

# Prophylaxis of Thromboembolic Disease and Platelet-Related Changes Following Total Hip Replacement: A Comparative Study of Aspirin and Heparin-Dihydroergotamine

M. J. Alfaro, J. A. Páramo and E. Rocha

From the Service of Hematology, University of Navarra, Pamplona, Spain

## Key words

Postoperative deep vein thrombosis – Aspirin – Heparin-dihydroergotamine

## Summary

A prospective study involving 120 consecutive patients undergoing total hip replacement was performed to compare the effectiveness of aspirin (high and low dose) or a combination of heparin plus dihydroergotamine (heparin-DHE) in preventing isotopic and phlebographic deep vein thrombosis (DVT), and to evaluate their effect on postoperative platelet changes. Phlebographic DVT was demonstrated in 9 cases (30%) in control group, in 1 (3.3%) in aspirin (high-dose) group ( $p < 0.01$ ), in 1 (3.3%) in aspirin (low-dose) group ( $p < 0.01$ ) and in 5 (16.6%) in heparin-DHE group ( $p = \text{NS}$ ). Aspirin was able to reduce the postoperative increase in circulating platelet aggregates, platelet factor 4 and  $\beta$ -thromboglobulin observed in control group. This study shows that aspirin is effective in the prevention of DVT for patients undergoing total hip replacement. Small aspirin dose (250 mg/day) represents an effective form of prophylaxis in these patients.

## Introduction

Venous thrombosis and pulmonary embolism are frequent postoperative complications in general surgical, orthopedic and gynecologic patients (1–4). They represent the commonest group of complications and the largest single cause of death after total hip surgery (5). However, prophylaxis remains a major problem in these patients. Despite several drugs having been employed (6–9) only aspirin and heparin-dihydroergotamine (heparin-DEH) seem to provide effective protection against deep vein thrombosis (DVT) and pulmonary embolism (10–16).

On the other hand, an impairment of the hemostatic system has been shown following hip surgery (17, 18), but a relationship between such an alteration and the incidence of DVT has not been established yet (18, 19).

In this study on 120 patients, we compared the efficacy of aspirin and heparin-DHE prophylaxis of DVT following total hip replacement. The modifications induced by both agents on the postoperative platelet related changes are also evaluated.

## Patients and Methods

The study was carried out on patients older than 40 years who were admitted for total hip replacement and who gave their informed consent. Patient exclusion criteria included: pregnant women; patients with a

history suggestive of peptic ulcer; haematemesis or sensitivity to salicylates. Patients who had ingested aspirin or other antiplatelet agents in the week before admission were also excluded.

## Prophylaxis

One hundred and twenty suitable patients were admitted to the trial and then randomly assigned to one of the following groups:

- Control group. No specific prophylaxis for DVT was given.
- Aspirin (high-dose) group. They received aspirin 0.5 g twice daily starting preoperatively until the seventh postoperative day.
- Aspirin low-dose group. They received aspirin 0.125 mg twice daily starting preoperatively until the seventh postoperative day.
- Heparin-DHE group. They received a combination of 5000 IU of sodium heparin (Roche®) plus 0.5 mg dihydroergotamine (Sandoz®) subcutaneously, starting preoperatively and repeated every 12 h for seven days.

Treated and control groups were well matched with respect to different risk factors known to be associated with the occurrence of DVT (20): age, sex, overweight percentage, previous thromboembolism, varicose veins, repeated surgery, heart disease, preoperative immobilization, duration of surgery, malignancy and Clayton index (21). No significant differences were found between the four groups of patients (Table 1).

## Diagnosis of DVT and Pulmonary Embolism

Each patient received 10  $\mu\text{Ci}$  of  $^{125}\text{I}$ -fibrinogen soon after surgery, and legs were scanned for a minimum of seven days according to the technique of Kakkar (22). DVT was diagnosed if the counts at any site differed by 20% or more from those at an adjacent point on the same leg or at the same point on the opposite limb and if this difference persisted in the subsequent 24 h. Ascending phlebography was performed in those patients who showed positive  $^{125}\text{I}$ -fibrinogen test. Pulmonary embolism was diagnosed if the patient had suggestive signs and symptoms confirmed by electrocardiogram, blood gas determination and lung scan.

