Results of Alternating Anticoagulant Prophylaxis in Surgery

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Preliminary Observations

Therapy with anticoagulants is accepted as the method of choice in certain thromboembolic disorders. The views on the value of *prophylaxis with anticoagulants* for the prevention of thromboembolism, however, are still divided. The following questions are of particular interest:

1) Does prophylactic inhibition of coagulation decrease the frequency of thromboembolism?

2) Do inevitable complications caused by anticoagulants restrict their value as to make them appear inappropriate?

3) Do frequency of thromboembolism or frequency of hemorrhage indicate a certain restriction in the use of prophylactic anticoagulation in certain age groups?

4) How important is the fact that a certain percentage of patients threatened by thromboembolism cannot profit of prophylactic anticoagulation because of existing contraindications?

A satisfactory solution of these problems is reached only by *comparative* investigations. As the frequency of thromboembolism fluctuates markedly with time, only *parallel* studies can yield proper results:

A comparison of thromboembolism-frequency covering *different* time periods has, therefore, only limited value as a criterion of the efficiency of measures preventing thromboembolism.

The Surgical Department of the University of Tübingen, has, for these reasons, introduced a strictly alternating anticoagulant prophylaxis observing the following principles: Patients were distributed among *anticoagulant group* A (even numbers) and *control group* B (odd numbers) according to their numbers on the admission chart.

Patients with generally accepted *contraindications* for anticoagulants were primarily eliminated from group A; in order to establish a ground for comparison as firm as possible

they were also eliminated from group B. These patients were then gathered into group C and defined as patients with contraindications with even or odd numbers on their admission chart.

The *practical details* of the prophylactic treatment will not be discussed here. They were entirely left to a specialist of thrombotic disease who was always available. Marcumar (3-l'-phenyl-propyl)-4-oxy-coumarin) was used exclusively. *An inhibition of coagulation* to 15—20% of normal Quick values was aimed at and maintained for the duration of the patient's bedrest and until regular mobilisation became possible.

The following system has been applied for *registering complications* evaluated in the statistical comparison: *Fatal embolism* only if confirmed by autopsy. *Pulmonary infarction* based on autopsy findings or clinical symptoms such as stiches in the side, shortness of breath, hemoptoe, and roentgenologic findings. *Deep venous thromboses in the legs* only when a difference of 2 cm in circumference at the largest part of the calf had been noted. Minor *hemorrhage* without necessity of transfusion, medium hemorrhage with transfusion volume up to 500 cc, major hemorrhage with transfusion volume over 500 cc (for details see page 13).

Results

The following *groups* resulted covering the period from december 1st, 1955 to march 31st, 1958 (table 1):

Anticoagulant Group: (even numbers) Group A	Control Group: (odd numbers) Group B	Contraindications: (even and odd numbers) Group C
3190	3336	1882

Table 1: Division of groups.

Frequency of thromboembolism: The frequency of thromboembolism in the different groups are tabulated in table 2:

Group:	Number of Patients:	Fatal pulmonary embolism (%)	Total of thromboembolic complications (%)	as compared to control group:
B	3336	17 (0.51)	94 (2.82)	100
A	3190	2 (0.06)	11 (0.35)	12.5
C	1822	35 (1.92)	76 (4.17)	150

Table 2: Frequency of thromboembolism in the different groups.

The frequency of fatal pulmonary embolism, and the total frequency of thromboembolism was reduced to 1/8 in the anticoagulant group as compared to the control group. As far as fatal pulmonary embolism is concerned the group with contraindications was 4 times more attained and regarding overall frequency of thromboembolism 1½ times more than the control group.

The thromboembolism-preventing action of anticoagulants is also remarkable regarding *different age groups* (table 3):

	Group A:		Group B:		
Age	Number of patients	Thromboembolic disorders	Number of patients	Thromboembolic disorders	Level of significance %
—39	1336	1	1460	14	< 1
40—59	1120	2	1090	40	< 0,1
60—80	704	8	746	37	< 0,1

Table 3: Thromboembolism-preventing action of anticoagulants in different age groups. The difference in thromboembolic disorders of group A and B is significant at the level shown in the respective column.

Bleeding frequency: In the anticoagulant group 0.97% of hemorrhagic complications occurred as compared to 0.27% in the control group (table 4):

Group	Number of patients	Hemorrhages
B	3336	9 (0.27%)
A	3190	31 (0.97%)
C	1822	11 (6.1%)

Table 4: Frequency of hemorrhage.

