PAPERS AND ORIGINALS

Preventing venous thromboembolism in elderly patients with hip fractures: studies of low-dose heparin, dipyridamole, aspirin, and flurbiprofen

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Summary

Low-dose heparin, dipyridamole (alone and in combination with aspirin), and flurbiprofen were evaluated as potential prophylactic agents against deep venous thrombosis in elderly patients with hip fractures. None of the agents that modify platelet behaviour could reduce the frequency of isotopically diagnosed venous thrombosis. Low-dose heparin reduced the overall frequency of venous thrombosis and its extent as judged by the frequency of bilaterally abnormal scans, but this reduction did not achieve statistical significance.

Introduction

Venous thromboembolism is a common cause of death in elderly patients with fractures of the femoral neck. The mortality due to this complication can be reduced by oral anticoagulation,[1 2] but the latter requires frequent laboratory tests and skilled supervision. Moreover, surgeons fear that it will increase the risk of operative and postoperative bleeding. At present only 3% of orthopaedic surgeons treating elderly patients with femoral fractures offer anticoagulant prophylaxis.[3]

It has been suggested that platelet masses, forming in valve pockets, are the source of deep venous thrombosis. As platelet behaviour in vitro or in animals can be modified by aspirin,[4] dipyridamole,[5 6] and the non-steroidal anti-inflammatory agent flurbiprofen,[7] it seemed possible that these agents might offer effective prophylaxis against venous thrombosis, without causing unacceptable bleeding or needing laboratory control. A conventional anticoagulant, heparin, used in an unconventional way has also been shown to reduce the risk of venous thrombosis in patients undergoing elective surgery. Given in small doses, insufficient to prolong clotting times, it is thought to activate an inhibitor of factor X generation,[8] but its value in elderly patients with femoral fractures has not been clarified.

We report here a series of prospective controlled studies on the ability of low-dose heparin, dipyridamole (alone and in combination with aspirin), and flurbiprofen to modify the incidence of isotopically diagnosed venous thrombosis in patients aged over 60 years with hip fractures.

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Patients and methods

The patients studied were aged 60 years and over and had been admitted to Nottingham General Hospital with fractures of the femoral neck, sustained within the preceding 24 hours. On admission to the ward each patient was examined, and if no grounds for exclusion were present, he or she was entered into the trial. Patients were excluded if they had (*a*) a bleeding tendency, (*b*) hypotension, (*c*) a pathological fracture, or (*d*) severe intellectual impairment or a recent stroke. In the studies of aspirin and flurbiprofen an additional reason for exclusion was a history of regular aspirin or ibuprofen use before admission to hospital.

After a patient had been entered into the trial treatment instructions were taken from a sealed and numbered random-allocation envelope. To avoid a seasonal imbalance in the allocation to the various regimens, we prepared groups of envelopes, each block having a complete random sequence. In the study in which patients on low-dose heparin or dipyridamole were compared with a group receiving no treatment blocks of 12 envelopes were prepared. In the other two studies, in which a single treatment group was compared with a control group, blocks of eight envelopes were prepared.

The randomised treatment instructions were printed on adhesive labels, which were immediately fixed to the patient's treatment chart so that the regimen could be started without delay. The design of the treatment charts allowed us to check daily that the schedule was being

followed. The treatment began at the first drug-round after admission, and in all cases the treatment regimens were started before operation.

TREATMENT SCHEDULES

All patients received routine physiotherapy throughout the study and were mobilised as rapidly as possible. Patients in the control groups received no additional treatment.

Trial 1—Patients in the treatment group received either dipyridamole 100 mg orally every eight hours for 10 days or subcutaneous heparin 5000 U every eight hours for 10 days. Aqueous sodium heparin 25 000 U/ml (Weddell Pharmaceuticals) was used, which enabled the injected volume to be only 0·2 ml. The injections were given into the abdominal wall by sisters or staff nurses who had been instructed in the technique.

Trial 2—Patients in the treatment group received dipyridamole 100 mg and acetylsalicylic acid 300 mg orally every eight hours for 10 days. During this period the orthopaedic surgeons gave no aspirin-containing analgesics, and any patient requiring an analgesic was given dihydrocodeine.

Trial 3—Patients in the treatment group were given flurbiprofen 50 mg orally every eight hours for 10 days. As in trial 2, dihydrocodeine was used if patients needed an analgesic.

