between: 1) patients who ceased aspirin preoperatively ≤ 6 days (aspirin group) and 2) patients who ceased aspirin ≥ 7 days or had no aspirin (no-aspirin group); between 1) patients who received intravenous heparin preoperatively (heparin group) and 2) patients who did not receive preoperative heparin infusion (no-heparin

group); and between 1) patients who received preoperative heparin and aspirin (heparin-aspirin group) and 2) patients who received aspirin alone (aspirin-alone group). A Pearson correlation was performed between the amount of postoperative blood loss and days of cessation of aspirin ingestion or preoperative heparin therapy.

Statistical analysis was performed using the Mann-Whitney and Chi-square exact tests. Results are presented as median with range. A $P < 0.05$ was considered statistically significant. The statistical software package Minitab (release 10.2, Minitab Inc. 3081 Enterprise Drive, State College, PA, USA) was used for data analysis.

## RESULTS

The median age of patients was 69 years (range, 41 - 79). There were 38 males and 7 females. The median number of internal mammary artery grafts was 1 (range, 0 - 2) and total grafts was 4 (range, 1 - 5). The median duration of CBP was 92 minutes (range, 26 - 173 minutes) and duration of aortic cross clamp was 60 minutes (range, 12 - 103 minutes). The median postoperative blood loss for all patients was 856 mL (range, 275 – 2800 mL). Perioperatively, 37.8 % of patients had packed red cells (mean 2 units, range 1 – 3 units), 15.6 % had platelets (mean 6 units, range 5 – 12 units), 11.1 % had fresh frozen plasma (mean 4, range 4 - 6 units) transfused. 17.8 % had retransfusion of autologous blood salvaged from the chest drains (mean 427 mL, range 156 - 600 mL).

Forty of the study patients took 150 mg of aspirin preoperatively and the duration of preoperative cessation of aspirin varied from one to twenty days. There were 35 patients in the aspirin group and the duration of cessation of aspirin therapy was from one to six days with a median of three days. There were 10 patients in the no-aspirin group. There were 10 patients in the heparin group and 35 in the no-heparin group. The percentage of patients who had preoperative intravenous heparin in the aspirin group (20%, i.e. 7 in 35) and the non-aspirin group (30% i.e. 3 in 10) was not significantly different.

Table 1 shows that neither preoperative aspirin nor heparin therapy was associated with increased blood loss in the postoperative periods. There were no differences in patients' age, duration of aortic cross clamp and cardiopulmonary bypass and perioperative transfusion of blood and blood products between patients of any group (Table 1).

There were no differences in CCT, ACT, TEG (Table 2), SBT and PLT AGG (Table 3) at pre-anaesthesia, post-protamine administration and post-skin closure between patients of the aspirin and no-aspirin groups.

Ten patients received preoperative intravenous

**Table 1. Age, surgical factors, postoperative blood loss and transfusion requirements with and without aspirin or heparin**

| | *Aspirin* (n = 35) | *No-aspirin* (n = 10) | *Heparin* (n = 10) | *No-heparin* (n = 35) | *Aspirin-alone* ( n = 30) | *Aspirin-heparin* (n = 9) |
|---|---|---|---|---|---|---|
| Age (yrs) | 69 (41-79) | 69 (49-78) | 69 (44-79) | 68 (41-78) | 69 (44-79) | 67 (41-78) |
| Duration of aortic clamp (minutes) | 60 (12-103) | 72 (21-83) | 66 (41-80) | 55 (12-103) | 58 (12-103) | 66 (41-80) |
| Duration of cardio-pulmonary bypass (minutes) | 94 (26-173) | 88 (40-145) | 105 (60-145) | 91 (26-173) | 93 (26-173) | 107 (60-145) |
| Postoperative 1st 24 h. chest drainage (mL) | 860 (275-2800) | 833 (500-1380) | 850 (700-1400) | 856 (275-2800) | 842 (275-2800) | 890 (700-1400) |
| *Perioperative blood product use* | | | | | | |
| Red packed cell (units) | 0 (n=15) (0-3) | 0 (n=2) (0-2) | 0 (n=3) (0-3) | 0 (n=14) (0-3) | 0 (n=13) (0-3) | 0 (n=3) (0-3) |
| Platelet (units) | 0 (n=7) (0-12) | 0 (n=0) | 0 (n=0) | 0 (n=7) (0-12) | 0 (n=7) (0-12) | 0 (n=0) |
| Fresh frozen plasma (units) | 0 (n=5) (0-6) | 0 (n=0) | 0 (n=0) | 0 (n=5) (0-6) | 0 (n=5) (0-6) | 0 (n=0) |
| Retransfusion of chest drained blood (mL) | 0 (n=6) (0-600) | 0 (n=2) (0-420) | 0 (n=2) (0-420) | 0 (n=6) (0-600) | 0 (n=5) (0-600) | 0 (n=2) (0-420) |