## Operative and Postoperative Bleeding

Surgical wounds were examined every day. Operative loss was determined by dry swab weighing, amount of blood transfused during surgery, and amount of blood collected in suction apparatus. Postoperative loss was assessed by blood transfusion requirements and the amount collected in the drainage bottles every day.

## Methods

Plasma samples were taken preoperatively and on the first, third and seventh postoperative day.

Platelet count, platelet-crit and mean platelet volume (MPV) were determined by a Counter S Plus. Circulating platelet aggregates were measured by the Wu and Hoak technique (23).

Platelet factor 4 (PF 4) was determined with a commercial radioimmunoassay (RIA) kit (Abbot Lab) (24).  $\beta$ -thromboglobulin ( $\beta$ -TG) was determined with a commercial RIA kit (Amersham Lab) (25).

## Statistical Methods

The data were statistically analysed by using mean values, standard deviations, Student's *t*-test and the chi-square test.

Correspondence to: E. Rocha, MD, Service of Hematology, University Clinic of Navarra, Apartado 192, 31080 Pamplona, Spain

Table 1 Risk factors associated with occurrence of DVT in the four groups of patients. No significant differences were observed

	Control group	Aspirin group (250 mg/d)	Aspirin group (1 g/d)	Heparin-DHE
Sex ratio M/F	19/11	17/13	15/15	14/16
Previous thromboembolism	0	2	1	1
Varicose veins	10	10	11	7
Repeated surgery	4	5	3	2
Heart disease	5	4	2	4
Preoperative immobilization	2	1	1	1
Duration of surgery >3 h	0	0	0	0
Malignancy	0	0	0	0
Mean age	61.99 ± 7.17	66.06 ± 8.93	62.04 ± 10.99	58.43 ± 10.39
Overweight percentage	7.44 ± 7.59	11.89 ± 11.76	7.95 ± 7.47	8.17 ± 8.37
Clayton index	-1.50 ± 1.65	-1.38 ± 2.04	-0.90 ± 2.92	-0.40 ± 3.29

Table 2 DVT incidence assessed by <sup>125</sup>I-fibrinogen and phlebography in the four groups of patients

	Number of patients	Isotopic DVT Number	%	Phlebographic DVT Number	%
Control	30	11	36.6	9	30
Low-dose aspirin (250 mg/d)	30	1*	3.3	1**	3.3
High-dose aspirin (1 g/d)	30	2*	6.6	1**	3.3
Heparin-DHE	30	6	20	5	16.6

\* p < 0.005 and \*\* p < 0.01 with respect to control group

Student's t-test was used to compare groups. Student's t-test for paired observations was used to compare the values of different days within each group. Multiple chi-square tests were used to measure both the total significance and the significance of each treated group with respect to control group. The data were processed in IBM 4341 computer and a BMDP program was used to perform the statistical analysis (26).

## Results

### 1. Incidence of DVT and Pulmonary Embolism

One hundred and twenty patients were investigated. The incidence rates of thrombosis for each of the treatment groups according to fibrinogen uptake test and phlebography are given in Table 2. Phlebographic DVT developed in 1 (3.3%) out of 30 patients receiving aspirin (high-dose), in 1 (3.3%) out of 30 patients receiving aspirin (low-dose) and in 5 (16.6%) patients receiving heparin-DHE compared with 9 (30%) out of 30 control group patients. The difference was statistically significant in favor of the two aspirin groups (p < 0.01) compared with control group, while no significant differences in reducing incidence of DVT was found in patients treated with heparin-DHE with respect to control group and both aspirin groups. It should be noticed that in the heparin-DHE group the probability, known as "beta", of missing a true reduction in the frequency of post-operative venous thrombosis of 50% or more by heparin-DHE was 47.6% due to

the small sample size. As shown in Table 2, good correlation with the results obtained by leg scanning was observed.

