Prevention of venous thromboembolism after total knee replacement by high-dose aspirin or intermittent calf and thigh compression

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Summary and conclusions

A prospective study of patients undergoing total knee replacement was carried out by using a combination of ^{125}I-fibrinogen scanning and phlebography, and showed a high incidence of venous thromboembolic disease (TE). Ventilation-perfusion lung scanning was performed to detect pulmonary emboli in most patients. High doses of aspirin and an intermittent low-pressure pneumatic compression device (IPCD) were effective, even in women, in preventing TE. Low doses of aspirin and placebo were equally ineffective in preventing TE. Lung-scan abnormalities compatible with pulmonary emboli were found in six out of 10 patients with isolated calf-vein thrombi. Conventional tests of platelet function did not predict the development of TE. No significant differences were found between the patients receiving low and high doses of aspirin with respect to the mean template bleeding time or platelet aggregation in response to adenosine diphosphate, collagen, and epinephrine, although these variables were significantly abnormal in the two groups receiving aspirin compared with those treated with placebo and the IPCD.

Thus high doses of aspirin and a new low-pressure IPCD were effective in preventing venous TE in patients (predominantly women) undergoing total knee replacement.

Introduction

Venous thromboembolism (TE), a common complication of orthopaedic surgery,[1-3] is also a major cause of postoperative death.[4] Although effective prophylaxis with low-dose heparin is feasible in many patients, its efficacy in those undergoing orthopaedic surgery remains controversial[5 6] and is compounded by bleeding complications.[6] Controversy exists regarding the effectiveness of aspirin as a mode of prophylaxis in venous TE,[7 8] particularly in women.[8] We conducted a pilot study, which showed a high incidence of TE (about 80%) in patients undergoing total knee replacement at our hospital.[9] Patients with a mean intake of 3·5 g aspirin/day had a significantly lower incidence of TE than patients who had not ingested any aspirin. We report here a prospective study designed to evaluate the efficacy of a low dose of aspirin (325 mg thrice daily), a high dose of aspirin (1·3 g thrice daily), and an intermittent low-pressure pneumatic compression device (IPCD) as compared with placebo (one tablet thrice daily) in preventing TE in patients undergoing total knee replacement.

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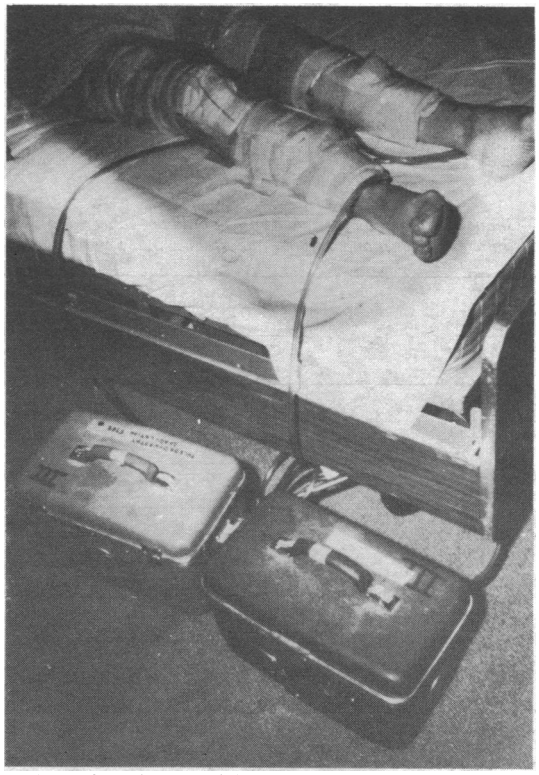
Patients and methods

We enrolled 46 consecutive patients, aged over 40 years, admitted for total knee replacement after we had obtained their written informed consent. The protocol and consent form were approved by the hospital's human investigation committee. Patients with a history of deep vein thrombosis (DVT) or pulmonary embolism in the six months before admission were excluded from the study. Randomisation was made at least one month before operation by using a computer-generated random-number table: group 1 received a placebo, one tablet thrice daily; group 2 received aspirin 325 mg thrice daily; group 3 received aspirin (Enseals, each capsule 650 mg) 1300 mg thrice daily; and patients in group 4 used an IPCD.

