EFFECT OF ANTICOAGULANT THERAPY AND MONO-AMINE OXIDASE INHIBITOR IN ACUTE MYOCARDIAL INFARCTION

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The use of anticoagulant therapy has gained increasing popularity since its inception, and of the publications current in America and United Kingdom, the majority were of the opinion that anticoagulants had a definite value in myocardial infarction during the acute stages. Gilchrist (1954) in a careful study with case to case comparison found that there was a reduction of mortality to 16%, and most of other workers using anticoagulants accepted as satisfactory results a mortality figure between 7% to 25% (Baer et al 1951, Smith 1953. Wooten et al 1953, London et al 1953, Burton 1954, Wilson et al 1954, Honey et al 1957, White et al 1958). Proponents of the value of this regime suggested that other than cardiac causes of death such as cardiac arrest, cardiac failure, and ventricular fibrillation, two possibly significant causes of mortality were pulmonary embolism and extension of coronary artery thrombosis. Evidence was adduced of the frequency of thrombosis of deep leg and pelvic veins particularly during strict bed rest, and careful necropsis showed definite and significant incidence of pulmonary embolism in fatal cases of myocardial infarction (Glueck 1956). There is, however, no conclusive evidence of extensions of coronary artery thrombosis either clinically or pathologically. On the other hand, there is evidence that in myocardial infarction, some coronary arteries showed subintimal haemorrhages which might conceivably contribute to a worsening of coronary thrombosis in that a narrowing of arterial lumen would be caused. Further, there is also evidence of serious and fatal haemorrhages arising as a result of anticoagulant therapy even when well controlled by prothrombin estimation and the regime accepted as satisfactory. Haemopericardium without or with rupture of the heart, and gastric or cerebral haemorrhage had all been reported (Waldron et al 1954, Spetz et al 1957).

In Singapore, moreover, it is a common experience of clinicians that pulmonary embolism as a result of thromboembolic episode is rare and instances of fatal embolism resulting from deep leg or pelvic vein thrombosis are seen most exceptionally. If the prevention of thromboembolic episode is one of the main values of anticoagulants therapy in myocardial infarction, then on the current disease pattern prevailing locally, the value of such a therapy would be less when compared to Western figures.

Locally, no valid study on the effect of anticoagulants in myocardial infarction has been made although there exist many strong local opinions about its beneficial influences. Ransome (1960) reported an improved mortality figure of 16% over cases receiving anticoagulants, but this was based on a retrospective study with the control cases in a different period of time. In a study of M.A.O. inhibitors on coronary heart disease, it was found that more cases of death occurred in the group receiving anticoagulants (Gwee 1961). Although the figure was small, in view of the relative uncertainty of the real value of anticoagulants in myocardial infarction in Singapore, the study was made on a larger number of cases with two questions in view: firstly, whether M.A.O. inhibitor is of any value in myocardial infarction, and secondly if anticoagulant therapy does exert a beneficial effect on survival chances.

METHOD

All patients diagnosed as coronary thrombosis admitted into Medical Unit 2 were assigned serially into 4 Groups:—

Group I: Routine with anticoagulant therapy and M.A.O. inhibitor.
Group II: Routine with anticoagulant therapy alone.
Group III: Routine with M.A.O. inhibitor alone.
and Group IV: Routine treatment only.

Routine treatment for coronary thrombosis included bed rest, light diet, morphine for pain, oxygen when required, digitalisation if heart failure is suspected, and treatment for other complications such as diabetes. Anticoagulant therapy was started by intramuscular heparin sodium 6 hourly for 24 hours together with oral Dindevan (Phenedione) 300 mg. a day for the first day, and Dindevan alone from 2nd day onwards with the aim of maintaining the prothrombin time at $1\frac{1}{2}$ to $2\frac{1}{2}$ times that of normal. Cases on M.A.O. inhibitors were given 60 mgm.*

* In this case, Nialamid.

TABLE 1. SHOWING DISTRIBUTION OF GROUPS

A I (Anticoagulant with M.A.O.)					
	25	(Reject 2) Real Number	(23)	D4 (1)	21.7%
A II (Anticoagulant)					
	25	(Transfer 1)	(26)	7 (1)	30.8%
A III (M.A.O.)					
	25	(Reject 3)	(22)	1 (1) [1]	14.5%
A IV (Control)					
	25	(Reject 3)	(22)	(2)	9.1%
Other death				10 (7 new, 3 old infarction)	

D = death ( ) = acute death where treatment probably has not made a difference.

[ ] = delayed death occurring after the period of 4 weeks' observation.

Other death = deaths due to C.T. but not diagnosed premortum.