Bleeding frequency under anticoagulant treatment does not show any significant difference (level of significance > 1%) in the different age groups (table 5).

Age:	—39	40—59	60—80	Total
Number of patients	1336	1120	704	3160
Hemorrhages (%)	8 (0.6)	11 (0.98)	11 (1.56)	30 (0.95)

Table 5: Bleeding frequency in different age groups under prophylactic anticoagulant treatment.

No differentiation between light and severe hemorrhage has been made here as the grade of bleeding is not always decisive for the course of the disease. A critical evaluation showed that of the 31 bleeding episodes occurring in group A, 2 contributed to the fatal issue. In group B 3 times as many connections with the lethal issue could be assumed. These are registered (table 6, 7, 10) as fatal hemorrhages, although the patients did not bleed to death.

Frequency of thromboembolism and hemorrhage. Whether the administration of anticoagulants is justified or not can only be decided based on the *total of*

prevented (thromboembolic) *plus induced* (hemorrhagic) *complications.* The resulting total load of the different groups is represented in table 6:

Group	Number of patients	Fatal complications (%)	Total of complications (%)	Comparison to control group	
		*	**	*	**
B	3336	20 (0.6)	103 (3.1)	1	1
A	3190	4 (0.125)	42 (1.32)	1/5	4/10
C	1822	35 (1.92)	87 (4.77)	3	3/2

Table 6: Total occurrence of thromboembolic and hemorrhagic complications.

Five times as many fatal complications occurred in the control group as compared to the anticoagulant group. The total of complications were less than one half of those occurring in the control group. The differentiation of the complications mentioned in table 2 to 6 as well as a mathematical approach as to their significance is presented in table 7. The difference in the frequency of complications in the two groups is quite apparent and the thromboembolism-preventing action of anticoagulants as well as their value inspite of the complications they may induce is evident.

	Anticoagulant Group without contraindications 3190 patients							*Control Group* without contraindications 3336 patients							Difference II — IV
	I						II	III						IV	V
	fatal pulm. embolism	infarctions	thromboses	bleedings: light	bleedings: severe	bleedings: fatal	Total	fatal pulm. embolism	infarctions	thromboses	bleedings: light	bleedings: severe	bleedings: fatal	Total	Level of significance %
1	2	5	4	19	10	2	42	17	27	50	3	3	3	103	0,02
2	2	5	4				11	17	27	50				94	0,02
3				19	10	2	31				3	3	3	9	0,04
4	2					2	4	17					3	20	0,21

Table 7: The Difference in the totals of the anticoagulant and the control group as specified in rows 1 to 4 is significant at the level indicated in column V.

The duration of treatment following comparable surgical interventions is tabulated in table 8:

	Group A			Group B		
	number	days	average	number	days	average
herniotomy	244	2513	10.3	274	2785	10.16
appendectomy	615	5883	9.56	618	5761	9.31
Total	859	8396	9.77	892	8546	9.58

Table 8: Duration of therapy following surgery.

Total mortality: A comparison of the fatal cases reveals no higher mortality in the anticoagulant group (A) than in the controls (B) (cf. table 9):

	Group A			Group B		
	number of patients	fatal cases	%	number of patients	fatal cases	%
men	1805	31	1.7	1961	43	2.2
women	1385	19	1.4	1375	33	2.4
Total	3190	50	1.56	3336	76	2.27

Table 9: Mortality in the two groups compared.

The merely academical question whether the value of anticoagulants is limited considering that almost one fourth of the patients cannot benefit of this treatment, is answered by the synopsis in table 10: Even if the patients in group C are also divided into group A and B according to their chart numbers a significant difference is still found in favor of the anticoagulant group as far as the frequency of complications is concerned.

	Anticoagulant Group with contraindications 4136 patients							*Control Group* with contraindications 4212 patients							Difference II — IV
	I						II	III						IV	V
	fatal pulm. embolism	infarctions	thromboses	bleedings: light	bleedings: severe	bleedings: fatal	Total	fatal pulm. embolism	infarctions	thromboses	bleedings: light	bleedings: severe	bleedings: fatal	Total	Level of significance %
1	22	16	19	19	14	2	92	32	37	55	3	10	3	140	0,27
2	22	16	19				57	32	37	55				124	0,02
3				19	14	2	35				3	10	3	16	0,90

Table 10: for details see table 7

Discussion of the Results

Respecting the obvious limitation that statistical results bear no indication for the single case and that our conclusions refer to comparable conditions*), the following points can be established:

1. Prophylactic anticoagulation leads to a *definite decrease in mortality* caused by thromboembolism. These very impressive figures alone, however, are insufficient for the evaluation of prophylactic anticoagulation. Even non-fatal complications (pulmonary infarction, deep venous leg thrombosis) may markedly prolong reconvalescence and may induce severe consequences possibly leading to invalidity. The prevention of these complications is therefore basicly as important as the prevention of fatal pulmonary infarction.