After randomisation all patients received a letter regarding medications they were allowed to ingest. Patients in groups 1 and 4 were asked not to use any aspirin-containing analgesics, but were allowed to take paracetamol, in the week before admission. Patients in group 2 were allowed to take up to three tablets (325 mg each) of aspirin per day, and patients in group 3 up to 12 tablets per day, in the week before admission. All patients were asked not to take indomethacin, phenylbutazone, or dipyridamole in the week before admission. Placebo or aspirin was started in the stated protocol dose immediately after admission. Patients in group 3 with plasma salicylate concentrations above 300 mg/l or with severe ringing in the ears or difficulty in hearing had their total daily dose of aspirin reduced by 650 mg. The IPCD (figure) consists of two thigh and calf cuffs that inflate alternately, twice a minute, achieving a maximum pressure of 30 mm Hg in five seconds; the cuffs deflate rapidly. Thigh and calf cuffs were applied to the non-operated limb on the operating table before anaesthesia, and to the operated limb at the end of the operation.



Patient after right total knee replacement, with the two thigh and two calf cuffs of the IPCD.

All methods of prophylaxis and scanning were continued postoperatively until the day on which the patients were discharged from hospital.

On admission each patient received an injection of 100 μCi of ^{125}I-fibrinogen. Patients were scanned as described,[9] and scanning was continued until they were discharged. Median hospital stay after operation was 16 days. Phlebography was performed on the operated limb in all patients one to two days before discharge. Whenever a ^{125}I-fibrinogen scan of the non-operated limb was positive phlebography was carried out. Tests for pulmonary emboli (chest *x*-ray examination and ventilation-perfusion lung scanning) were performed initially only on patients with positive phlebograms. Towards the end of the study, however, all patients, regardless of phlebographic findings, were evaluated for pulmonary emboli.

Activated partial thromboplastin time, one-stage prothrombin time, thrombin time, fibrinogen concentration, euglobulin lysis time, and antithrombin III and α_2 macroglobulin concentrations (commercially available plates) were measured and assays for fibrin split products by immunodiffusion, staphylococcal clumping test, and a tanned red-cell haemagglutination inhibition immunoassay done before and a few hours and three to five days after operation. Studies of platelet function were performed in all patients before operation and between days 3 and 5 postoperatively; the methodology has been described.[10] Plasma salicylate concentrations were measured before and regularly after operation. Liver function tests were carried out in all patients before and after operation.

Results

Forty-six patients were randomised to the four groups. In two patients receiving the low and one receiving the high dose of aspirin evaluation was incomplete or the aspirin was administered incorrectly; they were therefore excluded from the final assessment. All subsequent data therefore pertain to 43 patients: group 1 (control) 12 patients; group 2 (low-dose aspirin) nine; group 3 (high-dose aspirin) 12; and group 4 (IPCD) 10.

The highest incidences of DVT (confirmed by phlebography) were in groups 1 (9/12) and 2 (7/9). By contrast, the incidence of DVT was appreciably reduced in groups 3 (1/12) and 4 (1/10) (table I).

The ratio of women to men was 9:3 in group 1, 9:0 in group 2, 11:1 in group 3, and 7:3 in group 4. Thus only seven of the 43 patients studied were men. Patients who developed thrombosis had a mean age of 70 years as compared with 64 years in those who did not ($p=0.01$). The mean ages of the patients in groups 1 (66 years), 3 (63 years), and 4 (66 years) were well within normal chance variation; the mean age in group 2 (72 years) was somewhat high. An overall age comparison of the four groups did not quite reach significance ($p=0.055$). The mean age of patients in group 2 was significantly higher than that of patients in group 3, even after allowing for post hoc choice of comparison.

We evaluated our data to find out whether estimated treatment differences between groups might be an artefact of age differences. We concluded from this analysis that adjusting for age made only slight changes to the results of comparing treatments. There remained a significantly lower incidence of DVT in groups 3 and 4 as compared with groups 1 and 2. The analysis is described in detail below and the results summarised in table II.

Adjusting the estimated effects of treatment for the continuous variable age entailed using methods that are only approximate for groups as small as those here. These methods are based on linear logistic models,[11] in which the odds on DVT (the ratio of the incidence of DVT to no DVT) are analysed on a logarithmic scale. We used logarithms to base 10. All analyses were carried out by using the GLIM computer package.[12] The estimated effect of age was 0·06 per year on the log odds scale, which corresponds to a doubling of the odds for DVT for each five-year increase in age. The estimated age effect was just significant ($p=0.025$) but was consistent with other findings.

