

Departments of Orthopaedic Surgery, Blood Coagulation Research, Diagnostic Radiology and Thoracic Radiology, Karolinska Hospital, Stockholm, Sweden.

ACETYLSALICYLIC ACID IN A TRIAL TO DIMINISH THROMBOEMBOLIC COMPLICATIONS AFTER ELECTIVE HIP SURGERY

J. SOREFF, H. JOHANSSON, L. DIENER & L. GÖRANSSON

Accepted 23.xii.74

Thromboembolic complications after trauma as well as after elective surgery in the lower extremities and the pelvis are well documented (Sevitt & Gallagher 1959, Borgström et al. 1965, Ahlberg et al. 1968, Bergquist et al. 1972). The incidence of complications such as these has been reduced by prophylactic treatment with oral anticoagulants which, however, call for frequent laboratory controls, and with dextran which requires intravenous administration (Sevitt & Gallagher 1959, Borgström et al. 1965, Harris et al. 1967, Myhre & Holen 1969, Johnson et al. 1968, Ahlberg et al. 1968, Hamilton et al. 1970).

Drugs that directly affect the platelet function have also been tried in order to diminish the frequency of thromboembolic episodes (O'Brien et al. 1971, Salzman et al. 1971, Breddin & Scharrer 1972). In this way acetylsalicylic acid (ASA), a well-known inhibitor of platelet aggregation (O'Brien 1968, Zucker & Peterson 1968), has been tried with diverging results and since these have been inconclusive, we have attempted to further elucidate its merits. Acetylsalicylic acid was given in a double blind study and the incidence of postoperative thrombosis was evaluated using phlebographies.

MATERIAL AND METHODS

The study, performed during 1971-1973, included 51 patients with severe osteoarthritis of the hip, of whom 25 were female and 26 male. Their ages varied between 43 and 78 years.

The patients were operated on with displacement intertrochanteric osteotomy or with total hip arthroplasty (McKee-Farrar). All but two of the osteotomies were performed by one surgeon (JS) using the same approach, with division of vastus

lateralis postero-laterally and cutting of the iliopsoas muscle at its insertion to the lesser trochanter. All patients were kept in bed for one week, following which they were permitted partial weightbearing on crutches. The total hip replacements were performed by the senior surgeons of the department, using either a lateral approach or the anterior (Smith-Petersen) approach. All patients with replacement were kept in bed for 8-10 days, after which they were allowed partial weightbearing on crutches.

Patients with previous thromboembolic diseases were excluded from the study. All patients were carefully examined daily for clinical signs of deep venous thrombosis or pulmonary embolism postoperatively. Fever, tachycardia, chest pains, cough, tenderness of the calf, positive Homan's sign, and oedema were noted.

No analgetics containing acetylsalicylic acid, phenylbutazone or indomethazon were given.

The ascending phlebographies were performed in all patients 12 to 14 days post-operatively in the usual manner with the patients standing slightly recumbent to avoid "layering phenomena" of the contrast medium in the bloodstream (Lindblom 1941, Greitz 1954). From 50 to 200 ml Urografin 45 per cent was injected into a superficial vein of the foot. The examination in each case was, as a rule, performed with and without a tourniquet applied around the distal part of the lower leg just proximal to the ankle. (The function of the tourniquet, as is well known, is to direct the contrast medium from the superficial veins into the deep venous system of the lower leg.) The flow of the contrast medium was followed on the TV-monitor and exposures were made mainly in the antero-posterior and side projections.

In a few cases, in which an insufficient contrast-filling of deep venous trunks made it difficult to distinguish a suspected thrombus from a possible free-floating tail, the examination was supplemented with a centripetal descending phlebography. In this modification (Bergvall 1971) the patient lies supine and the leg to be examined is elevated approximately 30° or more. The injection of contrast medium is made into a superficial foot vein and to prevent a quick passage of the contrast medium a tourniquet can be applied around the upper part of the thigh.

In some cases where additional information about the iliofemoral segment was thought to be necessary, a descending phlebography was also performed. In these patients who, as a rule, were examined standing upright, the contrast medium was injected through a catheter inserted into the external iliac vein using the percutaneous approach.

