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THE VALUE OF PROPHYLACTIC ANTICOAGULANT THERAPY WITH WARFARIN AFTER HIP SURGERY

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The value of prophylactic anticoagulant therapy after surgery has remained in dispute following the report by Pinto (1970) who showed a similar incidence of deep-vein thrombosis in both treated and control groups, figures that refuted the earlier reports of Sevitt & Gallagher (1959), Salzman et al. (1966) and Harris et al. (1967).

Between January 1968 and December 1971 all patients undergoing total hip replacement and femoral osteotomy were considered for Warfarin therapy post-operatively, and the effects of therapy on thromboembolic phenomena were observed. At the same time the incidence of wound haematomata and systemic bleeding complications was recorded. Thus the merits and complications of anticoagulation therapy could be assessed in a prospective manner. Reliance was placed at the outset on the clinical diagnosis of deep-vein thrombosis and pulmonary embolism, whilst it is recognised now that thereby an underestimation of the frequency of venous thrombotic episodes is common (Kakkar et al. 1969).

PATIENTS AND METHODS

Three hundred and forty-six patients had undergone 112 McKee-Farrar total hip replacements, 97 Charnley total hip replacements, and 137 femoral osteotomies. There were 230 females and 116 males, a ratio of 2:1. Ages varied from 52 to 84 with an average of 68 years. The majority of patients (70 per cent) were over 60 years of age.

Post-operative Programme

At the end of the operation the limb was placed on a Hodgen's splint and active contraction of hip, knee and ankle muscles was encouraged on recovery of consciousness. Thereafter the patients spent 1 hour in each morning and afternoon

performing active exercises under the supervision of a physiotherapist whilst at other times moving the limb as much as possible. After 10 days for total hip replacements and 17 days for femoral osteotomies the splints were removed and sling exercises commenced in bed. Walking with crutches began 14 days after total hip replacement and 20 days after femoral osteotomy.

One closed suction drain of the Redivac type was placed deeply in all the wounds and remained for 48 hours after operation.

Warfarin 15 mg was given commencing at 8.00 a.m. on the second post-operative day. The prothrombin time was monitored daily and maintained between 20 per cent and 30 per cent by varying the Warfarin dosage. This range was based on the work of Sevitt & Gallagher (1959), Moschos et al. (1964) and Harris et al. (1967). Prothrombin levels above 35 per cent or fluctuating between 20 per cent and 50 per cent were considered to indicate inadequate anticoagulation. The over-administration of Warfarin led occasionally to levels well below 15 per cent. Warfarin therapy was continued until the patients were fully ambulant which was on the average 21 days for total hip replacement and 28 days for femoral osteotomies. Thus 4 groups of patients emerged, and were classed according to the prothrombin times as therapeutic, inadequate, low and excluded (Table 1).

Table 1. Adequacy of anticoagulation.

	Anticoagulation	Prothrombin time	Number of patients	Percentage
Group 1	Therapeutic	20–30 per cent	169	49
Group 2	Inadequate	35 per cent	79	23
Group 3	Low	15 per cent	12	3
Group 4	Excluded	–	86	25

Diagnosis of Deep Venous Thrombosis

A deep venous thrombosis was considered to have occurred when there was pain felt in the calf, together with tenderness on palpation and tenderness along the line of the deep veins compared with the opposite calf. The diagnosis was more certain if there was oedema of the lower leg and ankle, dilated superficial veins in the lower leg and foot and a positive Homan's sign. The diagnosis of pulmonary embolism was based on pleuritic pain, haemoptysis and occasionally dyspnoea together with the characteristic radiographic appearances and electrocardiographic changes.