Mortality	All groups	18.5%	M.A.O.	18%
	Anticoagulant	25.5%	No M.A.O.	20%
	Control	11.5%		

TABLE 2. DEATH

Group	Duration of acute attack		Condition Severe	E.C.G.		SGOT	Assoc. with Diabetes	Sex cum Age		Race cum Sex cum Assoc. with Diseases which Aggravated *				Previous Infarction	Steroid
	1/52	7 1/52		mild	severe	Positive		Male	Female						
										Malay	Chinese	Indian	Others (exclude Malay)		
I	4	1	4	1	1	0	0	(45 69 60 46 50)	0	0	(M) 3	(M) 2	0	0	1
II	6	2	4	1	7	4	(M60 F56 M51) 3	(60 37 51 69 40 78 71)	(56)	(M) 1	(M) 2	(M) 1	(M) 3 (F) 1	3	0
III	3	0	1	0	3	1	(F70) 1	(52 59)	(70)	0	(M) 1	(M) 1	(F) 1	1	0
IV	2	0	1	0	1	0	0	(71 66)	0	0	(M) 2	0	0	0	0
V	8	2	8	2	5	2	0	(70 38 58 51 60 58)	(65 71 60 59)	0	(M) 4 (F) 3	(M) 3	(M) 1	0	0
Total	23	5	18	4	17	7	4	22	6	1	15	7	6	4	1

* = Heart failure, Hypertension, Gross Debility, Hypercholesterolemia

M = male F = female. ( ) = age of patient.

TABLE 3. ASSOCIATED DISEASES AND SEX AND RACE — ALL CASES

			I	II	III	IV	TOTAL
	Diabetes		1	7	2	4	14
1	Diabetes with Hypertension		0	0	0	0	0
2	Previous history of Hypertension excluding raised B.P. at admission		2	1	6	1	10
3	Other heart disease		2	0	1	0	3
4	Previous infarct (including 3)		0	3	1	1	5
5	Previous angina (including 4 + 3)		2	7	5	6	20
6	On steroids for therapy		1	1	0	0	2
7	Others		1	7	3	2	13
8	Bleeding phenom. during treatment		2	2	0	0	4
	Chinese	Male	8	9	5	6	28
		Female	0	2	3	2	7
	Indian	Male	9	7	7	8	31
		Female	2	0	2	1	5
	Malay	Male	4	2	2	2	10
		Female	0	0	2	0	2
	Others	Male	0	5	0	1	6
		Female	0	1	1	2	4

TABLE 4. CLINICAL AND LABORATORY FINDINGS — ALL CASES

		I		II		III		IV	
		Male	Female	Male	Female	Male	Female	Male	Female
Cl. states	Mild	11	0	15	2	12	1	12	2
	Severe	10	2	9	0	8	1	5	3
ECG	Mild	2	0	7	0	4	0	3	1
	Severe	17	2	17	2	16	2	14	3
Death		5	0	7	0	1	0	2	0
Static		1	0	0	0	1	0	0	0
Improved (has angina)		7	0	16	1	12	2	13	4
Symptomless		9	2	1	1	5	1	3	0
SGOT	negative less than 45	6	2	8	0	12	1	7	4
	positive	11	0	13	1	6	1	8	0
Cholestrol	200 mg.%	2	2	8	1	5	1	7	0
	200 or more mg.%	13	0	10	1	13	0	7	4
SGOT not done		4	0	4	1	2	0	3	0
Cholestrol not done		6	0	5	1	2	1	3	0
ECC not done		2	0	0	0	0	0	1	0

TABLE 5. AGE AND DURATION OF ATTACK

	I		II		III		IV		TOTAL	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
20	0	0	0	0	0	0	0	0	0	0
21 - 30	0	0	0	0	0	0	0	0	0	0
31 - 40	3	0	5	0	1	2	4	0	13	2
41 - 50	10	1	5	1	6	3	2	2	23	7
51 - 60	4	0	9	2	5	1	7	2	25	5
61 - 70	3	1	2	0	2	2	3	1	10	4
70	1	0	2	0	0	0	1	0	4	0
Up to 1 day	10	2	11	1	5	3	7	2	33	8
1 — 2 day	4	0	3	0	0	0	1	0	5	0
3 — 4 day	2	0	2	0	2	1	4	2	10	3
5th day	0	0	2	1	3	1	2	0	7	2
2nd week	3	0	2	1	2	1	1	1	8	3
3rd week or more	1	0	2	1	0	1	1	0	4	2
Unknown	1	0	1	0	0	2	1	0	3	2