In evaluating the phlebograms a distinct outlined defect in a contrast-filled deep vein, seen in at least two different projections, as well as non-filled deep venous trunks or their segments, were considered to represent thrombi.

Acetylsalicylic acid (ASA—Colfarit*) was given to 26 randomly selected patients and the remaining 25 patients were given placebo. ASA as well as placebo were given in four daily doses of 0.5 g every 6 hours. The randomization of the patients was performed in the following way. The identical bottles containing acetylsalicylic acid and placebo pills, respectively, were already on delivery to the hospital numbered and randomized by chance, so that half of them contained ASA and the other half placebo. Twenty per cent of the packages were marked at random with P, indicating that platelet aggregation studies should be performed. Every patient

*) Colfarit and placebo were supplied by Bayer Pharmaceutical.

on admission to the hospital received his own bottle from which the nurses distributed the medicine. Neither the patient, hospital staff nor the investigators were aware of the contents of the bottles until the code was broken at the end of the study by the Bayer Pharma. Treatment commenced on the first postoperative day and continued until phlebography had been performed 10-15 days postoperatively.

The level of salicylate in serum for all the patients was determined according to the method described by Saltzman** (1948). In the first 32 patients only one morning fasting sample was taken on the 5th, 6th or 7th day postoperatively. In the last 19 patients two samples for determination of the salicylate level were taken daily on the 2nd and on the 7th postoperative day at 7 a.m. fasting and at 2 p.m., i.e. 2 hours after they had taken the medicine.

Platelet aggregation was investigated in nine randomized patients according to the method described by Born & Cross (1963) on the 5th-7th postoperative days.

The statistical difference between the different groups was analyzed by the chisquare test with Yates' correction.

RESULTS

Suspicion of a clinical deep venous thrombosis (DVT) arose in 11 of the 51 cases included in the study, i.e. 21 per cent. Of these 11 patients seven belonged to the group treated with ASA and four to the placebo group. In 35 of the 51 cases phlebography was successfully performed and interpreted. In the remaining 16 cases phlebography was not done because of: refusal in six patients, technical difficulties in five patients and administrative problems in five patients. In one patient the phlebography was dubious and this patient was excluded.

Of the 35 patients on whom phlebography was successfully performed (only these patients will be discussed further), 15 were men and 20 women. Twenty-one were treated with ASA and fourteen were given the placebo. Nine had had a total hip replacement performed and 26 an osteotomy.

The total incidence of DVT verified by phlebography was 43 per cent, i.e. 15 patients out of 35 (Table 1), in comparison with the incidence found by clinical investigation which was 21 per cent, i.e. 11 patients out of 51.

However, the correlation between the clinical findings and the X-ray findings was not absolute. In 24 cases there was an agreement between the clinical and the X-ray findings, i.e. in 19 patients there was neither clinical nor radiological evidence of DVT, and the remaining five patients had positive phleboographies with positive clinical signs. In 11

**) Determination of salicylates in serum was kindly performed by Dr. Ann-Catrine Teger-Nilsson, Clinical Chemistry Laboratory, Karolinska Hospital.

Table 1. Number of patients and incidence of DVT.

Patients	Clinical investigation	Phlebographical investigation
Total no. of patients investigated	51	35
No. of patients with signs of DVT	11 (21 %)	15 (43 %)

patients, however, there was a discrepancy between the clinical and the X-ray findings. In 10 of these patients there was no clinical suspicion of DVT but phlebography indicated thrombosis, and in one case the clinical investigation raised a suspicion of DVT but the X-ray was normal (Table 2).

In the group treated with placebo the incidence of DVT was 36 per cent (five out of 14 patients), and in the ASA-treated group it was 47 per cent (10 out of 21 patients), which yields no statistically significant difference between the groups (Table 3). The incidence of DVT with respect to age, sex and type of operation is shown in Table 4.

