ANTICOAGULANTS IN MYOCARDIAL INFARCTION

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The treatment of myocardial infarction with anticoagulants is generally accepted in the United States of America. In Great Britain a number of physicians do not treat their patients in this way, although most papers published here support the American view. The decision to use anticoagulants impels most physicians to admit their patients to hospital for a stay of several weeks, a matter of economic as well as medical importance. The present paper attempts to provide further evidence on the efficacy or otherwise of anticoagulant therapy and the suitability of certain types of patient for this treatment.

The problem was approached by a study of the effects of anticoagulant therapy on the prognosis of patients admitted to hospital with myocardial infarction, by determining if anticoagulant therapy was of equal benefit to all patients of all ages and with different degrees of shock, and by the analysis of notes and post-mortem reports to find how anticoagulant therapy affected the mortality.

Material

Two hundred patients admitted to the Radcliffe Infirmary as emergencies between January, 1945, and May, 1952, were suitable for the investigation; 125 of them were controls and 75 received anticoagulant therapy. In this hospital the duty of admitting medical emergencies is shared between four physicians. There is no selection of the type of case admitted under each physician; one physician admits medical emergencies on Mondays, and the other three in turn for periods of three days in succession.

The notes of all patients admitted between January, 1945, and May, 1952, with a diagnosis of myocardial infarction have been reviewed. Cases were rejected if the diagnosis was in doubt, if the notes were inadequate, or if the use of anticoagulant therapy was contraindicated,—for example, by an accompanying cerebrovascular accident or by a recent history of melaena. The diagnosis was based on the clinical history and positive electrocardiographic evidence in 179 cases, the clinical history and post-mortem evidence in 18 cases, and the clinical history alone in three cases. Of the 70 patients who died, 52 were submitted to a post-mortem examination.

The patients in the control group fell into two categories—75 admitted before 1950, in which year anticoagulant therapy was coming into general use in the Radcliffe Infirmary, and 50 admitted in and after that year. As the death rates in the two categories were 39% and 44% respectively it was felt that all the patients were suitable for inclusion in the control group. In fact, the use and choice of anticoagulants was determined by the views of the physician under whose care the patient was admitted, and there was no obvious medical reason why the patients in the second category did not have anticoagulant treatment.

The case notes of both series have been analysed to show the following facts:—(1) Age. (2) Sex. (3) Time from the onset of infarction to admission and to discharge or death.

(4) Cardiac function before the onset of infarction, four categories being used: (I) no cardiac symptoms, (II) mild angina pectoris or a reduction in exercise tolerance, (III) severe angina pectoris or a great reduction in exercise tolerance, and (IV) frank heart failure. (5) Signs of previous cardiovascular disease before admission: this was judged to be present, absent, or not recorded; if present, one or more of the following signs of cardiovascular disease had been recorded—abnormal rhythm, hypertension, enlarged heart, or evidence of previous infarction. (6) The degree of shock at onset and on admission was assessed as “none or mild,” “moderate,” “severe,” or “not recorded” by consideration of the severity of the pain and its duration and response to opiates, blood pressure, pulse rate, and appearance of the patient. (7) The electrocardiogram. (8) Further thrombo-embolic accidents. (9) The post-mortem report. (10) Cause of death.

In the treated group the following facts were also recorded: type of anticoagulant used, whether heparin, dicoumarol, or ethyl biscoumacetate (“tromexan”); time from the onset of infarction to the beginning of effective anticoagulant therapy, which was taken as the giving of 10,000 i.u. of heparin intravenously or a fall in prothrombin efficiency to under 20% of normal; the duration of effective anticoagulant therapy; and the occurrence of complications resulting from treatment.

