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PROPHYLACTIC ANTICOAGULANT THERAPY IN THE TREATMENT OF LOWER LIMB FRACTURES

By

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The present paper is concerned with a clinical study of the value of anticoagulant phophylaxis in patients with fractures. The aim was also to try to evaluate the effect of the anticoagulant on the healing of the fractures. The trial was restricted to a group of fracture patients susceptible to tromboembolic complications. Phophylaxis must consequently be regarded as justified especially as the methods employed and the laboratory control of treatment are routine hospital work.

The idea of this study was given by my chief who became interested in the subject after reading the excellent paper of *Sevitt & Gallagher* (1959). Their material consisted solely of patients with fractures of the femoral neck, and the anticoagulant used was phenindione. They established a sharp decrease in the incidence of venous thrombosis and pulmonary embolism in patients given prophylactic treatment but they failed to mention the effect of prophylaxis on the healing of the fractures. The healing of fractures in experimental animals given anticoagulants was studied e.g. by *Stinchfield et al.* (1956) who found that both ante- and postoperatively administered anticoagulant therapy (Heparin and Dicumarol) delay the healing of an experimental fracture of the os ileum (cancellous bone). The same observation was made by *Minolta et al.* (1958) in their study of the effect of heparin and dicumarol on the healing of fractured rabbit radius.

Sevitt et al. reported pulmonary embolism in c. 20 per cent of the autopsies in the Birmingham Accident Hospital and it was the cause of death in 14 per cent of the total series and as much as 40–50 per cent of "elderly patients who died after a fractured femur, tibia, or pelvis". Further, thrombosis of deep veins of the lower limbs was established in over 80 per cent of "elderly patients who died after a fractured femur".

Pulmonary embolism was reported by *Hermann et al.* (1961) in 0.94 per cent of operatively treated patients. They are convinced of the benefit of anticoagulant prophylaxis. In 4,391 autopsies *Coon et al.* (1959) established pulmonary emboli in 606 cases (13.8 per cent); they were the cause of death in 198 cases. *Marks et al.* (1954) estimated that "in a busy hospital of 500 beds an average of 10 fatal pulmonary emboli will occur each year".

Series.

The series consisted of patients aged 40 or over with one of the lower limb fractures listed in Table 1.

TABLE 1
Material.

Diagnosis	Anti-coagulant group	Control group	Total
Fracture of the femoral neck	20	22	42
Trochanteric fracture	16	16	32
Fracture of the shaft of the femur	17	15	32
Fracture of the shaft of the tibia (and fibula)	36	36	72
Total.....	89	89	178

The distribution by sex varied in the different groups but the total female: male ratio was c. 5: 3.

METHOD

Collection of the material.

To achieve the greatest reliability possible in the comparison between the prophylactic group and the control group the subjects for each group were taken from patients admitted at the same time to the clinic. Every other patient aged 40 or over who was admitted for treatment for the fractures mentioned in Table 1 was included in the prophylaxis group, and every other patient in the control group. However, some transfers had to be made from one group to the other, e.g. in cases with a contraindication for the use of an anticoagulant agent. All transfers from one group to the other or omissions from the total series (e.g.

moving to another hospital) were offset by a corresponding transfer or omission from the other group. Otherwise, however, the series is completely unselected.

The collection of the series was commenced in spring 1960 and ended in autumn 1961.

The trial.

Phenylindandione (Trombosol-"Star", 0.05/tabl.) was the anticoagulant employed in the present study. The initial phenylindandione dose, 150–300 mg., was selected as individually as possible. At the beginning of the trial the anticoagulant was administered from the post-traumatic or post-operative day, but half-way through it the phophylaxis was changed and was begun only on the 5th post-traumatic or post-operative day. The change was not because of complications but simply in an effort to achieve the greatest possible elimination of detrimental effects. Contraindications to anticoagulant therapy were sought at the outset on the basis of preliminary data and subsequent investigation. The appearance of haemorrhagic and thromboembolic complications in both groups was established at the earliest possible stage and managed accordingly and independently of the study in question. The phenylindandione dosage was controlled frequently by the Thrombotest method (Owren). The Thrombotest value was kept at 10–25 per cent as far as possible. In the absence of any impediment, the anticoalugant therapy was continued until the patient was mobilised satisfactory or discharged.