RESULTS

Adequacy of Anticoagulation

One hundred and sixty-nine patients (49 per cent) received anticoagulants in therapeutic dosage (Table 1). Seventy-nine patients (23 per cent) received inadequate doses of anticoagulant resulting in a

prothrombin level above 35 per cent, and in 12 patients (3 per cent) the dose given produced a prothrombin level which was too low. In 86 patients (25 per cent) Warfarin was withheld because the patients had some medical condition which made administration of Warfarin hazardous. These contra-indications were history of:

1. Dyspepsia, peptic ulcer or haemoptysis.
2. Blood dyscrasia or purpura.
3. Cerebro-vascular accident.
4. Haematuria or recurrent cystitis.
5. Gastro-intestinal or renal carcinoma.

Thrombo-embolic Episodes

Deep venous thrombosis. Through the series deep venous thrombosis was diagnosed only 19 times (6 per cent overall). In group 1 with adequate anticoagulation, only 1 of 169 patients (0.6 per cent) developed signs of deep venous thrombosis (Table 2). In group 2, where the prothrombin level was too high, 8 patients out of 79 (10 per cent) developed deep venous thrombosis which was comparable with the 10 cases out of 86 (11.6 per cent) in the untreated patients in group 4. Deep venous thrombosis did not occur in group 3 where the prothrombin level was too low. The differences between groups 1 and 2, groups 1 and 4 and between groups 3 and 2 and 3 and 4 were significant ($P < 0.05$).

Table 2. Incidence of thrombo-embolism.

	Group 1	Group 2	Group 3	Group 4
Prothrombin time	(20–30 %)	(35 %)	(15 %)	(not given)
Patients	169	79	12	86
Deep venous thrombosis	1 (0.6 %)	8 (10 %)	0	10 (11.6 %)
Pulmonary embolism	0	7 (8.7 %)	0	3 (3.4 %)

Table 3. Thromboembolic episodes following different procedures.

	McKee-Farrar	Charnley	Femoral osteotomy
Pulmonary embolism	3 (2.7 %)	2 (2 %)	5 (3.6 %)
Deep venous thrombosis	4 (3.5 %)	5 (5.2 %)	10 (7.3 %)
Average period of bed rest (days)	14.6	14.8	20

There was a slightly increased percentage of deep venous thrombosis in patients who had undergone femoral osteotomy but the differences were not statistically significant (Table 3).

Pulmonary embolism. Ten patients (3.4 per cent overall) developed pulmonary emboli and one who was in group 4 died (Table 2). Deep venous thrombosis was diagnosed prior to pulmonary embolism in 6 cases (60 per cent). It is notable that none of the pulmonary emboli occurred in patients who were adequately anticoagulated (group 1). However, 7 patients (8.7 per cent) with pulmonary emboli had received anticoagulants in inadequate dosage (group 2). The remaining 3 cases (3.4 per cent) of pulmonary embolism occurred in the non-treated group (group 4). The differences between groups 1 and 2 and groups 1 and 4 and between groups 3 and 2 and 3 and 4 were significant ($P < 0.05$).

Complications of Therapy—Bleeding Episodes

Wound haematomata. Forty-two patients (12 per cent overall) developed a wound haematoma. Seven were large (2 per cent) and required evacuation under general anaesthesia and transfusion of 3 pints of blood. The remaining 38 (10 per cent) were small and healed spontaneously (Table 4). The incidence of wound haematoma was 13 per cent overall in 260 patients who received Warfarin (groups 1, 2 and 3) compared with 10 per cent in the non-treated groups of 86 patients. However, there was the same incidence (9 per cent) in patients treated with adequate doses of Warfarin (group 1) and those not receiving Warfarin (group 4). The highest percentage of haematomata, 21 per cent, occurred in patients who were receiving inadequate doses of Warfarin (group 2). The reason for this is not obvious. The differences between groups 1 and 2, and groups 2 and 4 are significant ($P < 0.05$) but that between groups 2 and 3 is not.

All the wounds which developed haematomata healed and were not complicated by sepsis.

Table 4. Incidence of wound haematoma.