Control of Anticoagulant Therapy

Heparin was used in some cases, but only to initiate treatment, and no laboratory tests were necessary, because the dosage used was not large enough to cause lengthening of the clotting-time for a whole 24-hour period. Dicoumarol and ethyl biscoumacetate therapy were controlled by the one-stage prothrombin test as described by Biggs and Macfarlane (1949). When dicoumarol was used the aim of treatment was to maintain the clotting-time between one and a half and two times that of the normal control. This change in clotting-time interpreted from the dilution curve given by Biggs and Macfarlane represents a range of prothrombin efficiency between 10 and 20% of normal. With ethyl biscoumacetate a slightly smaller margin of safety was allowed because it was found that the level of clotting-time could be adjusted more rapidly. With this drug the therapeutic range of clotting-time was taken to be one and a half to two and a half times the control clotting-time, or 7.5 to 20% of prothrombin efficiency, a range similar to that used by Tulloch and Gilchrist (1950).

Results

The mortality in the two groups of cases is shown in Table I.

TABLE I.—Mortality

Group	No. of Cases	No. that Survived	No. that Died
Control	125	74 (59%)	51 (41%)
Treated	75	56 (75%)	19 (25%)

The calculation of χ^2 gives a value of 4.27, corresponding to a probability of about 0.04.

As the mortality rate might have been influenced by factors other than anticoagulant drugs, the two groups were further analysed to try to find out if there were any patients for whom the prognosis was strikingly good or bad in either the control or the treated group. The time from onset to admission was similar in the two groups (Table II). The importance of taking this into considera-

TABLE II.—Cases Admitted in First 48 Hours and in First Seven Days

Group	Admitted in	
	First 48 Hours	First 7 Days
Control	68%	83%
Treated	59%	82%

tion when comparing methods of treatment has been demonstrated by Tulloch and Gilchrist (1950) and by Yater *et al.* (1948).

Cassidy's (1946) series of 1,000 cases had a male-to-female ratio of 3.5 to 1. In the present series the ratio was approximately 2 to 1, the figures in the control group being 82:43 and in the treated group 50:25.

Other factors which might influence the prognosis are age, degree of shock, and cardiac function before the infarction. In Tables III, IV, and V the two groups are compared for each of these factors and shown to be similar, except in degree of shock at onset, where the number of severely shocked patients was larger in the treated group.

The notes of the two groups were examined for evidence of objective signs of previous cardiovascular disease, but it was found that in about half of the cases no information was available. In the remaining half there was a record of some kind of cardiovascular disease in all but four of the control group and all but two of the treated group. This means that the state of the myocardium before the infarction had to be assessed on the subjective evidence of cardiac function, since objective evidence was lacking in a large number of cases.

The cases were then divided up into those mildly, moderately, and severely shocked, and the mortality in each section was considered separately. The results are shown in Table VI, which brings out the influence of the severity of shock on the prognosis of patients not treated with anticoagulants, and suggests that anticoagulants are of value in patients who are moderately and severely shocked. This point is clearly emphasized by Gilchrist (1952), whose article appeared after the present paper had been prepared.

The state of the myocardium before the infarction naturally affects the prognosis, and the figures in Table VII

TABLE III.—*Number of Patients in Each Decade from 40 to 90*

Group	Age in Years				
	40-49	50-59	60-69	70-79	80-89
Control ..	19 (15%)	27 (22%)	45 (36%)	28 (22%)	6 (5%)
Treated ..	15 (20%)	23 (30%)	24 (33%)	13 (17%)	0

TABLE IV.—*Number of Patients in Each Category of Shock*

Group	Degree of Shock at Onset			
	None or Mild	Moderate	Severe	Not Recorded
Control ..	42 (33%)	48 (39%)	31 (25%)	4 (3%)
Treated ..	13 (18%)	37 (49%)	25 (33%)	0

TABLE V.—*Number of Patients in Each Category of Cardiac Function Before the Infarction*

Group	Cardiac Function				
	Category				Not Recorded
	I	II	III	IV	
Control ..	33 (26%)	60 (49%)	20 (16%)	4 (3%)	8 (6%)
Treated ..	18 (24%)	39 (52%)	15 (20%)	0	3 (4%)

TABLE VI.—*Influence on Death Rate of Degree of Shock Due to Infarction*

	Degree of Shock			
	None/Mild	Moderate	Severe	Not Recorded
Deaths and death rates in control group ..	10 (24%)	19 (40%)	21 (68%)	1 (2%)
Deaths and death rates in treated group ..	3 (23%)	7 (19%)	9 (36%)	0

The numbers in the treated group are too small for the result to be statistically significant.

