

cases, but that the general risk of such complications to women in the Netherlands is slight when abortion has been performed by early vacuum aspiration.

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References

- ¹ Wright, C S W, Campbell, S, and Beazley, J, *Lancet*, 1972, **1**, 1278.
- ² Wynn, M, and Wynn, A, *Some Consequences of Induced Abortion to Children Born Subsequently*. London, Foundation for Education and Research in Child-bearing, 1972.
- ³ Richardson, J A, and Dixon, G, *British Medical Journal*, 1976, **1**, 1303.
- ⁴ Kotásek, A, in *4th European Congress of Perinatal Medicine 1974*, ed Z K Stembera, et al, p 183. Stuttgart, Thieme, 1975.
- ⁵ Lembrich, V S, *Zentralblatt für Gynäkologie*, 1972, **94**, 164.
- ⁶ Pantelakis, S N, Papadimitriou, G C, and Doxiadis, S A, *American Journal of Obstetrics and Gynecology*, 1973, **116**, 799.
- ⁷ Papaevangelou, G, et al, *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1973, **80**, 418.
- ⁸ Treffers, P E, *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, 1973, **3**, 173.
- ⁹ Schnabel, P, *Abortus in Nederland*. The Hague, Stimezo Nederland, 1976.
- ¹⁰ Schnabel, P, *Medisch Contact*, 1976, **31**, 581.
- ¹¹ Hemel, O J S, van, *An Obstetric Data Base*, MD thesis. Amsterdam, Vrije Universiteit, 1977.
- ¹² Kloosterman, G J, in *4th European Congress of Perinatal Medicine 1974*, ed Z K Stembera et al, p 194. Stuttgart, Thieme, 1975.
- ¹³ Daling, J R, and Emanuel, I, *Lancet*, 1975, **2**, 170.

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Oral anticoagulants controlled by the British comparative thromboplastin versus low-dose heparin in prophylaxis of deep vein thrombosis

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Summary and conclusions

The British comparative thromboplastin (BCT) was used to monitor the effectiveness of oral anticoagulants in preventing deep vein thrombosis (DVT) in patients undergoing major gynaecological surgery. All patients were screened for DVT with the use of the ¹²⁵I-fibrinogen scan.

One hundred and forty-five patients aged 40 years or more were randomised into three groups. Group 1 received oral anticoagulant (nicoumalone) treatment, stabilised over five days before surgery and continuing into the second postoperative week. The other patients served as two contrast groups and were managed on a double-blind basis. Group 2 received a subcutaneous low-dose regimen of heparin calcium. Group 3 received subcutaneous saline. Eleven of 48 patients in the saline group, three of 49 patients in the heparin group, and three of 48 patients in the oral anticoagulant group developed DVT as judged by ¹²⁵I-fibrinogen scanning. The incidences in groups 1 and 2 were significantly lower than in the saline group. The falls in haemoglobin concentration and incidence of haemorrhage were similar in all three groups.

The study showed that oral anticoagulant prophylaxis stabilised preoperatively and low-dose heparin were equally effective in preventing deep vein thrombosis in a

moderate-risk group. Immediate preoperative prothrombin ratios of 2.0-2.5 and postoperative ratios of 2.0-4.0 with the BCT gave adequate protection without increased haemorrhagic risk.

Introduction

The value of oral anticoagulants in preventing venous thrombosis is generally accepted. With the advent of scanning techniques using ¹²⁵I-labelled fibrinogen their effectiveness in preventing deep vein thrombosis in surgical patients may be objectively assessed without having to rely on clinical signs. Morris and Mitchell¹ used the labelled fibrinogen scan to show that oral anticoagulants controlled by the Thrombotest method protect elderly patients with hip trauma from venous thrombosis. Nevertheless, studies on patients undergoing general² or gynaecological³ surgery have produced less favourable results with oral anticoagulants than with a low-dose heparin regimen. In both these studies oral anticoagulants were started only postoperatively, and thrombosis often occurred before the anticoagulants reached therapeutic concentrations.