An analysis of some prognostically important characteristics of the patients shows e.g. that c. 62 per cent were in good and c. 12 in poor condition on admission; 18 per cent were complicated by obesity, 2 per cent were incapable of walking before the accident; 18 per cent were in poor mental condition (senile, alcoholic dementia, sequela of apoplexy, psychosis, etc.); 21 per cent had hypertension of varying degree (systolic blood pressure over 170 mm.Hg); another 21 per cent had cardiac failure of varying severity, 17 per cent had cardiosclerosis; 3 per cent had post-apoplectic hemiparesis or hemiplegia, 8 per cent had varicose veins in the lower limbs.

The methods of treatment were the conservative or operative procedures commonly used at the clinic. When operation was decided, if anticoagulant prophylaxis had been initiated it was discontinued and the patient was given vitamin K_1 on the day preceding the operation

and on the day of the operation ifself. Prophylactic phenylindandione treatment was started again after the operation according to the schedule followed primarily.

The results of the investigation.

TABLE 2

Clinically established thrombosis of the deep vein of the lower limb.

Fracture	Phenylindandione group		Control group	
	Size of the group	Thrombosis established	Size of the group	Thrombosis established
Fracture of the femoral neck	20	–	22	4
Trochanteric fracture	16	–	16	5
Fracture of the shaft of the femur ...	17	–	15	1
Fracture of the shaft of the tibia (and fibula)	36	–	36	4
Total.....	89	–	89	14

The relative incidence of venous thrombosis of the lower limbs of the phenylindandione group was thus 0 and of the control series 16 per cent.

TABLE 3

Clinically established cases of pulmonary embolism (with or without diagnosed thromboses).

Fracture	Clinically established venous thrombosis (from Table 2)		Cases of pulmonary embolism			
			Patients with venous thrombosis		Patients without venous thrombosis	
	Phenylindandione group	Control group	Phenylindandione group	Control group	Phenylindandione group	Control group
Fracture of the femoral neck	–	4	–	2	1	1
Trochanteric fracture	–	5	–	–	–	1
Fracture of the shaft of the femur	–	1	–	–	–	1
Fracture of the shaft of the tibia (and fibula)...	–	4	–	–	–	2
Total.....	–	14	–	2	1	5

The thromboembolic complications established were treated routinely, including the use of anticoagulants, and independently of the investigation.

TABLE 4

Arterial thromboses of the heart and systemic circulation.

Fracture	Coronary thrombosis		Cerebral thrombosis		Mesenterial thrombosis		Thrombosis of the femoral artery	
	Phenylindandione group	Control group	Phenylindandione group	Control group	Phenylindandione group	Control group	Phenylindandione group	Control group
Fracture of the femoral neck	–	2	–	2	–	–	–	–
Trochanteric fracture	–	–	–	–	–	1	–	–
Fracture of the shaft of the femur	–	1	–	–	–	–	–	1
Fracture of the shaft of the tibia (and fibula)	–	–	–	–	–	–	–	–
Total.....	–	3	–	2	–	1	–	1

TABLE 5

Other complications.

Fracture	Haemorrhage (melaena, haematuria)		Decubitus		Pneumonia		Wound infection*		Fat embolism	
	Phenylindandione group	Control group	Phenylindandione group	Control group	Phenylindandione group	Control group	Phenylindandione group	Control group	Phenylindandione group	Control group
Fracture of the femoral neck	1	1	1	1	–	3	–	–	–	1
Trochanteric fracture ..	1	–	2	2	2	2	–	1	–	–
Fracture of the shaft of the femur	1	–	–	1	–	–	–	–	–	–
Fracture of the shaft of the tibia (and fibula)	–	–	1	1	2	–	–	–	–	–
Total.....	3	1	4	5	4	5	–	1	–	1

* Minor, rapidly healed wound infections were disregarded.

Pulmonary embolism was stated in c. 1 per cent of the anticoagulant prophylaxis group and in c. 8 per cent of the controls. Only the cases with a diagnosis that was considered certain were included in the calculation.

The age of these patients was 48–89 years (average 68). The general condition was assessed as good in only one case. Only one of them died and the diagnosis of embolism was confirmed at autopsy.

The haemorrhagic complications were significant in only one case, described in more detail in connection with Table 6. The haemorrhage was an indication for the discontinuation of anticoagulant therapy in all 3 cases of the phenylindandione group. Furthermore, one of the controls also developed a fairly mild but manifest melaena for reasons which remained obscure (Cf. *Hemley et al.* 1961).