Only 1 patient in the control group, and 1 patient in the heparin-DHE group developed pulmonary embolism diagnosed by lung scan. Thus, no statistically significant differences between the four groups could be established.

Sex-related phlebographic DVT incidence was found in 5 (26.3%) out of 19 males in the control group, in 2 (14%) out of 14 males in the heparin-DHE group, in none of 17 males treated with 1 g/d aspirin and in 1 (6%) out of 15 treated with low-dose aspirin.

### 2. Blood Loss, Haematoma and Other Complications

The rate of wound haematoma observed for all treatment groups was 3%. The measured blood loss at operation did not differ among the four groups (Table 3). Total blood replacement was not significantly greater for the aspirin and heparin-DHE groups as compared to control groups.

The other drug-related adverse effects included gastrointestinal pain in 2 patients treated with high-dose aspirin. Local pain in the injection side was observed in 5 patients of the heparin-DHE group. However, discontinuation of drug therapy was not required.

### 3. Postoperative Changes

Pre- and postoperative levels in the parameters studied are shown in Fig. 1. In the four groups, platelet count and platelet-crit showed a parallel and statistically significant decrease on postoperative days 1 and 3 (p < 0.005) with respect to the preoperative level followed by recovery on day 7. No changes in MVP were observed except for a decrease on day 7 in all groups. Circulating platelet aggregates were present throughout the postoperative period in both control and heparin-DHE groups (p < 0.002), but were absent in aspirin groups. PF 4 and β-TG showed a significant increase on postoperative days 3 and 7 (p < 0.01) both in control and heparin-DHE groups while no significant changes with respect to the preoperative levels were observed in either of the aspirin groups.

Table 3 Operative and postoperative bleeding and blood requirements. Values represent mean ± SD. No significant differences were observed

	Control group	Aspirin group (250 mg/d)	Aspirin group (1 g/d)	Heparin-DHE
Operative bleeding (ml)	820 ± 320	770 ± 205	770 ± 270	670 ± 320
Postoperative bleeding (ml)	760 ± 320	740 ± 430	790 ± 431	680 ± 235
Blood replacement (ml)	850 ± 390	740 ± 340	830 ± 530	640 ± 360

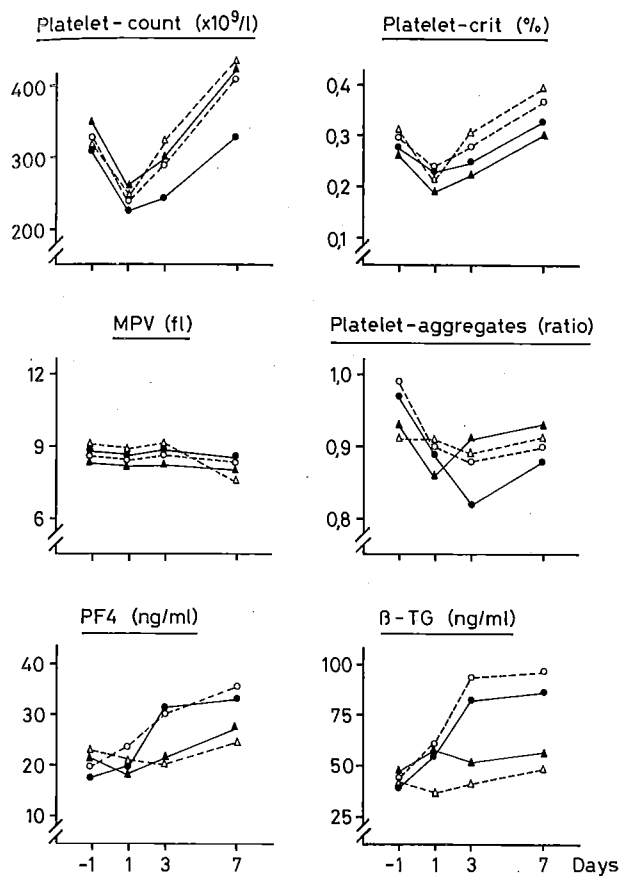


Fig. 1 Pre- and postoperative levels of platelet count, platelet-crit, MPV, platelet aggregates, PF 4 and  $\beta$ -TG in control group (●), aspirin (low-dose) group ( $\Delta$ ), aspirin (high-dose) group ( $\blacktriangle$ ) and heparin-DHE group (○)