Values are median (range), n = number of patients.

**Table 2. The effects of preoperative aspirin therapy on the perioperative coagulation tests (CCT), activated clotting time (ACT) and thrombelastography (TEG)**

| | | ***Pre anaesthesia*** | | ***Post protamine*** | | ***Post skin closure*** | |
|---|---|---|---|---|---|---|---|
| | | *Aspirin* (n = 35) | *No-aspirin* (n = 10) | *Aspirin* (n = 35) | *No-aspirin* (n = 10) | *Aspirin* (n = 35) | *No-aspirin* (n = 10) |
| **CCT** | INR | 1.1 (1-1.2) | 1 (1-1.2) | 1.4 (1.2-1.7) | 1.3 (1.1-1.4) | 1.2 (1.1-1.7) | 1.3 (1.1-1.6) |
| | aPTT (sec) | 35 (29-75) | 35 (30-127) | 50 (34-85) | 45 (32-68) | 43 (32-95) | 51 (37-168) |
| | TCT (sec) | 16 (11-60) | 17 (14-23) | 19 (15-60) | 19 (16-23) | 19 (15-60) | 24 (14-60) |
| | PT (sec) | 14 (13-16) | 13 (13-16) | 19 (16-22) | 18 (15-18) | 16 (14-22) | 17 (14-21) |
| | $PF_3$ (sec) | 32 (25-47) | 29 (25-63) | 58 (30-110) | 52 (38-90) | 49 (30-103) | 45 (31-56) |
| | Fibrinogen (g/L) | 3.2 (2.24-6.53) | 3.53 (2.74-5.03) | 2.02 (0.93-4.95) | 2.1 (1.48-3.03) | 2.31 (1.27-4.45) | 2.35 (1.85-5.3) |
| **ACT** | (min) | 134 (49-205) | 135 (104-227) | 129 (98-175) | 130 (110-155) | 131 (101-180) | 140 (92-164) |
| **TEG** | r (min) | 11 (2-20) | 10 (7-116) | 10 (5-46) | 10 (6-17) | 9 (4-47) | 11 (5-128) |
| | r+K (min) | 18.5 (4-35) | 16.5 (15-161) | 15 (7-73) | 16 (10-35) | 15 (6-89) | 18 (7-172) |
| | $\alpha$ (degree) | 37.5 (19-68) | 36 (9-48) | 44 (11-70) | 42 (16-61) | 38 (9-75) | 35 (6-72) |
| | MA (min) | 49 (34-67) | 50.5 (35-59) | 50 (27-74) | 50 (39-64) | 48 (32-71) | 51 (33-71) |
| | WBCLI (%) | 86.5 (48-94) | 86 (62-94) | 90 (0-100) | 92 (86-97) | 92 (71-100) | 93 (87-100) |

Values are median (range), n = number of patients, INR = international normalized ratio, aPTT = activated partial thromboplastin time, TCT = thrombin clotting time, PT = prothrombin time, $PF_3$ = platelet factor 3, r = reaction time, r+k = coagulation time, $\alpha$ = clot formation rate, MA = maximum amplitude, WBCLI = whole blood clot lysis index.

heparin therapy with rate adjustment according to the aPTT. Heparin infusion was ceased two to three hours before surgery. Heparin administration prior to CPB was identical for all patients (3 mg/kg) regardless of preoperative heparin therapy. There was no significant difference in the duration (in days) of cessation of preoperative aspirin therapy between the heparin treated (median of 2 days) and untreated patients (median of 3 days).