Table II shows all intercomparisons of treatment groups, both with adjustment for age and ignoring age. The comparison of groups 2 and 3 (low- and high-dose aspirin) illustrates the results obtained. In the best analysis, adjusting for age, the difference in log odds was estimated at 1·30 with a standard error of 0·61 and a significance of 0·016. The antilog of 1·30 is 20·0 and is the relative risk between the two groups: the odds on DVT for a patient receiving a low dose of aspirin are estimated as 20 times higher than those for a patient of the same age receiving a high dose of aspirin. The analysis ignoring age gave an estimated difference of log odds of 1·59 corresponding to a relative risk of 39 between the low- and high-dose groups. While the adjustment for age reduced the apparent advantage over the low-dose group, a substantial and significant advantage remained. The adjustment for age caused smaller changes in all other comparisons, leaving the initial findings intact.

When the association between the most proximal site of DVT (determined by phlebography) and the presence of pulmonary emboli (ventilation-perfusion lung scanning) was examined, six out of 10 patients with calf-vein thrombi had evidence compatible with pulmonary embolism (table III). None of the eight patients with a positive lung scan had clinical symptoms suggestive of pulmonary embolism. In the latter part of the study lung scanning was performed in nine patients with negative ^{125}I-fibrinogen scans and phlebograms. None of these lung scans were positive. Fifteen patients had DVT on the operated side alone and three bilateral DVT; none had thrombi on the non-operated side alone.

Table IV shows an evaluation of the data on platelet function. Before surgery collagen-induced platelet aggregation was significantly impaired in the patients in groups 2 and 3, who had been allowed to ingest aspirin in the week before surgery, and the template bleeding time was longer as compared with that in groups 1 and 4 combined (mean ±SE of mean 5·1±0·52 min *v* 4·0±0·27 min; $p=0.06$). Template bleeding times tended to be higher in the patients in group 3 (5·9±0·8 min) as compared with those in group 2 (4·0±0·5 min; $p=0.08$). Interestingly, an analysis of failures versus successes of prophylaxis in the patients in groups 2 and 3 combined showed that the template bleeding time before operation in patients who subsequently did not develop thrombosis was 5·9±0·7 min compared with 3·7±0·4 min in those who did ($p=0.04$). None of the other platelet-function tests performed could distinguish patients in groups 2 and 3 before or after operation. The bleeding time was appreciably prolonged in groups 2 and 3 compared with 1 and 4 postoperatively, and

TABLE I—*Incidence of deep vein thrombosis (DVT) in the four groups of patients*

Group	No of patients	DVT present	DVT absent	Incidence of DVT
1: Control	12	9	3	75%
2: Low-dose asprin (325 mg thrice daily)	9	7	2	78%
3: High-dose aspirin (1·3 g thrice daily)	12	1	11	8%
4: IPCD	10	1	9	10%

Significance of differences between groups (Fisher's exact test, one-tailed): 1 *v* 3 $p=0.001$; 1 *v* 4 $p=0.004$; 2 *v* 3 $p=0.002$; 2 *v* 4 $p=0.005$; 1 *v* 2 and 3 *v* 4 not significant.

TABLE II—*Comparison of log odds of DVT according to whether analysis done adjusting for age or ignoring age. (Age coefficient = 0·06 per year; standard error of difference = 0·033)*

	Adjusting for age			Ignoring age		
	Low-dose aspirin	High-dose aspirin	IPCD	Low-dose aspirin	High-dose aspirin	IPCD
Control	0·26±0·57 NS	1·56±0·59 p=0·004	1·64±0·59 p=0·003	−0·07±0·54 NS	1·52±0·54 p=0·003	1·43±0·54 p=0·004
Low-dose aspirin		1·30±0·61 p=0·016	1·38±0·60 p=0·011		1·59±0·57 p=0·003	1·50±0·57 p=0·004
High-dose aspirin			0·08±0·67 NS			−0·09±0·64 NS

Each set of entries corresponds to a comparison between the treatment group for the row and the treatment group for the column. The top entry is the estimated difference between the common logarithms of the odds on DVT ± the standard error of the difference. The bottom figure is the probability (one-tailed test).
NS = Not significant

TABLE III—*Correlation between most proximal site of DVT and pulmonary embolism. Figures are numbers of patients*

Site of DVT			Lung scan	
Calf	Popliteal	Femoral	Positive	Negative
		Group 1: control		
4			3	1
	2		1	1
		3		3
		Group 2: low-dose aspirin		
4			1	3
	1		1	
		2		1*
		Group 3: high-dose aspirin		
1			1	
		Group 4: IPCD		
1			1	
		Total		
10	3	5	8	9

*In one patient with femoral DVT lung scanning could not be performed.