TABLE VII.—*Influence of Cardiac Function Before Infarction on Death Rate*

	Cardiac Function Before Onset		
	Categories I and II	Categories III and IV	Not Recorded
Deaths and death rates in control group ..	37 (41%)	9 (38%)	5
Deaths and death rates in treated group ..	12 (21%)	7 (46%)	0

TABLE VIII.—*Death Rate of Patients Over and Under 60*

	Under 60	Over 60
Deaths and death rates in control group ..	16 out of 46 (35%)	35 out of 79 (44%)
Deaths and death rates in treated group ..	11 out of 38 (29%)	8 out of 37 (21.5%)

TABLE IX.—*Number of Patients Over and Under 60 in Each Category of Shock and in Each Category of Cardiac Function*

	Under 60	Over 60
Shock:		
Mild ..	18 (21%)	37 (32%)
Moderate ..	40 (48%)	45 (39%)
Severe ..	23 (31%)	33 (29%)
Cardiac function:		
Categories I and II ..	65 (81%)	84 (77%)
Categories III and IV ..	15 (19%)	25 (23%)

TABLE X.—*Degree of Shock Resulting from Infarction in Relation to the Cardiac Function Before the Infarction*

	Cardiac Function	
	Categories I and II	Categories III and IV
Mild shock ..	42 (29%)	13 (32.5%)
Moderate shock ..	67 (46%)	14 (35%)
Severe shock ..	37 (25%)	13 (32.5%)

TABLE XI.—*Death Rate in Men and Women*

Group	Male		Female	
	Survived	Died	Survived	Died
Control ..	49	33 (40%)	25	18 (42%)
Treated ..	35	15 (30%)	21	4 (16%)

suggest that only those patients with a good cardiac function before infarction receive benefit from anticoagulant treatment. In Table VIII the influence of age on mortality in the control and treated groups is considered.

The results in the present series suggest that older patients have a worse prognosis if untreated, but a more striking reduction in mortality when anticoagulants are used. Thus age, degree of shock, and cardiac function are shown to influence the mortality from myocardial infarction and the benefit received from anticoagulants. Tables IX and X show that these three factors are independent of one another and are not, as might be expected, due only to the influence of age. In 11 cases it was impossible to decide from the notes what the cardiac function was before the infarction.

It is generally accepted that the prognosis is better for older patients and better for women than for men. In Table XI the greater reduction in mortality for women as a result of the use of anticoagulant therapy may be due to the fact that the women were on the whole older, 70% being over 60, whereas only 50% of the men were over 60.

Discussion

The prognosis of so common a disease as myocardial infarction is uncertain because it is difficult to ascertain the incidence and death rate. In the present paper we

have necessarily had to confine ourselves to a study of those patients who survived long enough to reach hospital. We found that the mortality rate was reduced by anticoagulant therapy from 41 to 25%, a difference that is statistically significant and comparable with the figures of Tulloch and Gilchrist (1950).

The groups of patients who appeared to receive most benefit from anticoagulants were those over 60 years of age, those who were moderately and severely shocked, and those whose cardiac function immediately before the myocardial infarction was impaired slightly or not at all.

It is not merely a question of academic interest to decide what type of patient is most likely to benefit from anticoagulants, because most physicians find treatment practicable only in hospital, and many more cases of myocardial infarction are admitted now than formerly. Table XII

TABLE XII.—Number of Patients Admitted with Myocardial Infarction each Year from 1945 to May, 1952, and the Proportion Receiving Anticoagulant Therapy (Only the Cases Included in the Present Series are Recorded)