The effects of preoperative heparin therapy on perioperative coagulation tests are shown in Tables 4 and 5. Before anaesthesia, INR, aPTT, TCT, PT, ACT and coagulation time of TEG (Table 4), and epinephrine induced PLT AGG (Table 5) were all statistically different between the heparin treated and untreated patients. The above differences disappeared following routine protamine administration and after skin closure except for epinephrine-induced PLT AGG (Table 5). Apart from the above tests, ACT data following heparin administration were compared between two groups. Median ACT in the no-heparin group of 624 seconds (range, 444 to 1035 seconds) was not significantly different to the median ACT of 551 seconds in the heparin group (range of 445 to 691 seconds). There was also no difference in the doses of protamine administrated following discontinuation of CPB between the two groups (i.e. 300 mg versus 275 mg, respectively). There were no differences in the periods of cessation of preoperative aspirin ingestion (3 days vs 3 days) and in postoperative blood loss (Table 1) between the aspirin-alone and aspirin-heparin groups.

The results of laboratory tests are presented in Table6 and 7. An anticoagulation effect of heparin was evident before anaesthesia, demonstrated by prolonged INR, aPTT, TCT, PT and ACT, and the effect disappeared following protamine administration and after skin closure. There were statistical differences in PLT AGG induced by epinephrine before anaesthesia,

**Table 3. The effects of preoperative aspirin therapy on the perioperative skin bleeding time (SBT), platelet count and platelet aggregation (PLT AGG)**

| | | ***Pre anaesthesia*** | | ***Post protamine*** | | ***Post skin closure*** | |
|---|---|---|---|---|---|---|---|
| | | *Aspirin* (n = 35) | *No-aspirin* (n = 10) | *Aspirin* (n = 35) | *No-aspirin* (n = 10) | *Aspirin* (n = 35) | *No-aspirin* (n = 10) |
| **SBT** | (min) | 4 .1 (2-14) | 4.3 (2-7) | — | — | 6.2 (2-16) | 6.1 (4-15) |
| **Platelet count** | ($1000/mm^3$) | 185 (107-332) | 194 (146-308) | 116 (30-217) | 134 (77-198) | 149 (69-224) | 131 (105-198) |
| **PLT AGG (% max. )** | ADP (4 μmol/L) | 42 (8-100) | 40 (14-80) | 29 (2-90) | 40 (22-64) | 36 (14-72) | 53 (28-100) |
| | Epinephrine (50 μmol/L) | 35 (4-100) | 44 (18-100) | 27 (0-100) | 36 (7-76) | 35 (1-84) | 48 (24-71) |
| | Ristocetin (1.5 μg/L) | 59 (9-100) | 76 (37-100) | 46 (0-100) | 14 (-3-100) | 36 (-1-104) | 41 (1-112) |

Values are median (range), n = number of patients, PLT AGG (% max. ) = maximum percent platelet aggregation, ADP = adenosine diphosphate.

**Table 4. The effects of preoperative heparin therapy on the perioperative coagulation tests (CCT), activated clotting time (ACT) and thrombelastography (TEG)**