TABLE 6
Causes of death.

Main causes of death	Secondary causes	Phenylindandione series	Control series
Pulmonary embolism	Pneumonia	–	3
Bronchopneumonia	Pulmonary embolism	1*	–
	Heart disease	–	1
	Diabetes	–	1**
	Melaena	1***	1
Hypertension	Heart failure	2****	1
	Mesenterial thrombosis	–	1
Carcinoma		1	–
Other causes		1*****	–
	Total.....	6	8

* An infirm woman of 74 who was found at autopsy to have minor thromboses of the pulmonary artery.

** A woman of 83 who died of diabetic coma. No autopsy was performed.

*** A woman of 79 who showed neither anamnestically nor clinically contraindications for the use of anticoagulants. Was given only 425 mg. of phenylindandione altogether in 3 days. The Thrombotest value fell to 24. Autopsy established in addition to bronchopneumonia also definite haemorrhagic enteritis, colitis and cystitis probably caused by the anticoagulant.

**** One of these patients, a woman of 67, had in addition purulent cholecystitis and gangrenous (*not* haemorrhagic) cystitis.

***** A woman of 87 who was gradually prostrated: Senile exhaustion. No autopsy was performed.

Six patients (c. 7 per cent) of the anticoagulant group and 8 (c. 9 per cent) of the controls died during treatment, all with either trochanteric fractures or fractures of the femoral neck. The causes of death are collected in Table 6; unfortunately, not all of them were autopsied (see Table 6).

The average age of the dead patients was over 82. Most of them were already in poor condition on admission. Ten of these 14 patients sustained the fracture in their own room, falling on the floor, 1 fell out of bed in a home for the aged, 1 fell down in the X-ray department of the hospital, 1 on the stairs at home and 1 on the street.

The patients were followed up for 13–18 months after discharge. The results of fracture treatment were about the same in the two groups. Pseudarthrosis developed in about 4 per cent of the diaphyseal fractures of both groups. Delayed union was established in two cases of the phenylindandione group only. There was nothing to indicate that the ossification disturbance occurring in fractures among the patients given phenylindandione would not have developed if the anticoagulant had not been administered.

The series is limited in size, and especially the number of the representatives of each sub-group small. Hence it is impossible to draw conclusions concerning the end results of the fractures. In particular, comparison of the consolidation times of the two groups requires a large material which is homogeneous ar regards age, type of fracture and details of treatment. It is impossible in clinical work to establish the consolidation times accurately, and the length of the treatment period is also affected by so many, even secondary, factors that comparison is precluded. The answer to many important questions must be left to animal experiments which have been conducted concurrently with this study by *Rokkanen & Slätis* (1963).

DISCUSSION

The duration of phenylindandione prophylaxis varied. The period was governed not by the conditions of the investigation but by the clinical requirements and the patient's recovery.

Venous thrombosis was successfully prevented by using phenylindandione—in the prophylaxis group there was not a single clinically manifest venous thrombosis, whereas nearly 16 per cent of the controls were thus affected. The latter figure would surely have been considerably

higher had the earliest and most complete possible activation, exercise and ambulation not always been a rule in the hospital (*Kallio* 1960).

Pulmonary embolism was established clinically in only c. 1 per cent of the patients receiving anticoagulant therapy, but in 8 per cent of the control. It was the main cause of death in 3 per cent of the control group as a whole and in over 37 per cent of the fatalities of the group.

Other arterial thromboembolisms were established in another 7 patients in the control series alone. All these embolisms were very serious complications. In only one, a case of mesenterial thrombosis, was the arterial thromboembolism the direct cause of death.

Of the other complications, the haemorrhagic complication deserves especial attention. The phenylindandione and control groups did not differ as regards the course of the trauma-induced wound or fracture haematoma. The same is true of operation wounds and even of the cases in which anticoagulant prophylaxis was initiated on the first post-operative day. Three of the phenylindandione patients, however, had melaena or haematuria. This was not clinically significant in 2 cases and ceased when the anticoagulant was discontinued. It was a secondary cause of death in 1 case. It is obivous that although no recognised contraindications can be demonstrated, special care must be observed in the administration of phenylindandione to the aged (*Hueber* 1961).

No difference was established between the anticoagulant and the control groups regarding the incidence and severity of decubitus (*Leypold et al.* 1961), wound infections and other complications.