2. The *total frequency of thromboembolism* is significantly reduced in the anticoagulant group as compared to the control group.

3. Even if *complications* caused by anticoagulants are taken into account this fact remains without restrictions: The difference in thromboembolic complications *and* hemorrhagic incidents between the two groups is statistically significant (table 4 and 7).

4. *No* age group is free of thromboembolism (table 3) or specifically outstanding regarding hemorrhages (table 5).

5. In all groups, which means also *without previous administration of anticoagulants,* hemorrhages do occur. The a priori assumption of a causal relation between bleeding and anticoagulation seems, therefore, in some cases to be problematic.

6. Except for hemorrhages, the significance of which is to be evaluated from case to case, prophylactic anticoagulation does not lead to any *damage* in the further course of the disease such as prolonged duration of therapy following surgical intervention or increased mortality in the group concerned.

7. Patients, who for known *contraindications* cannot benefit of anticoagulants are strongly prone to thromboembolism (table 2 and 4). The essentially *limitating* factor of prophylactic therapy with anticoagulant drugs is the confined field of its application and the particular danger for patients with contraindications. Considering even this restriction the value of anticoagulants can be proved and the difference in total frequency of thromboembolism in the two groups is statistically significant (table 10).

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*) Considering the marked *regional variations* in the frequency of thromboembolism the assembling of numerous statistics in order to obtain a collective statistic would not provide a better foundation for the solution of the basic questions mentioned above than do small *homogenous* synopses.

8. A further improvement of the results will undoubtedly be possible first of all by *enlarging the field of indications* with simultaneous restriction of contraindications and this above all can be achieved by surpressing the side-effects of the anticoagulant drug.

9. The decision whether a patient should prophylactically be treated with anticoagulants or not should less depend on an only vaguely defined danger but primarily on the *existence of concrete contraindications.*

Discussion des Resultats

Tenant compte des limitations évidentes des résultats statistiques sur un cas déterminé et considérant que nos conclusions se rapportent à des conditions comparables, nous pouvons établir les données suivantes:

1) Le traitement prophylactique aux anticoagulants permet une réduction certaine de la mortalité causée par des thromboemboles. Les résultats impressionants sont, à eux seuls, insuffisants pour évaluer la valeur d'une médicamentation anticoagulante prophylactique. Même des complications non mortelles (infarctus pulmonaire, thrombose des veines profondes des membres) peuvent prolonger la réconvalescence et mener à des consequences sévères et éventuellement à une invalidité. Prévenir ces complications est tout aussi important que prévenir un infarctus pulmonaire mortel.

2) La fréquence totale d'accidents thromboemboliques est nettement réduite dans le groupe de malades traités aux anticoagulants comparé au groupe contrôlé.

3) Même en tenant compte des complications dues aux anticoagulants, on peut maintenir les mêmes conclusions: la différence d'accidents thromboemboliques et d'hémorragies entre les deux groupes est statistiquement certaine (tableaux 4 et 7).

4) Aucun âge n'est exempt de thromboemboles et les hémorragies se retrouvent à tout âge (tableau 5).

5) On retrouve des hémorragies dans tous les groupes, également avant l'administration d'anticoagulants. On ne peut donc a priori établir une relation de cause à effet entre ces hémorragies et l'administration d'anticoagulants.

6) A part certaines hémorragies qui doivent être évaluées pour chaque cas déterminé, l'administration prophylactique d'anticoagulants ne prolonge pas la durée d'hospitalisation après une intervention chirurgicale ni la mortalité du groupe en question.

7) Les malades qui ne peuvent pas être traités aux anticoagulant à cause d'une contra-indication formelle sont prônes aux accidents thromboemboliques (tableaux 2 et 4). Le facteur limitant du traitement prophylactique aux anticoagulants est le groupe limité des indications et le danger particulier des contra-indications. En tenant compte de ses restrictions, la valeur des anticoagulants peut être prouvée et la différence de la fréquence totale des thromboemboles dans les deux groupes est statistiquement interprétable (tableau nr 10).