| | | ***Pre anaesthesia*** | | ***Post protamine*** | | ***Post skin closure*** | |
|---|---|---|---|---|---|---|---|
| | | *Heparin* (n = 10) | *No-heparin* (n = 35) | *Heparin* (n = 10) | *No-heparin* (n = 35) | *Heparin* (n = 10) | *No-heparin* (n = 35) |
| **CCT** | INR | 1.14 * (1-1.2) | 1.1 (1-1.2) | 1.4 (1.2-1.6) | 1.4 (1.1-1.7) | 1.3 (1.1-1.6) | 1.2 (1.1-1.7) |
| | aPTT(sec) | 45 ** (36-127) | 34 (29-45) | 49 (39-85) | 48 (32-84) | 51 (37-168) | 43 (32-95) |
| | TCT(sec) | 28 ** (16-60) | 16 (11-23) | 20 (16-60) | 19 (15-33) | 24 (14-60) | 19 (15-60) |
| | PT(sec) | 15 ** (13-16) | 14 (13-15) | 18 (16-21) | 18 (15-22) | 17 (14-21) | 16 (14-22) |
| | $PF_3$ (sec) | 33 (29-63) | 31 (25-45) | 57 (38-73) | 58 (30-110) | 45 (31-56) | 49 (30-103) |
| | Fibrinogen (g/L) | 3.56 (2.75-6.53) | 3.19 (2.24-6.39) | 2.08 (1.84-4.95) | 2.02 (0.93-3.7) | 2.35 (1.85-5.3) | 2.31 (1.27-4.45) |
| **ACT** | (sec) | 156 ** (114-227) | 131 (49-192) | 131 (98-175) | 128 (104-163) | 140 (92-164) | 131 (101-180) |
| **TEG** | r (min) | 13 (5-45) | 11 (2-14) | 11 (6-46) | 10 (2-22) | 7.5 (5-128) | 7 (4-47) |
| | r+K (min) | 25 * (11-161) | 17 (4-28) | 16 (10-73) | 14 (7-39) | 48 (7-172) | 51 (6-89) |
| | α (degree) | 24 (9-48) | 37 (22-68) | 46 (11-62) | 47 (12-70) | 35 (6-72) | 38 (9-75) |
| | MA (min) | 45 (34-63) | 50 (35-67) | 46 (35-74) | 52 (27-64) | 48 (32-71) | 51 (33-71) |
| | WBCLI (%) | 89 (62-95) | 86 (48-94) | 91 (85-97) | 90 (0-100) | 93 (87-100) | 92 (71-100) |

Values are median (range), n = number of patients, * $P < 0.05$, ** $P < 0.01$ between the heparin and no-heparin groups. INR = international normalized ratio, aPTT = activated partial thromboplastin time, TCT = thrombin clotting time, PT = prothrombin time, $PF_3$ = platelet factor 3, r = reaction time, r+k = total coagulation time, α = clot formation rate, MA = maximum amplitude, WBCLI = whole blood clot lysis index.

**Table 5. The effects of preoperative heparin therapy on the perioperative skin bleeding time (SBT), platelet count and platelet aggregation (PLT AGG)**

| | | ***Pre anaesthesia*** | | ***Post protamine*** | | ***Post skin closure*** | |
|---|---|---|---|---|---|---|---|
| | | *Heparin* (n = 10) | *No-heparin* (n = 35) | *Heparin* (n = 10) | *No-heparin* (n = 35) | *Heparin* (n = 10) | *No-heparin* (n = 35) |
| **SBT** | (min) | 3.4 (1.9-5.6) | 4.4 (1.8-14) | – | – | 6.1 (4-15) | 6.2 (1.5-16) |
| **Platelet count** | ($1000/mm^3$) | 178 (160-275) | 188 (107-332) | 120 (77-161) | 125 (30-217) | 131 (105-198) | 149 (69-224) |
| **PLT AGG (% max.)** | ADP (4 μmol/L) | 63 (20-90) | 41 (8-100) | 40 (5-90) | 30 (2-64) | 61 (30-100) | 37 (14-82) |
| | Epinephrine (50 μmol/L) | 63 ** (28-100) | 33 (4-100) | 47 * (19-100) | 25 (0-62) | 57 * (12-71) | 33 (1-84) |
| | Ristocetin (1.5 μg/mL) | 81 (36-100) | 60 (9-100) | 54 (16-100) | 36 (–3-100) | 65 (–1-104) | 37 (1-112) |

Values are median (range), n = number of patients, *P < 0.05, ** P < 0.01 between the heparin and no-heparin groups, PLT AGG (% max) = maximum percent platelet aggregation, ADP = adenosine diphosphate.