MONITORING THE PATIENTS

^{125}I-labelled fibrinogen scanning was performed.[2 9] A scan was considered to be positive if a difference in uptake of 20% persisted for 24 hours between adjacent counting sites on the same lower leg or between comparable sites on the two limbs.

The surgeons were asked to report excessive bleeding at operation, and we noted the frequency of leaking wounds and haematomas. The patients were examined daily for clinical signs of venous thrombosis and pulmonary embolism, and necropsies, with detailed dissection of the leg veins, were performed in those who died. Too few patients died for conclusions to be drawn from the mortality and necropsy findings, so the treatment regimens were evaluated on the scanning results, as validated for this group of patients by Morris and Mitchell.[9]

Results

Trial 1—Seventy-two patients were admitted to this study and were equally divided among the three groups. Details of the patients' sex, age, delay between admission and operation, and unfitness for operation are shown in table I. Dipyridamole had no effect on isotopic venous thrombosis, while low-dose heparin reduced the incidence of bilaterally abnormal scans, but the reduction did not achieve statistical significance with the numbers studied (table II). Four patients developed clear-cut clinical evidence of venous thrombosis.[2] Two were in the control group, one was receiving low-dose heparin, and one was receiving dipyridamole. Ten patients developed doubtful signs of venous thrombosis (three controls, two on heparin, and five on dipyridamole).

Trial 2—Sixty-four patients were admitted to this study and were equally divided between the control and treated groups (table I). The combination of aspirin and dipyridamole did not influence the incidence of positive leg scans (see table II). Three patients developed clear-cut clinical venous thrombosis (one control and two on aspirin and dipyridamole), and nine developed doubtful signs of venous thrombosis (four controls and five on aspirin and dipyridamole)

Trial 3—Forty patients were admitted to this study and were equally divided between the groups (table I). Flurbiprofen did not affect the incidence of isotopically diagnosed venous thrombosis (table II). One patient from each group developed clear clinical evidence of venous thrombosis, and seven patients developed less definite signs (three controls and four on flurbiprofen).

No significant complications were observed in any of the treatment groups and no patient had to be withdrawn from the study because of side effects.

Discussion

Unlike warfarin, which significantly reduces the incidence of isotopically diagnosed venous thrombosis in elderly patients with fractures of the femoral neck,[2] the four regimens tested here had no significant effect on the incidence of isotopically diagnosed thrombosis. Only the patients receiving low-dose heparin showed any deviation from the pattern observed in the control groups, but this trend was too small to be significant. Our findings thus support the negative findings reported in an uncontrolled study of patients with femoral fractures[10] and do not confirm the significant reduction in isotopic calf-vein thrombosis observed by Gallus *et al.*[11]

These findings are very different from the consistent reduction in the incidence of isotopic venous thrombosis that has been reported when low-dose heparin has been used in patients undergoing elective surgery.[12–14] There are two possible

TABLE I—*Details of patients studied in each trial*

Clinical data	Trial 1			Trial 2		Trial 3	
	Control	Heparin	Dipyridamole	Control	Aspirin and dipyridamole	Control	Flurbiprofen
No of patients	24	24	24	32	32	20	20
Sex:							
No of men	5	5	5	7	4	4	6
No of women	19	19	19	25	28	16	14
No aged (years):							
60-69	5	4	4	4	5	4	2
-79	10	10	7	13	15	6	8
-89	9	7	10	12	9	9	10
-100	0	3	3	3	3	1	0
Mean age (years)	76·5	77·5	79	78·2	78·1	78·7	78·8
Mean delay between admission and operation (days)	3·2	3·9	3·1	3	3·1	4·1	4·7
No treated conservatively	2	4	1	4	4	1	2

TABLE II—*Proportion of patients with isotopically diagnosed venous thrombosis in the three trials*