	Group 1 (20–30 %)	Group 2 (35 %)	Group 3 (15 %)	Group 4 (Nil)
Patients	169	79	12	86
Haematoma	15	17	2	8
Percentage	9%	21%	17%	9%

Bleeding from other sites. Bleeding attributed to Warfarin overdosage occurred as shown in Table 5. Ten patients were involved (4 per cent) of a total of 260. All the patients recovered following a transfusion of between 3 and 6 pints of blood except the patient with cerebral haemorrhage. This was a diagnosis based on the development of a hemiplegia 5 days after operation in a 72-year-old patient, who survived but with some residual weakness and spasticity in the left arm and leg.

Table 5. Bleeding associated with Warfarin overdosage.

Haematuria	3
Malaena	2
Extensive bruising	2
Cerebral haemorrhage	1
Retroperitoneal haematoma	1
Bleeding from sacral sore	1

DISCUSSION

The Value of Warfarin as a Prophylaxis for Deep Venous Thrombosis and Pulmonary Embolism

The effectiveness of Warfarin as a prophylactic measure was demonstrated by the fact that only one patient out of 169 (0.6 per cent) maintained with adequate levels of anticoagulant developed a clinically-obvious deep venous thrombosis and no pulmonary emboli were found in this group. By contrast inadequate therapy, resulting in prothrombin levels greater than 35 per cent in 79 patients, was associated with 8 cases (10 per cent) of deep venous thrombosis and 7 cases (8.7 per cent) of pulmonary emboli, figures which compare with 10 cases (11.6 per cent) of deep venous thrombosis and 3 (3.4 per cent) pulmonary emboli in the 86 patients in the non-treated group (Tables 2 and 3).

Many authors have recorded similar beneficial effects of Warfarin therapy in reducing deep venous thrombosis and pulmonary emboli (Table 6) and this appeared to be so in the present series. However, the time between the loading dose and operation is such that in most of the series, including this one, the desired prothrombin level was not reached until 48 to 72 hours post-operatively. Pinto (1970) who gave Warfarin with the premedication, emphasized the importance of early anticoagulation. In view of the fact that 66 per cent of all deep venous thromboses occur within 48 hours of surgery (Negus et al. 1969) the

effect of Warfarin in preventing clinical deep venous thrombosis is difficult to explain. It is probable that Warfarin prevents extension of the thrombus so that it rarely becomes extensive enough to produce clinical signs. This same mechanism might explain its more certainly established effect of preventing pulmonary embolism. This latter effect is, we consider, the most powerful argument for its use.

Table 6. Incidence of thromboembolism reported following hip surgery.

Author		Incidence of thromboembolism	
		Control	Treated
Sevitt & Gallagher	(1959)	29.0 %	2.7 %
Neu et al.	(1965)	10.0 %	0 %
Salzman et al.	(1966)	22.0 %	7.0 %
Harris et al.	(1967)	34.0 %	7.0 %
Pinto	(1970)	36.0 %	32.0 %

Diagnosis of Deep Venous Thrombosis and Pulmonary Embolism

The recorded incidence of deep venous thrombosis and pulmonary emboli varies from series to series according to the method of diagnosis used. Charnley (1972) in a series of 201 hip arthroplasties reported a clinical incidence of deep venous thrombosis of only 3 per cent and 3.2 per cent for pulmonary embolism. The limitations of clinical signs as an indication of venous thrombosis are now well-recognised and Kemble (1971) recorded an underestimation of 50 per cent when he checked clinical diagnosis against the ^{125}I – labelled fibrinogen method. This agrees with the findings of Sevitt & Gallagher who in 1961 showed that, of patients with deep venous thrombosis at post-mortem, only ⅓ were diagnosed clinically during life.