Estimation of the salicylate concentration in serum was made once in the first 32 patients investigated. Samples were drawn in the morning about 6–8 hours after the last medication. Of those treated with ASA, the salicylate-concentrations varied between 0.4 and 9.5 mg per cent. In the last 19 patients investigated four samples were drawn, two as a morning sample and two in the afternoon about 2 hours after medication. The concentration of salicylates in the ASA-treated group varied between 0.8 and 22 mg per cent where the noon samples exceeded the morning samples by 1.2–6 mg per cent.

To evaluate if the incidence of DVT was dependent on the salicylate concentration, the salicylate group was divided into two groups, one with the lowest determined salicylate concentration below 2 mg per

Table 2. Number of patients with and without signs of DVT in the clinically and phlebographically investigated patients, respectively.

Clinical judgement	Phlebography			Total no.
	DVT	Non-DVT	Not performed	
DVT	5	1	5	11
Non-DVT	10	19	11	40
Total no.	15	20	16	51

Table 3. Number of patients with and without phlebographically verified DVT in the ASA- and placebo-treated patients, respectively. Chi_1^2 (with Yates' correction) = 0.30 (non-significant).

Treatment	Diagnosis		Total no.
	DVT	Non-DVT	
ASA	10	11	21
Placebo	5	9	14
Total no.	15	20	35

cent and the other with the lowest determined salicylate concentration above 2 mg per cent. When these groups were compared with the placebo-treated group almost the same incidence of DVT was found in all three groups (Table 5).

The platelet aggregation test was performed to verify if ASA would alter platelet aggregation. This test was performed once in nine patients. Four of these were treated with placebo, only one showed an inhibited platelet aggregation induced by collagen, whereas the other three had a normal aggregation. None of these four patients had any measurable amounts of salicylate in serum. The other five patients belonged to the ASA-treated group. Four of these had an inhibited platelet aggregation and in one the aggregation curves were not reliable. None of these patients had an observed salicylate concentration below 1.4 mg per cent.

Table 4. Total number of ASA- and placebo-treated patients, respectively, and total number (and per cent) of patients with phlebographically verified DVT in the different groups.

Subgroups		ASA		Placebo	
		Total no.	DVT No. (%)	Total no.	DVT No. (%)
Ages	40-50	5	3 (60)	2	0 (—)
	56-65	9	3 (33)	7	2 (29)
	66-80	7	4 (57)	5	3 (60)
Sexes	Female	14	8 (57)	6	2 (33)
	Male	7	2 (29)	8	3 (37)
Type of operation	Total hip	6	3 (50)	3	1 (33)
	Osteotomy	15	7 (47)	11	4 (36)

Table 5. Total number of patients treated with placebo and ASA, respectively, and incidence of DVT. The ASA-treated group is divided into those with the lowest observed salicylate concentration above and below 2 mg per cent, respectively.

Subgroups	Placebo		ASA lowest conc. above 2 mg %		ASA lowest conc. below 2 mg %	
	Total no. (%)	DVT Total no. (%)	Total no. (%)	DVT Total no. (%)	Total no. (%)	DVT Total no. (%)
Ages	40-55	2	0 (—)	2	1 (50)	2 (66)
	56-65	7	2 (29)	2	0 (—)	3 (50)
	66-80	5	3 (60)	7	4 (57)	0 (—)
Sexes	Female	6	2 (33)	9	5 (55)	3 (60)
	Male	8	3 (37)	3	0 (—)	2 (40)
Type of operation	Total hip	3	1 (33)	4	2 (50)	1 (50)
	Osteotomy	11	4 (36)	7	3 (43)	4 (50)

No side effects after ASA in the form of anaphylaxis or increased bleeding were noticed, but because of gastrointestinal disturbances in five patients the treatment had to be stopped. These patients were then excluded from the study, and are not included with the 51 patients.

DISCUSSION

The reported incidence of deep venous thrombosis (DVT) following hip surgery, documented in various publications (Hamilton et al. 1970, Bergquist et al. 1972), varies between 30 and 50 per cent. These results are in accordance with our findings, i.e. 43 per cent.