**Table 6. The effects of preoperative aspirin therapy and combination of aspirin and heparin on the perioperative coagulation tests (CCT), activated clotting time (ACT) and thrombelastography (TEG)**

| | | ***Pre anaesthesia*** | | ***Post protamine*** | | ***Post skin closure*** | |
|---|---|---|---|---|---|---|---|
| | | *Aspirin* (n = 30) | *Aspirin-heparin* (n = 9) | *Aspirin* (n = 30) | *Aspirin-heparin* (n = 9) | *Aspirin* (n = 30) | *Aspirin-heparin* (n = 9) |
| **CCT** | INR | 1.1 (1-1.2) | 1 (1-1.2) | 1.4 (1.2-1.7) | 1.3 (1.1-1.4) | 1.2 (1.1-1.7) | 1.3 (1.1-1.6) |
| | aPTT (sec) | 35 (29-75) | 35 (30-127) | 50 (34-85) | 45 (32-68) | 43 (32-95) | 51 (37-168) |
| | TCT (sec) | 16 (11-60) | 17 (14-23) | 19 (15-60) | 19 (16-23) | 19 (15-60) | 24 (14-60) |
| | PT (sec) | 14 (13-16) | 13 (13-16) | 19 (16-22) | 18 (15-18) | 16 (14-22) | 17 (14-21) |
| | $PF_3$ (sec) | 32 (25-47) | 29 (25-63) | 58 (30-110) | 52 (38-90) | 49 (30-103) | 45 (31-56) |
| | Fibrinogen (g/L) | 3.2 (2.24-6.53) | 3.53 (2.74-5.03) | 2.02 (0.93-4.95) | 2.1 (1.48-3.03) | 2.31 (1.27-4.45) | 2.35 (1.85-5.3) |
| **ACT** | (min) | 134 (49-205) | 135 (104-227) | 129 (98-175) | 130 (110-155) | 131 (101-180) | 140 (92-164) |
| **TEG** | r (min) | 11 (2-20) | 10 (7-116) | 10 (5-46) | 10 (6-17) | 9 (4-47) | 11 (5-128) |
| | r+K (min) | 18.5 (4-35) | 16.5 (15-161) | 15 (7-73) | 16 (10-35) | 15 (6-89) | 18 (7-172) |
| | α (degree) | 37.5 (19-68) | 36 (9-48) | 44 (11-70) | 42 (16-61) | 38 (9-75) | 35 (6-72) |
| | MA (min) | 49 (34-67) | 50.5 (35-59) | 50 (27-74) | 50 (39-64) | 48 (32-71) | 51 (33-71) |
| | WBCLI (%) | 86.5 (48-94) | 86 (62-94) | 90 (0-100) | 92 (86-97) | 92 (71-100) | 93 (87-100) |

Values are median (range), INR = international normalized ratio, aPTT = activated partial thromboplastin time, TCT = thrombin clotting time, PT = prothrombin time, $PF_3$ = platelet factor 3, r = reaction time, r+k = coagulation time, α = clot formation rate, MA = maximum amplitude, WBCLI = whole blood clot lysis index.

**Table 7. The effects of preoperative aspirin therapy and combination of aspirin and heparin on the perioperative skin bleeding time (SBT), platelet count and platelet aggregation (PLT AGG)**