	Trial 1			Trial 2		Trial 3	
	Control (n = 24)	Heparin (n = 24)	Dipyridamole (n = 24)	Control (n = 32)	Aspirin and dipyridamole (n = 32)	Control (n = 20)	Flurbiprofen (n = 20)
No (%) with unilateral thrombosis:							
On side of fracture	6 (25)	7 (29)	7 (29)	11 (34)	10 (31)	6 (30)	7 (35)
On opposite side	2 (8)	2 (8)	1 (4)	2 (6)	1 (3)	2 (10)	1 (5)
No (%) with bilateral thrombosis	8 (33)	3 (13)	7 (29)	8 (25)	9 (28)	4 (20)	5 (25)
Total (%) with thrombosis	16 (67)	12 (50)	15 (63)	21 (66)	20 (63)	12 (60)	13 (65)

reasons for this difference. Firstly, the magnitude of the thrombotic challenge may have been much greater in our patients because of their advanced age, their immobility, and the severity of their injury. Secondly, in injured patients heparin can be given only after the event, whereas in elective surgery the regimen can be started before operation. Wessler and Yin[8] have suggested that low-dose heparin acts by enhancing the inhibition or neutralisation of activated factor X and this action would obviously not be of value if considerable quantities of activated factor X had already been generated by injury and had initiated the thrombotic process.

The three agents that modify platelet behaviour had no effect on isotopically diagnosed venous thrombosis. Emmons *et al*[5] found that dipyridamole abolished platelet thrombus formation at sites of arterial injury in rabbits and modified the in-vitro aggregation behaviour of human platelets.[6] It inhibits platelet thrombus formation on dialyser membranes[15] and reduces the frequency of embolic complications in patients with prosthetic heart valves.[16] Nevertheless, dipyridamole was found to have no effect in two studies of venous thrombosis.[17 18] In both trials venous thrombosis was diagnosed only clinically, but our study shows that the drug also has no effect when a more sensitive endpoint is used.

Acetylsalicylic acid inhibits the second phase of platelet aggregation and prevents the release reaction in citrated plasma systems studied in vitro.[4 19 20] On this basis it has been claimed that it should exert an antithrombotic effect in vivo but in a daily dose of 600 mg it did not prevent the development of venous thrombosis in elective surgical patients.[21] Some have suggested, however, that even though dipyridamole and aspirin fail to prevent venous thrombosis when used separately, they might still be effective when used together. A synergism between the two agents was observed by Harker and Schlichter,[16] who found that the reduction of the abnormal platelet consumption produced by dipyridamole in patients with prosthetic heart valves was potentiated by aspirin, although aspirin alone had no effect. Renney *et al*[22] have reported that the combination of aspirin and dipyridamole significantly reduced the incidence of isotopic venous thrombosis in elective surgical patients, but our study has failed to show a similar reduction in patients with femoral fractures.

Flurbiprofen inhibits collagen-induced platelet aggregation in citrated systems in vitro, and prevents death from pulmonary thromboembolism after the injection of collagen in animals. Its mode of action on platelets seems to be different from those of dipyridamole and aspirin,[7] but, like them, it proved incapable of modifying deep venous thrombosis in our patients.

There are two possible reasons why these two agents that modify in-vitro platelet behaviour (aspirin and flurbiprofen) proved ineffective in suppressing deep venous thrombosis. Firstly, unlike an arterial thrombus, in which platelet masses make a major contribution to the thrombotic structure a venous thrombus has a relatively small "white head" and a larger, clot-like "red tail."[23] Although platelet masses in valve pockets have been proposed as the origin of leg-vein thrombi,[24] it is the unattached tail which may break off as a lethal pulmonary embolus. Thus the ability of anticoagulants to modify venous thrombosis in patients with femoral fractures,[1 2] the inability of antiplatelet agents to do so, and the equivocal position of low-dose heparin may reflect the negligible contribution made by platelets and the more major contribution made by blood coagulation to venous thromboembolism. Secondly, although platelets play a part in the genesis of the thrombi, the systems used to identify antiplatelet agents may be irrelevant to conditions in vivo.[16] Behaviour observed in citrated platelet-rich plasma, stimulated by collagen or adenosine diphosphate, cannot in our present state of knowledge be described as a "platelet function." Until we have carried out clinical trials on the agents which these so-called function tests have identified we shall not know which in-vitro tests are of value and which are not.

Unlike aspirin and flurbiprofen, dipyridamole does considerably inhibit platelet thrombus formation in vivo in animals, and yet in our hands it proved no more active than aspirin and flurbiprofen in preventing venous thrombosis. Perhaps this indicates that the first explanation advanced above is the correct one, and that platelets play a minor role in venous thrombosis.

Our studies have thus failed to find a regimen that can take the place of conventional oral anticoagulation in preventing deep venous thrombosis in elderly patients with hip fractures. If orthopaedic surgeons want to use effective prophylaxis the present evidence indicates that they must use oral anticoagulants.

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