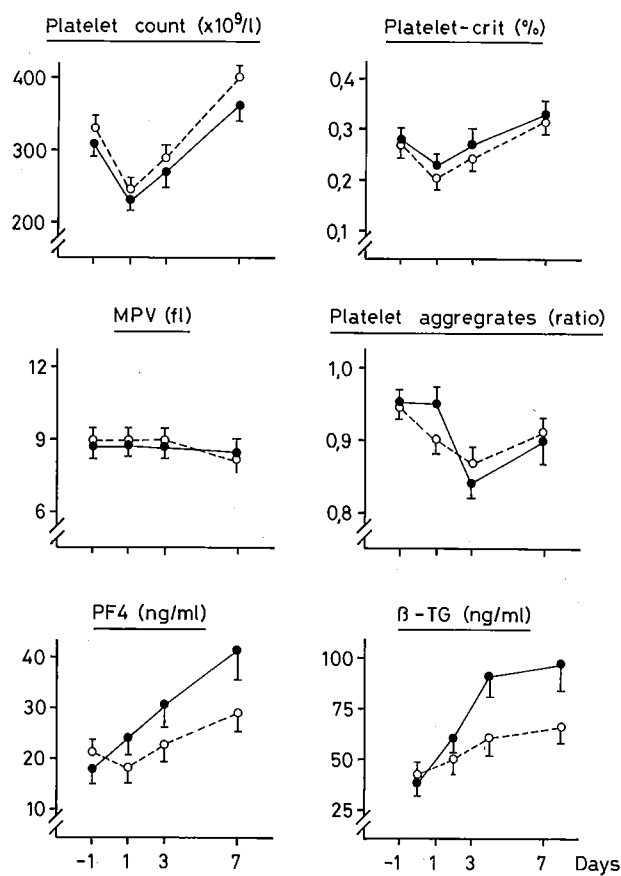


Fig. 2 Pre- and postoperative levels of platelet count, platelet-crit, MPV, platelet aggregates, PF 4 and  $\beta$ -TG in patients with (—) and without (---) postoperative DVT. Mean  $\pm$  SEM is reported

#### 4. Correlation with DVT

In 16 out of 120 patients phlebographic DVT was diagnosed postoperatively. Pre- and postoperative levels in the parameters studied for patients with and without DVT are shown in Fig. 2. There were no significant differences between the groups with regard to postoperative platelet count, platelet-crit, MPV and circulating platelet aggregates. However, PF 4 on postoperative day 7 ( $p < 0.002$ ) and  $\beta$ -TG on postoperative days 3 and 7 ( $p < 0.0003$ ) were higher in those patients who developed DVT.

#### Discussion

Aspirin and heparin-dihydroergotamine have been the only agents found to be effective in the prophylaxis of thrombosis following hip surgery (10–16), but studies comparing both types are still lacking.

This study shows that aspirin is an effective agent in reducing incidence of DVT after total hip replacement in agreement with previous reports (10–12). Postoperative phlebographic venous thrombosis occurred in 30% of patients in the control group, 16% in heparin-DHE group and 3% in both aspirin groups, suggesting that aspirin is effective as a prophylactic agent in hip surgery. One interesting finding was that low-dose aspirin (250 mg/d) was effective in the prophylaxis of DVT in hip surgery. According to the number of patients included in both aspirin groups, further evaluation will be necessary to assess whether low-dose aspirin is as effective as high-dose in the prophylaxis of DVT after total hip replacement.

We were not able to show that the combination of heparin plus dihydroergotamine significantly reduced postoperative DVT as suggested by several authors (13–16), although a true reduction in the frequency of postoperative DVT of 50% or more would have had a 47% chance of remaining undetected by the sample size used in the current study. The incidence of DVT in this group is similar to that recently reported by Kakkar et al. (27).

No significant differences in the wound haemorrhage complications for treated groups as compared to control group were observed. In none of the patients was it necessary to remove the arthroplasty because of these complications.