The recommended method for laboratory control of anticoagulants in Britain is based on the British comparative thromboplastin (BCT), which is also widely used as a reference reagent abroad. The recommended therapeutic range based on clinical experience is a prothrombin ratio from 2.0 to 4.0 with this reagent. We therefore set out to evaluate the effectiveness of this therapeutic range in preventing venous thrombosis by using ¹²⁵I-fibrinogen scanning. We studied patients aged over 40 years who were undergoing major gynaecological surgery. One group received oral anticoagulants and two parallel groups were given either subcutaneous low-dose heparin or saline on a double-blind basis. Low-dose heparin has been shown to be an effective prophylaxis in such patients.⁴

Patients and methods

One hundred and forty-five patients aged 40 years or more who were having major abdominal or vaginal surgery were randomly allocated

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into three groups with the use of random-number tables to ensure that the groups remained moderately well balanced during the trial. Patients with a history of deep vein thrombosis (DVT) were excluded, as we thought it unwise to deny them prophylaxis. Two of us (RWB and JBJ) performed the operations, and the study was limited to our two wards, where postoperative care was similar.

Group 1: oral anticoagulants—Patients were started on treatment with a small induction dose of 6 mg nicoumalone (Sinthrome) at least five days before surgery to avoid the initial exaggerated response to a loading dose. The optimum preoperative prothrombin ratio was considered to be 2.0-2.5 using the BCT. In this hospital it has also been routine to measure the partial thromboplastin time (PTT) in parallel with the prothrombin time in all patients, so that depression of intrinsic clotting factors may be monitored. Assessment of intrinsic clotting was thought to be particularly important in patients on oral anticoagulants undergoing surgery. A prolongation of the PTT test of 5-15 s over baseline values using the standardised PTT method⁵ was considered to be the optimum on the day of operation. Dosage was subsequently monitored using the recommended range for the prothrombin ratio of 2.0-4.0 with the BCT.⁶ Oral anticoagulants were continued for 14 days, then gradually withdrawn over three days. In two patients preoperative anticoagulation was excessive. Prothrombin ratios were greater than 3.0 and the PTT was prolonged for more than 15 s. In each case partial correction was performed by intravenous administration of a concentrate containing factors II, IX, and X (Oxford DE1).

Group 2: low-dose heparin—Patients received twice-daily doses of heparin calcium (Choay) 5000 units (0.2 ml of 25 000 U/ml in single-dose phials) subcutaneously. Treatment began two hours preoperatively and continued for seven days. This twice-daily regimen of low-dose heparin was chosen as it was effective in a similar group of patients.⁴

Group 3: saline—Patients received saline (0.2 ml in phials identical with those containing heparin) subcutaneously twice daily, beginning two hours preoperatively and continuing for seven days.

Although we would have preferred to make this trial double-blind for all three groups, this was not practicable in the case of group 1 (oral anticoagulants) because of the need to monitor the dose response. Groups 2 and 3 were, however, managed in a double-blind manner. All patients were monitored by the ¹²⁵I-fibrinogen scan.⁷ A 20%

increase in counts over the immediate postoperative reading, adjacent readings, or corresponding part in the opposite leg was adopted as the criterion for deep vein thrombosis. Scanning began immediately after operation and continued daily for seven days. At the weekend all patients were monitored on at least one day. Haemoglobin was measured routinely before operation and on the second postoperative day.

Results

The three groups were well matched for age and type of operation, though the incidence of malignancy was slightly higher in the saline group (see table I). Both oral anticoagulant and low-dose heparin groups showed a significantly lower incidence of DVT (about 6%) than the saline-treated controls (about 23%) (see table II). As there were more malignancies in the control group, further analysis excluding them from all three series was performed. This showed that there was still a significant difference between the incidence in the saline group and oral anticoagulant group ($P < 0.05$), but the protection by low-dose heparin was significant only at the 10% level.

Forty-seven per cent of the prothrombin ratios in the oral anticoagulant group were considered to be at the optimum therapeutic level—namely, between 2.0 and 2.5 immediately before operation and 2.0-4.0 postoperatively. Of immediate preoperative values, 31% were considered to be at the optimum level on the prothrombin time test and 77% on the PTT test. With both tests, only 21% were thought to be inadequately dosed. During the first postoperative week 33% of patients were insufficiently anticoagulated; the prothrombin ratios were below the therapeutic range on two or more occasions.