| | | Pre anaesthesia | | Post protamine | | Post skin closure | |
|---|---|---|---|---|---|---|---|
| | | Aspirin (n = 30) | Aspirin-heparin (n = 9) | Aspirin (n = 30) | Aspirin-heparin (n = 9) | Aspirin (n = 30) | Aspirin-heparin (n = 9) |
| **SBT** | (min) | 4.3 (1.8-11.6) | 3.4 (1.9-5.6) | _ | _ | 6.4 (1.5-16) | 6.8 (4-8.4) |
| **Platelet count** | ($1000/mm^3$) | 196 (107-332) | 169 (160-275) | 125 (30-217) | 100 (77-161) | 149 (69-224) | 123 (105-198) |
| **PLT AGG (% max.)** | ADP (4 μmol/L) | 41 (8-100) | 56 (20-90) | 29 (2-90) | 40 (18-59) | 36 * (14-72) | 61 (30-76) |
| | Epinephrine (50 μmol/L) | 33 ** (4-100) | 62 (28-91) | 25 (3-100) | 41 (19-62) | 29 (1-84) | 55 (12-70) |
| | Ristocetin (1.5 μg/mL) | 58 (9-100) | 77 (36-100) | 18 * (–3-100) | 57 (25-100) | 30 (2-100) | 62 (–1-104) |

Values are median (range). * $P < 0.05$, ** $P < 0.01$ between the heparin and no-heparin groups, PLT AGG (% max) = maximum percent platelet aggregation, ADP = adenosine diphosphate.

by ristocetin following administration of protamine and by adenosine diphosphate after skin closure between two groups. There was only one patient who received heparin without aspirin and 5 patients who received neither heparin nor aspirin preoperatively. No comparison was made for these patients because of the small number.

The post operative blood loss did not correlate significantly with days of either cessation of aspirin ingestion ($r = 0.02$) or preoperative heparin therapy ($r = -0.01$).

## DISCUSSION

Aspirin therapy prolongs bleeding time for at least seven days after cessation.[20] To reverse this effect would therefore require at least one week without aspirin ingestion. The patients who stopped aspirin therapy for more than seven days prior to surgery or those who did not have aspirin were, therefore, regarded as one group in this study. In our study, all patients who were on aspirin therapy preoperatively had only 150 mg daily. There were no significant differences in either pre-anaesthesia coagulation tests including SBT and PLT AGG studies or in postoperative blood loss between patients receiving aspirin within six days of surgery and the patients either on no aspirin or ceasing more than 7 days before surgery. There were no statistical differences in perioperative transfusion of blood or blood product between two groups even though only two patients had packed red cells and none had blood products in the no-aspirin group.

Ingestion of low dose of 150 mg of aspirin still affects SBT and PLT AGG, as we demonstrated in a previous study on healthy volunteers.[21] The reasons for the lack of difference in the above tests include the variation of cessation of aspirin prior to surgery, and the effects of other medications and intraoperative conditions on platelet reactivity, such as preoperative heparin therapy, cardiopulmonary bypass, blood scavenging deficit and changes in temperature and pH. Nevertheless, postoperative blood loss was not increased by preoperative low dose aspirin therapy. Larger doses of aspirin, from 325 to 975 mg, however, taken daily within a seven days of the preoperative period, may increase postoperative bleeding as Goldman and associates reported.[11]

Ingestion of 600 mg aspirin prolonged the reaction time (r), the clotting speed (k) and coagulation time (r + k) of TEG in an early study.[22] However, the same dose of aspirin ingestion did not affect TEG variables even though SBT was prolonged in another report.[23] Moreover, oral low dose aspirin of 150 mg does not affect any TEG variable compared to pre-ingestion control values in healthy volunteer subjects.[21] It is likely that TEG is not a sensitive monitor of the antiplatelet activity of aspirin. TEG has been used to monitor intravenous heparin therapy,[24] and reaction (r) and coagulation time (r + k) can be prolonged depending on the dose, time and route of administration. Like most conventional coagulation tests, the coagulation time (r + k) of TEG was prolonged in the preoperative heparin treated patients before anaesthesia.