TABLE IV—*Comparison of platelet function*

Test	Significance			
	Group 2 *v* group 3		Groups 1 and 4 *v* groups 2 and 3	
	Before operation	After operation	Before operation	After operation
Template bleeding time* ..	p = 0·08	NS	p = 0·06	p = 0·01
Induced aggregation†:				
Collagen 1·8 mg/ml	NS	NS	p < 0·01	p < 0·0001
Epinephrine 550μM	NS	NS	NS	p < 0·0002
Adenosine diphosphate 3μM ..	NS	NS	NS	p < 0·05
Platelet retention†	NS	NS	NS	NS
Platelet factor 3†	NS	NS	NS	NS

*Student's *t* test. †U test.
NS = Not significant.

this was associated with abnormal platelet aggregation induced by adenosine diphosphate, collagen, and epinephrine.

Although activated partial thromboplastin times were significantly shorter (30·6 ± 0·8s) a few hours after operation than before operation (33·4 ± 0·8s; paired Student's *t* test: $p < 0·01$) and the mean concentration of antithrombin III fell from 33·4 ± 0·9 to 29·8 ± 1·1 mg/100 ml ($p < 0·001$), these differences did not persist on days 3-5. None of the coagulation tests used could predict patients at subsequent risk for thrombosis.

Finally, there was no difference with regards to the tourniquet time at operation, duration of operation, postoperative management, or other known risk factors for DVT in the four groups; none of the patients received oestrogen treatment, had a malignant tumour, was greatly obese, or had congestive heart failure or arterial insufficiency. One patient in group 3, who was omitted from the final evaluation, developed active bleeding from a hiatal hernia and salicylate gastritis on the fourth postoperative day and required blood transfusions. In three additional patients receiving high doses of aspirin the total daily dose had to be reduced to 3·25 g/day because of tinnitus. One of these three patients developed DVT. There was no difference in blood loss or the amount of blood transfused between the four groups. None of the patients developed any evidence of appreciable hepatocellular dysfunction during the study period. None of the patients died.

Discussion

This prospective study has confirmed our previous finding[10] of a high incidence of venous TE in patients undergoing total knee replacement. TE was significantly reduced by large doses of aspirin (1·3 g thrice daily) and the IPCD, but not by small doses of aspirin (325 mg thrice daily) or the placebo. Most patients in this study were women. There was some evidence of a lower incidence of TE in younger patients. After adjusting our results for the age difference between patients receiving low and high doses of aspirin, however, the incidence of TE was still significantly reduced by high doses of aspirin and the IPCD. Our data suggest that higher doses of aspirin than heretofore used in men may be necessary to reduce TE in women at a high risk of developing this complication; and that the antithrombotic effect of aspirin is not solely due to its effect on commonly measured parameters of platelet function, since both low and high doses caused similar platelet dysfunction postoperatively. Larger doses of aspirin may possibly exert an appreciable anti-inflammatory effect and hence reduce oedema at the site of operation, thereby diminishing venous stasis.

Aspirin in doses of 1·2-2·0 g/day effectively prevents postoperative DVT in man,[8 13] and in a dose of 1·5 g/day reduces mortality from pulmonary emboli shown at necropsy.[14] Women undergoing total hip replacement, however, were not protected against TE by aspirin in a dose of 1200 mg/day.[8]

Conflicting data exist regarding the antithrombotic effect of aspirin in animals. Female albino rabbits receiving a single dose of between 15 and 100 mg of aspirin/kg had a lower incidence of femoral-vein thrombi induced by sodium morrhuate than control animals or those receiving sodium salicylate or aspirin in doses between 3·5 and 8·5 mg/kg body weight.[15] In another study aspirin in doses of 100 mg/kg not only failed to protect New Zealand White rabbits (sex not stated) but actually had a potentiating effect on thrombus formation when administered in doses of 200 mg/kg 30 minutes before the induction of stenosis and stasis in the jugular veins.[16] Giving aspirin once a day in man permits the presence of 10% normal platelets in the circulation, thereby normalising platelet function.[17] These data emphasise the importance as regards the thrombotic event of variables such as sex and the dosage and timing of administration of aspirin. Our patients received aspirin three times daily, starting at least 48 hours before operation, in a dose ranging between 43 and 69 mg/kg.