In two of the three patients from group 1 who developed DVT, preoperative prothrombin ratios were below 2.0, but the PTT test results were in the required range. Both were judged to be inadequately anticoagulated during the postoperative week; the prothrombin ratios were below 2.0 on two or more occasions. The third patient from group 1 who developed a DVT had a malignant ovarian tumour. She had an initial preoperative prothrombin ratio of 3.3 and PTT of 61 s (baseline value 37 s). The defect was partially corrected with factor IX concentrate. The subsequent preoperative results were a prothrombin ratio of 1.7 and a PTT of 50 s. Postoperative bleeding was not excessive, but she developed bilateral DVT on the third postoperative day, though her postoperative anticoagulant control was adequate. One other patient received concentrate preoperatively. Her initial preoperative prothrombin ratio was >5.0 (78 s) and PTT was 63 s (baseline 39 s). After concentrate infusion immediately before surgery the prothrombin ratio was 3.3 and the PTT 47.5 s. There was no excessive haemorrhage and no increase in the fibrinogen uptake or other evidence of DVT.

Mean changes in haemoglobin are shown in table III. The difference between the three groups is not significant. The incidences of excessive blood loss are shown in table IV, and at the 5% level show no significant difference between the three groups. Two patients on oral anticoagulants developed late wound haemorrhage, which may have been due to the treatment. At the time of haemorrhage the prothrombin ratio was 3.9 in one patient and >5.0 in the other. Anticoagulant reversal was not needed in either case.

TABLE I—Mean age and types of operations performed in the three treatment groups, and numbers of patients with malignancy. Numbers who developed deep vein thrombosis given in parentheses

Group:	Oral anticoagulant	Heparin	Saline
Mean age (years)	51.6	52.4	50.3
Hysterectomy or laparotomy	26 (1)	29 (0)	30 (4)
Pelvic floor repair	22 (2)	20 (3)	18 (7)
Malignancy { Ovarian	1 (1)	1 (0)	1 (0)
Uterine body	1 (0)	1 (0)	3 (2)
Total No of patients	48 (3)	49 (3)	48 (11)

TABLE II—Incidence of deep vein thrombosis (DVT) in all patients in the three treatment groups and after exclusion of patients with malignancy

Group	All patients		Incidence excluding patients with malignancy	
	Total No of patients	No with DVT	Total No of patients	No with DVT
Oral anticoagulant	48	3] $P < 0.05$	46	2] $P < 0.05$
Heparin	49	3] $P < 0.05$	47	3] $0.05 < P < 0.10$
Saline	48	11]]	44	9]]

χ^2 test with Yates's correction used for analysis.

TABLE IV—Incidence of excessive haemorrhage (wound haematoma or transfusion for excessive haemorrhage or both) in the three treatment groups

	Oral anticoagulant	Heparin	Saline
Excessive haemorrhage	3	5	0
Total No analysed	42	43	40

Fisher's exact test: Oral anticoagulant *v* saline not significant; heparin *v* saline not significant.

TABLE III—Mean (\pm SD) fall in haemoglobin concentrations from preoperative values on second postoperative day. (Transfused patients excluded)

Group:	Hysterectomy			Pelvic floor repair		
	Oral anticoagulant	Heparin	Saline	Oral anticoagulant	Heparin	Saline
Mean fall in haemoglobin (g/dl)	1.39 \pm 1.66	1.25 \pm 0.90	1.01 \pm 0.86	1.02 \pm 0.95	0.43 \pm 0.58	0.82 \pm 0.59
No analysed	17	23	21	12	13	15

Discussion

The British comparative thromboplastin or its routine counterpart the Manchester comparative reagent is used in almost all hospitals in Britain. The BCT is also used throughout the world as a reference material. Hitherto the lower limits of the therapeutic range have been defined by clinical experience and correlation with other monitoring systems used in Britain and overseas. Our study allows an objective evaluation of the effectiveness of oral anticoagulant dosage monitored by the BCT to be made. The DVT incidence in untreated patients (23%) agrees with other series. It is similar to that in the study of Ballard *et al*⁴ in gynaecological patients (29%) and to that in the multicentre trial study⁸ of mixed surgical patients (24%). The incidence in patients treated with low-dose heparin (our positive control group) approximates to that reported by Ballard *et al*,⁴ who studied a similar group of patients using the same dosage regimen.