8) Un progrès important sera sans aucun doute obtenu en étendant les indications tout en limitant les contra-indications. Ceci pourrait être obtenu en supprimant les effets secondaires de la médicamentation anticoagulante.

9) La décision d'instituer un traitement prophylactique aux anticoagulants ou non, devrait plutôt dépendre des contra-indications concrètes que d'une vague impression de danger.

Zusammenfassende Besprechung

Mit der selbstverständlichen Einschränkung, daß statistische Aussagen keine Aussagen für den Einzelfall zulassen und unsere Ergebnisse zunächst für vergleichbare Verhältnisse*) gelten, dürfen folgende Feststellungen getroffen werden:

1. Die prophylaktische Gerinnungshemmung führt zu einer *eindeutigen Senkung* der Thromboembolie*mortalität*. Diese sehr eindrucksvollen Zahlen allein genügen jedoch nicht zur Beurteilung des Nutzens der Antikoagulantienprophylaxe, da auch die nicht tödlichen Komplikationen (Lungeninfarkte, Thrombosen der tiefen Beinvenen) eine erhebliche Beeinträchtigung des Heilverlaufes und schwerwiegende bis zur Invalidität reichende Spätfolgen nach sich ziehen können. Der Verhütung dieser Komplikationen kommt grundsätzlich die gleiche Bedeutung zu wie der Verhütung tödlicher Lungenembolien.

2. Die *Gesamt-Thromboembolie-Frequenz* ist in der Antikoagulantiengruppe der Vergleichsgruppe gegenüber deutlich herabgesetzt.

3. Auch unter *Berücksichtigung der Komplikationen* gerinnungshemmender Maßnahmen erfährt diese Aussage keine Einschränkung: Der Unterschied hin-

*) Im Hinblick auf die *regional* stark verschiedene Thromboembolie-Häufigkeit bietet die Zusammenlegung mehrerer Statistiken zu einer Sammelstatistik kaum bessere Möglichkeiten zur Beantwortung der eingangs gestellten Fragen als homogene, wenn auch kleinere Zusammenstellungen.

sichtlich thromboembolischer *und* Blutungskomplikation in beiden Gruppen ist statistisch gesichert (Tab. 4, 7).

4. *Keine* Altersklasse ist thromboemboliefrei (Tab. 3) oder in überzufälliger Weise mit *Blutungen* belastet (Tab. 5).

5. In allen Gruppen, also auch *ohne vorhergehende Antikoagulantiengaben* werden Blutungen registriert. Die grundsätzliche Annahme eines kausalen Zusammenhanges zwischen Blutung und Gerinnungshemmung erscheint demnach in vereinzelten Fällen problematisch.

6. Die prophylaktische Gerinnungshemmung führt, abgesehen von den in ihrer Bedeutung von Fall zu Fall einzuschätzenden Blutungen für den weiteren Heilverlauf keinerlei *Schädigung* herbei, die sich in einer verlängerten Behandlungsdauer nach operativen Eingriffen oder erhöhter Mortalität in der betreffenden Gruppe manifestiert.

7. Die Patienten, die wegen der bekannten *Gegenindikationen* einer Antikoagulantienprophylaxe nicht zugeführt werden können, sind erheblich thromboemboliegefährdet (Tab. 2, 4). Die beschränkte Anwendbarkeit der Antikoagulantia und die besondere Gefährdung derjenigen Patienten, bei denen Gegenindikationen bestehen, sind der wesentliche *begrenzende* Faktor einer Thromboembolie-Prophylaxe mit gerinnungshemmenden Stoffen. Auch unter Berücksichtigung dieser Beschränkung läßt sich jedoch noch der Nutzen der Antikoagulantien darstellen und die Differenz der Thromboembolie-Gesamtfrequenz in beiden Gruppen statistisch sichern (Tab. 10).

8. Eine weitere, zweifellos mögliche Verbesserung der Ergebnisse erscheint demnach vor allem durch ein *Ausweiten des Indikationsgebietes* unter Einschränkung der Gegenindikationen — wohl vordringlich über eine Bekämpfung der Nebenwirkungen der Antikoagulantia — möglich.

9. Der Entscheidung, ob ein Patient der Antikoagulantien-Prophylaxe zugeführt wird oder nicht, sollte weniger von einer nur sehr unvollkommen erfaßbaren Gefährdung, als in erster Linie vom *Bestehen etwaiger Gegenindikationen* abhängig gemacht werden.