Preoperative intravenous heparin therapy is not uncommon in patients with coronary artery disease, and 22.2% (10/45) of our patients received intravenous heparin with the infusion ceasing two to three hours prior to surgery. Heparin therapy significantly prolonged most pre-anaesthesia coagulation tests. However, the differences in the coagulation variables between the heparin-treated and untreated patients disappeared after

termination of CBP and routine protamine administration. In addition, preoperative heparin therapy did not increase postoperative blood loss. Previous studies have shown controversial results, with some concluding that it increased perioperative bleeding[4] and others that it did not.[5,6] Patients on preoperative intravenous heparin therapy may need a larger dose of heparin for CBP than patients not on such therapy, due to a state of relative heparin resistance. Inadequate anticoagulation with a standard dose of heparin before CPB may lead to increased platelet activity and fibrinolysis, and greater postoperative blood loss in these patients.[3] There was no increased requirement of heparin dosing for CPB in the 10 patients who received preoperative heparin therapy, and the only difference in ACT between the heparin-treated and untreated patients was from the pre-anaesthesia period. There was a trend to a lower ACT following heparin administration in the heparin-treated patients. Neither ACT following protamine administration and after skin closure nor postoperative blood loss were different.

Dietrich and co-authors have reported the interesting finding that preoperative warfarin therapy reduced post-operative blood loss even though it prolonged INR both preoperatively and postoperatively.[25] The influences of preoperative heparin and warfarin on coagulation tests are different. The effect of heparin disappeared following its neutralisation by protamine, however, the effect of warfarin is known to persist postoperatively as evidenced by a persistently prolonged INR. As Dietrich's result is in contrast to a previous report[26] and common clinical practice, further controlled clinical trials are warranted.

CPB attenuates platelet aggregability.[27,28] However, the reports on the effects of heparin on PLT AGG have been controversial.[3,29-34] Kestin *et al*, have suggested that heparin has at least two distinct effects on platelet activation/function. *In vitro*, heparin augments platelet activation, yet *in vivo* it suppresses platelet activation by inhibiting endogenous thrombin.[3] It seems, from our data, that there was no suppression of platelet function in the preoperative heparin-treated patients when compared with the control values of PLT AGG from our healthy volunteers.[21]

By contrast, platelet aggregation was reduced in the no-heparin group with epinephrine-induced PLT AGG consistently lower compared to that in the heparin-treated patients. Again, there was no suppressive effect of co-administration of heparin and aspirin and the antiplatelet activity of aspirin occurred only in the aspirin-alone group. The results suggest that preoperative heparin therapy may preserve or even enhance platelet activation and prevent the antiplatelet activity of aspirin. On the other hand, heparin-induced platelet activation could not be prevented by aspirin in vitro as Kappa and co-authors reported.[35]

The co-administration of antiplatelet and anti-coagulant agents may increase the risk of bleeding. The addition of aspirin to intravenous heparin therapy led to an increase in the template bleeding time which was much more pronounced than the effect of aspirin alone.[15] In fact, it is not uncommon for cardiac patients to receive both aspirin and subcutaneous or intravenous heparin simultaneously, often preoperatively. An early report showed that such combined use increased the risk of bleeding in non-surgical patients.[16] However, it has not been well documented whether or not the combination of two agents has a significant impact on perioperative haemostasis and blood loss in cardiac patients. There was neither increased post operative blood loss nor a worse coagulation state in the patients with preoperative co-administration of heparin and aspirin when compared with patients who received aspirin only. Moreover, suppression of platelet aggregation was demonstrated only in the aspirin-alone group rather than in the aspirin-heparin group.

In conclusion, although the patient population was relative small and preoperative drug therapy was not controlled, careful data collection and multiple comprehensive coagulation tests and analysis reveal that preoperative low dose aspirin therapy (150 mg daily) does not affect either perioperative coagulation tests or postoperative blood loss. Such data also reveal that preoperative intravenous heparin therapy affects preoperative coagulation tests, but that such effects disappear after protamine neutralisation. Heparin did not increase postoperative blood loss. There was no perioperative suppression of platelet activity in patients receiving preoperative intravenous heparin therapy. Finally, the preoperative co-administration of heparin and low dose aspirin was not associated with increased risk of postoperative blood loss. The findings of our study suggest that preoperative low dose aspirin and intravenous heparin therapy are safe and should be given as indicated. Concerns about the risk of postoperative bleeding should not lead to modification or cessation of such therapy.

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