There was a significant progressive increase in circulating platelet aggregates, PF 4 and  $\beta$ -TG following total hip replacement as previously reported (18). Interestingly, PF 4 and  $\beta$ -TG were found to be higher in those patients who developed postoperative DVT which might indicate an "in vivo" platelet activation (28, 29) and could confirm the role of platelets in the pathogenesis of DVT after hip surgery. Aspirin may serve to prevent these thromboembolic events, since it blocks several platelet functions. In this study we show a decrease in circulating platelet aggregates, PF 4 and  $\beta$ -TG and consequently an inhibition of platelet activation correlating with a lower incidence of postoperative DVT. This effect was achieved with doses of aspirin as low as 250 mg/d. Our study indicates that aspirin reduces the increase of platelet-vessel and platelet-platelet interactions, both of which contribute to the genesis of thromboembolic phenomena following total hip replacement (30–32).

Moreover, our results clearly show that aspirin is effective in the prophylaxis of DVT after hip surgery. Small aspirin dose

represents an effective form of prophylaxis in patients undergoing total hip replacement.

#### Acknowledgements

Financial support was obtained from the "Comisión Asesora de Investigación Científica y Técnica" (No. 1414-82) of the Spanish Ministerio de Educación y Ciencia. We are grateful to I. Paz for technical assistance.