In the diaphyseal fractures of the phenylindandione group delayed union occurred in c. 4 per cent and pseudarthrosis in c. 4 per cent. Pseudarthrosis was established also in c. 4 per cent of the diaphyseal fractures of the controls.

Fractures of the cancellous area, the proximal part of the femur, healed similarly in both groups. The fact that there was only one pseudarthrosis following fracture of the femoral neck in both groups is probably due to the individual non-schematic selection of therapeutic methods for this fracture.

There seemed to be an unusually extensive cloud-like callus formation, of the sort often seen after intramedullary nailing, in 2 conservatively treated cases of femoral fracture in the anticoagulant group. One of them resulted in pseudarthrosis, the other in union. This observation is by no means unique in a fracture material, but in these cases may have been due to the anticoagulant administered.

CONCLUSIONS

Anticoagulant prophylaxis with phenylindandione seems to be well suited for the prevention of venous thrombosis and, hence, of pulmonary embolism in middle-aged or older patients with lower limb fracture.

It has also a distinctly preventing effect on arterial thromboses. Hence anticoagulant prophylaxis obviously reduces mortality in patients with a susceptibility for venous or arterial thrombosis.

The anticoagulant used may in some cases delay union of diaphyseal fracture.

Carefully controlled anticoalugant therapy does not seem to increase the haemorrhagic complications of traumatic and operative wounds.

Points to be remembered, specially in treating elderly persons in poor physial condition with phenylindandione, are mucosal haemorrhages or an enhanced susceptibility to bleeding for unknown reasons.

SUMMARY

Eighty-nine patients, aged 40 or more, who had fractures of the femoral neck, trochanteric fractures, fractures of the femoral diaphysis or of the tibial (and fibular) diaphysis were treated conservatively or operatively. In addition, they were given phenylindandione prophylactically from the 2nd–5th post-traumatic or post-operative day until they were discharged or had become satisfactorily mobile. An equal number of similar fracture patients were treated concurrently by the same methods but without anticoalugant prophylaxis.

No clinically demonstrable case of thrombosis of the peripheral deep veins occurred in the anticoagulant prohylaxis group as compared with 16 per cent in the control series. Pulmonary embolism was diagnosed clinically in 1 per cent of the anticoagulant group and in 8 per cent of the control group; in the latter it was also the main cause of death in 3 per cent of the group as a whole and 37 per cent of the fatalities in the group. In no case was pulmonary embolism the cause of death in the prophylaxis group.

Other arterial thromboembolisms were established in the control group only (8 per cent). One of them was fatal. In the phenylindandione series, blood appeared in the urine or faeces of 3 old persons in poor health. The bleeding ceased in 2 after the discontinuance of anticoagulant administration, but in the third patient haemorrhages from mucous mem-

branes were a contributory factor to death. One of the controls showed a similar haemorrhagic complication the cause of which was not established.

No other haemorrhagic complications were found.

The incidence of other complications was practically the same in both groups.

The end results of the fractures were about the same in the two groups. Pseudarthrosis developed with equal frequency, i.e. in about 4 per cent of the diaphyseal fractures of both groups. Delayed union was seen in two cases of the phenylindandione group only.

The impression gained is that anticoagulant prophylaxis with phenylindandione is beneficial for elderly fracture patients immobilised for long periods, but caution is necessary in the treatment of old people in poor condition and careful control is even more important than usually.

RESUME

89 malades, âgés de plus de 40 ans, avec fracture du col fémoral, du trochanter, de la diaphyse fémorale ou tibiale (et fibulaire) ont subi un traitement conservateur ou chirurgical. En plus, il a été administré aux malades, entre les 2ème et 5ème jours qui ont suivi le traumatisme ou l'opération de la phénylindandione à titre prophylactique jusqu'au jour où le malade a quitté l'hôpital ou est devenu suffisamment mobile. Un nombre égal de malades souffrant de fractures similaires ont été traités simultanément par les mêmes méthodes mais sans prophylaxie anticoagulante.

Aucun cas de thrombose des veines profondes périphériques n'a été observé cliniquement dans le groupe traité par prophylaxie anticoagulante, alors qu'il y en eut 16 % dans les séries de contrôle. L'embolie pulmonaire a été diagnostiquée cliniquement dans 1 % du groupe anticoagulant et dans 8 % du groupe de contrôle; dans ce dernier groupe, il a été la principale cause du décès dans 3 % de l'ensemble du groupe et dans 37 % des cas de mortalité du groupe. Dans le groupe prophylactique, l'embolie pulmonaire n'a été dans aucun cas la cause du décès.