Year	No.	No. Treated with Anticoagulants
1945	4	0
1946	20	0
1947	14	0
1948	24	4 (17%)
1949	18	2 (11%)
1950	32	15 (48%)
1951	66	36 (55%)
Jan.-May, 1952	22	18 (82%)

shows that more patients were admitted to the Radcliffe Infirmary in 1951 (66) than in the four years 1945-8 (62). Unless there is a change in the management of patients with myocardial infarction which allows satisfactory treatment in the home, the number of patients admitted to hospital will increase. This is an important economic fact, because anticoagulant therapy does not shorten the period in hospital. In the control group the average stay was 39 days and in the treated group 45 days. The number of persons in the age groups with the highest incidence is increasing, and the cost of a hospital bed in the Radcliffe Infirmary reached the figure of £17 12s. 3d. a week in 1951.

The death rate in the series of 800 cases reported by the American Heart Association was 24% in the controls and 15% in the treated group. The difference was thought to be due chiefly to a reduced incidence of thrombo-embolic deaths. One of our chief difficulties in making a retrospective survey was that vital information about the patient's mode of death is so often lacking, and even with very comprehensive post-mortem notes the exact cause cannot be found, although contributory causes may be evident, and in many cases no more precise diagnoses than those listed in Table XIII could be made. It is for this reason that the admittedly vague terms "sudden death," "continued shock," and "heart failure" had to be used.

TABLE XIII.—Causes of Death

Cause	Control Group	Treated Group
Sudden death	25	11
Continued shock	10	2
Heart failure	12	6
Ruptured ventricle	2	0
Haematemesis	2	0

An attempt is made to answer the question posed in a leading article in the *British Medical Journal* of October 28, 1950 (p. 991), of how many of the deaths were inevitable. By inevitable we mean, for instance, a severely shocked patient dying within an hour of admission or a patient found after death to have a ruptured ventricle.

Table XIV shows the numbers in each category after the inevitable deaths have been subtracted, and has been

TABLE XIV.—Causes of Death After Subtraction of Inevitable Deaths

Cause	Control Group	Treated Group
Sudden death	25	9
Continued shock	4	2
Heart failure	10	4

included although we realize that the word inevitable as used here has no absolute value but is a retrospective assessment. For the same reason no deduction of inevitable deaths has been made throughout the paper.

Thrombo-embolic accidents other than myocardial infarction which developed while the patients were in hospital numbered 27 (21%) in the control group and 11 (15%) in the treated group. The incidence is low because adequate records of suspicious incidents were sometimes lacking.

Thus in the present paper there is no definite indication how anticoagulant therapy lowers the mortality rate from myocardial infarction, although it is quite clear that there is a significant reduction.

While we do not feel that it is yet justifiable to withhold anticoagulant therapy from any patient suffering from myocardial infarction, provided no contraindication exists and proper laboratory facilities are available, our results suggest that certain types of patient may be specially suitable for that treatment.

Summary

The case histories of 200 patients admitted to the Radcliffe Infirmary with myocardial infarction between January, 1948, and May, 1952, have been reviewed.

The death rate in hospital was 41% in the control group of 125 cases and 25% in the treated group of 75 cases, a difference which is statistically significant.

Anticoagulant therapy seemed to be of most value to patients over 60 years of age, moderately or severely shocked, and with little or no previous impairment of cardiac function.

No complications resulted from anticoagulant therapy.

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The Sixth Laboratory Animals Bureau Congress was held at the Royal Veterinary College, London, on March 27 and 28. Some 250 technicians from all parts of the country attended. The congress was opened by the secretary of the Medical Research Council, Sir Harold Himsworth. Six short papers were read by technicians, and one long one, on reproduction in mammals, by Dr. I. W. Rowlands, of the Agricultural Research Council Institute of Animal Physiology, Babraham. Visits were paid to the National Institute for Medical Research, Mill Hill, and to the Lister Institute at Elstree, and a programme of films of zoological interest was shown at the College. The final session was "Question Time." Chairmen at the four sessions were Professor S. P. Bedson, F.R.S., Dr. L. Harrison Matthews, Dr. R. Lovell, and Professor R. E. Glover. The proceedings of the Congress will be published in full in the journal of the Animal Technicians Association.