The efficacy of our low-pressure IPCD re-emphasises the well-known role of stasis in the pathogenesis of DVT. Improvement in venous flow at the groin can occur with intermittent compression of the calves at pressures achieved by our device.[18] This is the first device of its kind that is easy to put on and take off and results in minimal patient discomfort.

We have therefore established the clinical efficacy of a new IPCD and of large doses of aspirin in preventing venous TE in patients, primarily women, undergoing total knee replacement. We are continuing our studies to accumulate a larger group of patients to avoid the pitfalls inherent in small samples. The controversy over the suppressive effect of large doses of aspirin on prostaglandin I_2 synthesis and the efficacy of larger doses of aspirin in preventing TE in man can only be resolved by further studies.

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Increasing importance of plasmid-mediated trimethoprim resistance in enterobacteria: two six-month clinical surveys

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Summary and conclusions

All clinical isolates of enterobacteria received at the laboratory were monitored for trimethoprim resistance over six months in 1978. The survey was repeated in 1979 and the incidence of trimethoprim resistance showed a slight decrease, but the proportion of resistant strains owing their trimethoprim resistance to transferable R plasmids had almost trebled. There was also a large increase in the proportion of resistant strains exhibiting high-level non-transferable trimethoprim resistance.

These findings suggest transposition of genes conferring trimethoprim resistance from plasmids to the bacterial chromosome.

Introduction

Trimethoprim combined with sulphamethoxazole (co-trimoxazole) has been used in Great Britain since 1969. During the first 10 years several different forms of trimethoprim resistance were reported.[1-4] One of the original reasons for prescribing trimethoprim in combination with sulphamethoxazole was the assumption that the sulphonamide would exert appreciable control over the emergence of at least one form of resistance. Sulphonamide resistance, however, is common in many of the species responsible for infections often treated with co-trimoxazole, and there may be grounds for using trimethoprim alone for certain infections.[5-7] If trimethoprim is to be released for use alone it will be important to monitor any effect of the separation on the incidence of resistance to trimethoprim.

We have reported on the emergence of trimethoprim resistance in patients treated with low doses of co-trimoxazole for prolonged periods.[4 8] Such patients offer a particular opportunity to observe the extent to which treatment may be compromised by resistance but throw little light on the overall prevalence of organisms exhibiting the various forms of trimethoprim resistance. To provide such information and establish a basis for observing any future changes in the incidence and types of trimethoprim resistance encountered clinically, we report the results of two six-month surveys of enterobacteria isolated from clinical specimens during January to June 1978 and January to June 1979. In addition to testing for trimethoprim resistance, we also tested each resistant isolate (*a*) for the presence of R plasmids conferring transferable trimethoprim resistance and (*b*) for resistance to sulphonamides.

Methods

Trimethoprim-resistant bacteria—During the survey periods enterobacteria from all types of clinical specimens received at this laboratory were identified by standard laboratory techniques and their resistance to trimethoprim measured by multipoint inoculation (with a final inoculum of about 100 colony-forming units) on to plates of Oxoid DST agar containing 4% lysed horse blood plus doubling dilutions of trimethoprim lactate (Burroughs Wellcome). Repeat specimens from the same patient were excluded.

Transfer of trimethoprim resistance—Isolates resistant to $\geqslant 8$ mg trimethoprim/l were tested for their ability to transfer resistance to a standard genetically characterised strain of *Escherichia coli*, as described.[8] In cases where transfer occurred single colonies were tested with antibiotic discs (Mast) to determine whether other resistances had been co-transferred. When transfer of several resistances had occurred the experiment was repeated, selecting for the transfer of each resistance independently. Transconjugants of each type were then tested to see whether the resistances were transferable separately —that is, on different plasmids—or always together—that is, on the same plasmid.

Resistance to sulphonamides—Isolates resistant to $\geqslant 8$ mg trimethoprim/l were tested for sulphonamide resistance by multipoint inoculation on to plates of Oxoid DST agar containing 4% lysed horse blood plus 256 mg sulphamethoxazole/l (Roche).

Statistical analysis was as described.[9]

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Results

INCIDENCE OF TRIMETHOPRIM-RESISTANT ISOLATES

A total of 3998 isolates of enterobacteria were screened for trimethoprim resistance in 1978 and 4069 in 1979. For the surveys resistant enterobacteria were divided into *E coli*, *Klebsiella/Enterobacter* sp, and