Agents directly affecting the platelet function, i.e. acetylsalicylic acid that inhibits the platelet release reaction and thus interferes with the platelet aggregation, have also been used in trials to prevent thromboembolic diseases, and it is reasoned that if the initial platelet thrombosis can be avoided the subsequent development of a fibrin clot might be prevented.

Probably this kind of drug would be of more value in preventing arterial thrombi, due to their relatively larger number of aggregated platelets, but ASA has been tried with diverging results as a prophylaxis against venous thrombosis. O'Brien et al. (1971) reported no decrease in postoperative thrombosis detected with I^{125} -labelled fibrinogen in patients treated with ASA compared with placebo; they used ASA in two doses, 0.6 and 2.4 g/day, respectively. On the other hand, Salzman et al. (1971) suggested a positive effect regarding clinically diagnosed thrombosis after postoperative treatment with 1.2 g ASA/day with patients on whom elective arthroplasty of the hip had been performed. Their data suggested ASA to be as effective as dextran and warfarin but they advised further examination before ASA could be considered as a drug of choice. Furthermore, Breddin & Scharrer (1972) reported a decrease in clinically diagnosed thromboembolic episodes postoperatively in patients treated with ASA, 1.5 g daily, compared with patients given placebo.

We are aware that criticism can be raised against our starting with ASA the first postoperative day, when a thrombosis might have already been formed during the operation and it would thus be too late to achieve any effective prophylaxis.

However, in elderly patients, with more or less pronounced arteriosclerosis, and varying degrees of congestive heart failure and varicose

veins of varying severity (factors predisposing to venous stasis and increased risk for development of thrombi) there will not only be progress in thrombi formed during the operation, but probably also formation of new thrombi will take place postoperatively (Culver et al. 1970). Thus, we assumed that if ASA had any significant effect in abolishing DVT this would take place also if the treatment were started on the first postoperative day. Furthermore, if it were documented that ASA could prevent thrombus formation when administered postoperatively, it would also be of benefit to patients with traumatic injuries.

The platelet aggregation performed with collagen was inhibited in those patients treated with ASA. One patient in the placebo group had an inhibited collagen-induced platelet aggregation without any detectable amounts of salicylates in serum and it was assumed that the effect of some drug taken prior to admission to hospital was still detectable in the aggregation test of this patient.

In spite of the altered platelet function and irrespective of the salicylate concentration in serum, our results do not show any altered incidence of DVT after hip surgery in patients treated with 2 g ASA daily, administered from the first postoperative day.

SUMMARY

Fifty-one patients were investigated concerning thromboembolic complications in the operated leg after elective surgery of the hip. Suspicion of clinical deep venous thrombosis (DVT) arose in 11 patients, i.e. 21 per cent. Thirty-five patients were investigated with phlebography. The incidence of DVT among those patients was 15 cases, i.e. 43 per cent.

It is concluded that acetylsalicylic acid, a drug which inhibits the platelet release reaction and thereby blocks the platelet aggregation, given orally in a dose of 2 gram per day from the first postoperative day, is not effective in diminishing the incidence of postoperative deep venous thrombosis.

ACKNOWLEDGEMENTS

We express our sincere gratitude to Dr. Margareta Blombäck for valuable support and discussions. This work was supported by grants from the Swedish Medical Research Council (19X-520) and from Ulla and Gustaf af Ugglas' foundation.