In contrast, the incidence in our oral anticoagulant group (6%) differs greatly from that found by Vroonhoven⁵ using the Thrombotest method of anticoagulant control. In Vroonhoven's study² oral anticoagulants were, however, started on the first postoperative evening, and nine patients (18%) developed DVT. In eight of these patients this occurred during the first three days after operation when anticoagulation could not have reached a fully effective level. Our patients were started on oral anticoagulants at least five days preoperatively to achieve prolongation of both intrinsic and extrinsic clotting. This may explain the better protection attained with oral anticoagulants, which was equal to that of low-dose heparin. The three patients who developed DVT in the oral anticoagulant group had preoperative prothrombin ratios below 2.0, the recommended lower limit of the therapeutic range with the BCT. These results therefore confirm that this doubling of the normal prothrombin time is needed to achieve prophylaxis with our method of laboratory control. In all three cases, however, the preoperative PTT seemed adequately prolonged, which suggests that intrinsic clotting tests alone may not be a reliable guide to protection by oral anticoagulants in patients undergoing surgery.

The incidence of haemorrhagic complications was not significantly increased in patients on oral anticoagulants. Hence our study confirms the view that it is safe to operate when patients are anticoagulated at levels within the therapeutic range. Other experience, however, on the effectiveness of prophylaxis and

haemorrhagic side effects has been based on trials in which anticoagulant dosage was determined by extrinsic clotting tests alone—that is, Quick prothrombin time test or Thrombotest. Our results also show the interesting and important finding that surgery is safe when intrinsic clotting is depressed, as judged by a prolongation of PTT, provided that this is not excessive.

For moderate-risk patients, the necessary preoperative stabilisation period for oral anticoagulants makes this type of prophylaxis unnecessarily troublesome. For these patients the present study endorses the effectiveness of the fixed low-dose heparin regimen. If, however, a patient is already stabilised on oral anticoagulants, it is apparently not worth changing to low-dose heparin for the operative period, as has recently been suggested.⁹ The incidence of DVT and excessive haemorrhage is similar with both forms of prophylaxis, and stopping oral anticoagulants abruptly to change to heparin may well produce hypercoagulability.¹⁰

Morris and Mitchell¹ have shown that oral anticoagulants are effective in patients with hip trauma when low-dose heparin in a fixed dosage regimen is not. High-risk patients were, however, largely excluded from our study, and in moderate-risk patients the two treatments were equally beneficial. Further study is needed to see whether monitoring the low-dose heparin dosage will improve prophylaxis in high-risk patients, or whether oral anticoagulants are preferable.

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References

- 1 Morris, G K, and Mitchell, R A, *Lancet*, 1976, **2**, 869.
- 2 Vroonhoven, T J M V, van Zijl, J, and Müller, H, *Lancet*, 1974, **1**, 375.
- 3 Baertschi, U, *et al*, *Geburtshilfe und Frauenheilkunde*, 1975, **35**, 754.
- 4 Ballard, R M, *et al*, *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1973, **80**, 469.
- 5 Poller, L, Thomson, J M, and Palmer, M K, *Lancet*, 1976, **2**, 842.
- 6 Blackburn, E K, *Prescribers' Journal*, 1977, **17**, 73.
- 7 Kakkar, V V, *et al*, *Lancet*, 1970, **1**, 540.
- 8 International Multicentre Trial, *Lancet*, 1975, **2**, 45.
- 9 Brozovic, M, and Mibishan, R S P, in *Recent Advances in Surgery*, ed S Taylor. Edinburgh, Churchill Livingstone, 1977.
- 10 Poller, L, and Thomson, J M, *Lancet*, 1964, **11**, 62.

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Indoprofen and naproxen in the treatment of rheumatoid arthritis: a clinical trial

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Summary and conclusions

Thirty-six patients suffering from rheumatoid arthritis took part in a double-blind crossover trial, in which they

received either indoprofen 800 mg/day, naproxen 500 mg/day, or a matching placebo. Indoprofen was shown to be significantly superior as an analgesic and in improving grip strength and the patients preferred it. Adverse effects were comparable, although indigestion was seen slightly more often during indoprofen treatment.

Indoprofen is therefore at least as effective as existing anti-inflammatory drugs in rheumatoid arthritis and seems to be better tolerated.

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Introduction

Aspirin has been the standard treatment for rheumatoid arthritis and remains so in many centres. In some patients, however, aspirin causes adverse effects severe enough to prevent them