#### References

- 1 Kakkar V V. Prevention of venous thromboembolism. *Clin Haematol* 1981; 10: 543-82.
- 2 International Multicentre trial. Prevention of fatal post-operative pulmonary embolism by low-doses of heparin. *Lancet* 1975; 2: 45-51.
- 3 Clagett G P, Salzman E W. Prevention of venous thromboembolism in surgical patients. *N Engl J Med* 1974; 290: 93-6.
- 4 Sikorski J M, Hampson W G, Staddon G E. The natural history and etiology of deep vein thrombosis after total hip replacement. *J Bone Joint Surg* 1981; 63 B: 171-7.
- 5 Crawford W J, Hillman F, Charnley J. Internal publication Wrightington Centre for hip surgery. No 14. May, 1968.
- 6 Morris G G, Mitchell J R A. Preventing venous thromboembolism in elderly patients with hip fractures. Studies of low dose heparin, dipyridamole, aspirin and flurbiprofen. *Br Med J* 1977; 1: 535-7.
- 7 Cooke E D, Dawson M H O, Ibbotson R M, Path M R C, Bowcock S D, Ainsworth M E, Pilcher M F. Failure of orally administered hydroxychloroquine sulphate to prevent venous thromboembolism following elective hip operations. *J Bone Joint Surg* 1977; 59 A: 496-500.
- 8 Harris W H, Salzman E W, Athanasoulis C, Waltman A C, Baum S, DeSanctis R W. Comparison of warfarin, low molecular weight dextran, aspirin and subcutaneous heparin in prevention of venous thromboembolism following total hip replacement. *J Bone Joint Surg* 1974; 56 A: 1552-62.
- 9 Hampson W G J, Harris F C, Lucas H K, Roberts P H, McCall I W, Jackson N C, Powell N L, Staddon G E. Failure of low dose heparin to prevent deep vein thrombosis after hip replacement arthroplasty. *Lancet* 1974; 2: 795-7.
- 10 Salzman E W, Harris W H, DeSanctis R W. Reduction in venous thromboembolism by agents affecting platelet function. *N Engl J Med* 1971; 284: 1287-92.
- 11 Jennings J J, Harris W H, Sarmiento A. A clinical evaluation of aspirin prophylaxis of thromboembolic disease after total hip arthroplasty. *J Bone Joint Surg* 1976; 58 A: 926-8.
- 12 Harris W H, Salzman E W, Athanasoulis C A, Waltman A C, DeSanctis R W. Aspirin prophylaxis of venous thromboembolism after total hip replacement. *N Engl J Med* 1977; 297: 1246-9.
- 13 Kakkar V V, Stamatakis J D, Bentley P G, Lawrence D, Haas H A, Ward V P. Prophylaxis for postoperative deep-vein thrombosis. Synergistic effect of heparin and dihydroergotamine. *JAMA* 1979; 241: 39-42.
- 14 Schöndorf T H, Weber U. Heparin prophylaxis combined with DHE or dextran in hip operations. *Thromb Haemostas* 1979; 42: 249 (Abstr).
- 15 Gruber U F. Prevention of fatal postoperative pulmonary embolism by heparin dihydroergotamine or dextran 70. *Br J Surg* 1982; 69 (Suppl): 54-8.
- 16 Comerota A J, Diserio F J, Sasahara A A. Dihydroergotamine-heparin prophylaxis of DVT in total hip replacement patients: A multicentre trial. *Thromb Haemostas* 1985; 54: 99 (Abstr).
- 17 Houghton G R, Papadakis E G, Rizza C R. Changes in blood coagulation during total hip replacement. *Lancet* 1978; 1: 1336-8.
- 18 Páramo J A, Rocha E. Deep vein thrombosis and related platelet changes after total hip replacement. *Haemostasis* 1985; 15: 389-94.
- 19 Páramo J A, Alfaro M J, Rocha E. Postoperative changes in the plasmatic levels of tissue-type plasminogen activator and its fast-acting inhibitor. Relationship to deep vein thrombosis and influence of prophylaxis. *Thromb Haemostas* 1985; 54: 713-6.
- 20 Morris G K. Preoperative prediction of postoperative deep vein thrombosis. *Thromb Haemostas* 1979; 41: 27-32.
- 21 Clayton J F, Anderson J A, McNicol G P. Preoperative prediction of postoperative deep vein thrombosis. *Br Med J* 1976; 2: 910-2.
- 22 Kakkar V V. The diagnosis of deep vein thrombosis using the <sup>125</sup>I-fibrinogen test. *Arch Surg* 1972; 104: 152.
- 23 Wu K K, Hoak J C. A new method for the quantitative detection of platelet aggregates in patients with arterial insufficiency. *Lancet* 1974; 2: 924-6.
- 24 Bolton A E, Ludlam C A, Pepper D S, Moore S, Cash J D. A radioimmunoassay for platelet factor 4. *Thromb Res* 1976; 8: 51-8.
- 25 Ludlam C A, Cash J D. Studies on the liberation of  $\beta$ -thromboglobulin from human platelets in vitro. *Br J Haematol* 1976; 33: 239-47.
- 26 Dixon W J. BMDP statistical software. University of California, Los Angeles 1981.
- 27 Kakkar V V, Fok P J, Murray W J G, Paes T, Merenstein D, Dodds R, Farrel R, Crellin R Q, Thomas E M, Morley T R, Price A J. Heparin and dihydroergotamine prophylaxis against thromboembolism after hip arthroplasty. *J Bone Joint Surg* 1985; 67 B: 538-42.
- 28 Zahavi J, Kakkar V V.  $\beta$ -thromboglobulin: a specific marker of in vivo platelet release reaction. *Thromb Haemostas* 1980; 44: 23-9.
- 29 Kaplan K L, Owen J. Plasma levels of  $\beta$ -thromboglobulin and platelet factor 4 as indices of platelet activation in vivo. *Blood* 1981; 57: 199-202.
- 30 Salzman E W, Harris W H. Acetylsalicylic acid for prevention of venous thromboembolic disease in surgical patients. In: *Acetylsalicylic acid: new uses for an old drug*. Barnett H J M, Hirsh J, Mustard J F (eds). pp. 238-55. Raven Press, New York 1982.
- 31 Stamatakis J D, Kakkar V V, Sagar S, Lawrence D, Nairn D, Bentley P G. Femoral vein thrombosis and total hip replacement. *Br Med J* 1977; 2: 223-5.
- 32 Stamatakis J D, Kakkar V V, Lawrence D, Bentley P G. The origin of thrombi in the deep veins of the lower limb: a venographic study. *Br J Surg* 1978; 65: 449-51.

Received November 12, 1985 Resubmitted May 1, 1986  
Accepted May 26, 1986