REFERENCES

- Ahlberg, A., Nylander, G., Robertson, B., Cronberg, E. & Nilsson, I.-M. (1968) Dextran in prophylaxis of thrombosis in fractures of the hip. *Acta chir. scand.*, Suppl. 387, 83.
- Bergquist, E., Bergquist, D., Bronge, A., Dahlgren, S. & Lindquist, B. (1972) An evaluation of early thrombosis prophylaxis following fracture of the femoral neck. *Acta chir. scand.* **138**, 688.
- Bergvall, U. (1971) Phlebography in acute deep venous thrombosis of the lower extremity. A comparison between centripetal ascending and descending phlebography. *Acta radiol. (Stockh.)* **11**, 148.
- Borgström, S., Greitz, T., van der Linden, W., Molin, I. & Rudics, I. (1965) Anticoagulant prophylaxis of venous thrombosis in patients with fracture of the neck of the femur. *Acta chir. scand.* **129**, 500.
- Born, G. V. R. & Cross, M. J. (1963) The aggregation of blood platelets. *J. Physiol. (Lond.)* **168**, 178.
- Breddin, K. & Scharrer, I. (1972) Clinical trials of platelet antiaggregating drugs. Thrombosis: Mechanisms and control. At the meeting of the International Society for Thrombosis and Haemostasis held in Washington D.C. August 1972.
- Bronge, A., Dahlgren, S. & Lindquist, B. (1971) Prophylaxis against thrombosis in femoral neck fractures—a comparison between dextran 70 and dikumarol. *Acta chir. scand.* **137**, 29.
- Culver, D., Crawford, J. S., Gardiner, J. H. & Wiley, A. M. (1970) Venous thrombosis of the upper end of the femur. *J. Bone Jt Surg.* **52-B**, 61.
- Greitz, T. (1954) The technique of ascending phlebography of the lower extremity. *Acta radiol. (Stockh.)* **42**, 421.
- Hamilton, H. W., Crawford, J. S., Gardiner, J. H. & Wiley, A. M. (1970) Venous thrombosis in patients with fracture of the upper end of the femur. A phlebographic study of the effect of prophylactic anticoagulant. *J. Bone Jt Surg.* **52-B**, 268.
- Harris, W., Salzman, E. & de Sanctis, R. (1967) The prevention of thromboembolic disease by prophylactic anticoagulation. A controlled study in elective hip surgery. *J. Bone Jt Surg.* **49-A**, 81.
- Johnson, S. R., Bygdeman, S. & Eliasson, R. (1968) Effect of Dextran on post-operative thrombosis. *Acta chir. scand.*, Suppl. 387, 80.
- Lindblom, K. (1941) Phlebographische Untersuchung des Unterschenkels bei Kontrastinjektion in eine subkutane Vene. *Acta radiol. (Stockh.)* **22**, 288.
- Myhre, H. O. & Hølen, A. (1969) Tromboseprofylakse. Dextran eller Warfarinatrium? Et kontrollert klinisk forsök. *Nord. Med.* **82**, 1534.
- O'Brien, J. R., Path, F. C., Heywood, J. B. & Heady, J. A. (1966) The quantitation of platelet aggregation induced by four compounds. A study in relation to myocardial infarction. *Thrombos. Diathes. haemorrh. (Stuttg.)* **16**, 752.
- O'Brien, J. R. (1968) Effects of salicylates on human platelets. *Lancet* **i**, 779.
- O'Brien, J. R., Tulevski, V. & Etherington, M. (1971) Two in vivo studies comparing high and low aspirin dosage. *Lancet* **i**, 399.
- Saltzman, A. (1948) Fluorophotometric method for estimation of salicylate in blood. *J. biol. Chem.* **174**, 399.

- Salzman, E. W., Harris, W. H. & de Sanctis, R. W. (1966) Anticoagulation for prevention of thromboembolism following hip fractures. *New Engl. J. Med.* **275**, 122.
- Salzman, E. W., Harris, W. H. & de Sanctis, R. W. (1971) Reduction in venous thromboembolism by agents affecting platelet function. *New Engl. J. Med.* **284**, 1287.
- Sevitt, S. & Gallagher, N. G. (1959) Prevention of venous thrombosis and pulmonary embolism in injured patients. A trial of anticoagulant prophylaxis with phenindione in middle-aged and elderly patients with fractured necks of femur. *Lancet* **ii**, 981.
- Zucker, M. B. & Peterson, J. (1968) Inhibition of adenosindiphosphate-induced secondary aggregation and other platelet functions by acetylsalicylic acid ingestion. *Proc. Soc. exp. Biol. (N.Y.)* **127**, 547.

Key words: acetylsalicylic acid; thromboembolism; hip surgery; osteoarthritis

Correspondence to:

Julius Soreff, M.D.
Department of Orthopaedic Surgery
Karolinska Hospital
Stockholm, Sweden