Silent Thrombosis

The importance of "silent" thrombosis in the pathogenesis of pulmonary emboli has rightly been given emphasis in the literature although Sevitt & Gallagher (1961) reported a greater incidence of fatal pulmonary emboli when a previous clinical diagnosis of deep venous thrombosis had been made. In this series 6 out of 10 pulmonary emboli were associated with a prior diagnosis of deep venous thrombosis. Pinto (1970) reported that only 5 of 17 patients with venous thrombosis, shown by the radioactive fibrinogen method, had physical signs. This

method is valueless for the diagnosis of ilio-femoral occlusions following hip surgery because of the high count around the operation zone. This is a serious defect when it is considered that an ilio-femoral thrombosis was implicated in 66 per cent of pulmonary emboli (Mavor & Galloway 1969). Venography appears to be a much more satisfactory method of diagnosing occlusions in the important ilio-femoral veins (Flanc et al. 1968).

Clinical, radiological and electrocardiographic diagnosis of pulmonary embolism is reliable in a majority of cases and this appears to be reduced significantly with Warfarin therapy in adequate dosage.

Complications of Warfarin Therapy

The commonest complication of Warfarin therapy was wound haematoma. There was a 13 per cent incidence of wound haematoma in the 260 patients receiving anticoagulants, compared with 10 per cent in 86 patients not treated. However, there was no difference in the frequency of wound haematoma (Table 4) in patients receiving adequate anticoagulation and those not receiving therapy at all. Moreover, large haematomata were not necessarily associated with low prothrombin levels and of 7 large haematomas, 6 patients had prothrombin times in the region of over 35 per cent and one patient did not receive Warfarin. All of the patients recovered from the haematomata and none developed chronic wound sepsis. Potentially serious visceral bleeding for example, haematuria and malaena (Table 5) were complications of very low prothrombin levels in the 5 to 10 per cent range. Although the patients required transfusion all survived the episodes without further complications.

The use of anticoagulants for the prevention of deep venous thrombosis and particularly pulmonary embolism remains a subject of controversy. With the use of more sophisticated techniques, diagnosis and response to therapy will become more precise. All agents currently available have disadvantages (Murray & Kakkar 1972). As a result a prospective study employing Warfarin, low dose heparin and dextran 70 is under way in this department. Meanwhile this review suggests that Warfarin therapy has reduced the incidence of clinical deep venous thrombosis following elective hip surgery. Pulmonary embolism has been reduced significantly by Warfarin therapy and it is probable that the value of Warfarin lies in an ability to prevent clot propagation and thereby embolism. The incidence of wound haematoma was not

increased in patients who were adequately anticoagulated. Careful control of Warfarin therapy is essential since erratic control due to incorrect dosage or the interaction of other drugs can lead to dangerously low prothrombin levels with the risk of wound haematomata and potentially serious bleeding from other sites.

SUMMARY

1. A total of 346 patients underwent 112 McKee-Farrar, 97 Charnley replacements and 137 intertrochanteric femoral osteotomies. All were considered for prophylactic anticoagulation therapy with Warfarin post-operatively.
2. The patients were in 4 groups depending on the degree of anticoagulation achieved as measured by the prothrombin time.
3. Only one deep venous thrombosis and no pulmonary emboli occurred amongst 169 patients in group 1 who received adequate Warfarin therapy.
4. There was a comparable incidence of deep venous thrombosis in 79 patients who were inadequately anticoagulated (group 2) and 86 patients who received no anticoagulant for medical reasons (group 4). Pulmonary embolism occurred in 8.7 per cent of patients in group 2 and 3.4 patients in group 4. The differences between groups 1 and 2 and groups 1 and 4 are significant ($P < 0.05$).
5. Wound haematomata occurred with equal frequency (9 per cent) in patients who were adequately anticoagulated (group 1) and the non-treated group 4 but were twice as common (21 per cent) in the inadequately-controlled group 2. The differences between groups 1 and 2 and groups 4 and 2 were significant ($P < 0.05$).
6. Well-controlled Warfarin therapy commencing on the second post-operative day was effective in reducing clinically obvious deep venous thrombosis and pulmonary embolism was completely prevented.

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