D'autres thromboembolies artérielles ont été observées, mais seulement dans le groupe de contrôle (8 %). L'une d'entre elles amena le décès. Chez les malades auxquels de la phénylindandione a été administrée, on a observé du sang dans l'urine et les selles de 3 personnes âgées en mauvais état de santé. L'hémorragie cessa lorsqu'on suspendit

l'administration de l'anticoagulant deux jours de suite, mais chez le troisième malade les hémorrhagies des membranes muqueuses ont été un facteur contributaire du décès. Chez un malade du groupe de contrôle, il y a eu des complications hémorragiques similaires dont la cause n'a pas été établie.

Aucune autre complication hémorragique n'a été observée.

L'incidence des autres complications a pratiquement été la même dans les deux groupes.

Le résultat final du traitement de ces fractures a été à peu près le même dans les deux groupes. Une pseudarthrose se développe avec une fréquence égale dans environ 4 % des fractures diaphysaires des deux groupes. Un retard de soudure a été constaté dans deux cas, mais seulement dans le groupe à la phénylindandione.

L'impression retirée est que la prophylaxie anticoagulante à la phénylindandione est bonne pour les malades âgés souffrant de fractures et qui sont immobilisés pendant une longue période, mais qu'il est nécessaire d'être prudent lorsque le malade âgé est en mauvais état de santé et qu'un contrôle minutieux est encore plus important que d'ordinaire.

ZUSAMMENFASSUNG

Achtundneunzig Patienten im Alter von 40 Jahren oder darüber hinaus, die Brüche des Schenkelhalses, Trochanterbrüche, Brüche der Femurdiaphyse oder der Tibia (und Fibula) diaphyse hatten wurden konservativ oder operativ behandelt. Ausserdem bekamen sie Phenylindandion prophylaktisch vom 2.–5. postoperativen oder posttraumatischen Tag bis sie entlassen wurden oder zufriedenstellend beweglich waren. Eine gleiche Anzahl von Patienten mit ähnlichen Brüchen wurde übereinstimmend mit gleichen Methoden aber ohne antikoagulierender Prophylaxe behandelt.

Kein klinisch nachweisbarer Fall von Thrombose der peripheren tiefen Venen entstand in der Gruppe mit Antikoagulationsprophylaxe, während 16 % in der Kontrolreihe auftraten. Lungenembolie wurde klinisch in 1 % der Antikoagulationsgruppe und in 8 % der Kontrolgruppe diagnostiziert. In der letzteren Gruppe war sie auch die Hauptursache des Todes in 3 % der Gesamtgruppe und in 37 % der Todesursachen in der Gruppe. In keinem Falle war sie die Todesursache in der prophylaktischen Gruppe.

Andere Thrombo-embolismen entstanden nur in der Kontrolgruppe

(8 %). Einer davon war letal. In der Phenylindandiongruppe wurde bei 3 alten und schwächlichen Personen Blut im Urin oder den Fæces beobachtet. Die Blutung hörte bei zweien nach der Unterbrechung der Antikoagulantverabreichung auf, aber bei der dritten Patienten waren Schleimhautblutungen ein Faktor, der zum Tode beitrug. Einer der Kontrolpatienten zeigte eine ähnliche Blutungskomplikation deren Ursache nicht ermittelt werden konnte.

Keinerlei andere Blutungskomplikationen wurden gefunden.

Das Vorkommen anderer Komplikationen war das Gleiche in beiden Gruppen.

Die Endergebnisse hinsichtlich der Brüche waren ungefähr die gleichen in beiden Gruppen. Pseudarthrosen entwickelten sich mitgleicher Häufigkeit, d.h. in ungefähr 4 % der Diaphysenbrüche bei der Gruppen. Verzögerte Heilung wurde in zwei Fällen der Phenylindandion-gruppe allein gesehen.

Man erhält den Eindruck, dass antikoagulierende Prophylaxe mit Phenylindandion bei älteren Patienten mit Brüchen, die für eine längere Zeit ruhiggestellt werden, günstig wirkt. Vorsicht ist jedoch nötig bei der Behandlung von alten Menschen, die sich in schlechtem Zustand befinden und eine genaue Überwachung ist hier besonder notwendig.

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