TABLE 6. ASSOCIATED DISEASES WITH CORRECTION FACTORS

Group	Number of Cases	ASSOCIATED WITH DIABETES			PREVIOUS INFARCTION			HYPERTENSION			STEROID			After Correction
		Actual	Expected	Correction Factor	Actual	Expected	Correction Factor	Actual	Expected	Correction Factor	Actual	Expected	Correction Factor	
I	5	1 (20%)	1 (21%)	0	0 (0%)	0.7	+ 0.7	0 (0%)	0.7	+ 0.7	1 (20%)	0.2	— 0.8	5 — 1.4 (4)
II	8	4 (50%)	1.7 (21%)	— 2.3	3 (38%)	1.1	— 1.9	0 (0%)	1.1	+ 1.1	0 (0%)	0.3	+ 0.3	8 — 2.8 (5)
III	3	1 (33%)	0.6 (21%)	— 0.4	1 (33%)	0.4	— 0.6	2 (67%)	0.4	— 1.6	0 (0%)	0.1	+ 0.1	3 — 2.6 (0)
IV	2	0 (0%)	0.4 (21%)	+ 0.4	0 (0%)	0.3	+ 0.3	1 (33%)	0.3	— 0.7	0 (0%)	0.1	+ 0.1	2 — 0.3 (2)
V	10	0 (0%)	2.1 (21%)	+ 2.1	0 (0%)	1.4	+ 1.4	1 (33%)	1.4	+ 0.4	0 (0%)	0.4	+ 0.4	10 4.3 (14)
Total	28	6 (21%)			4 14%			4 14%			1 4%			

Fig 1. MORTALITY DISTRIBUTION

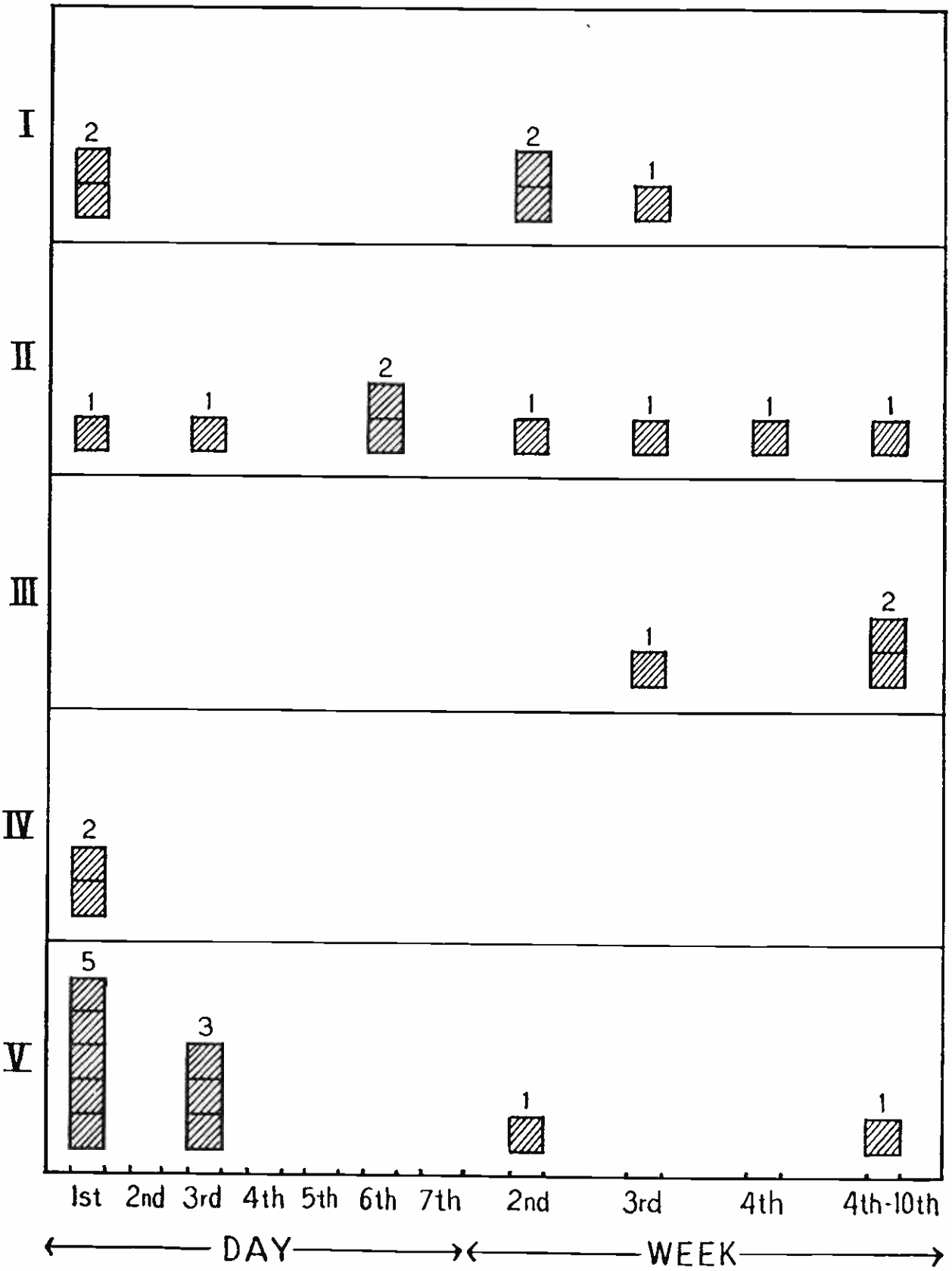


Fig 2. TREND OF TOTAL DEATH (28 CASES)

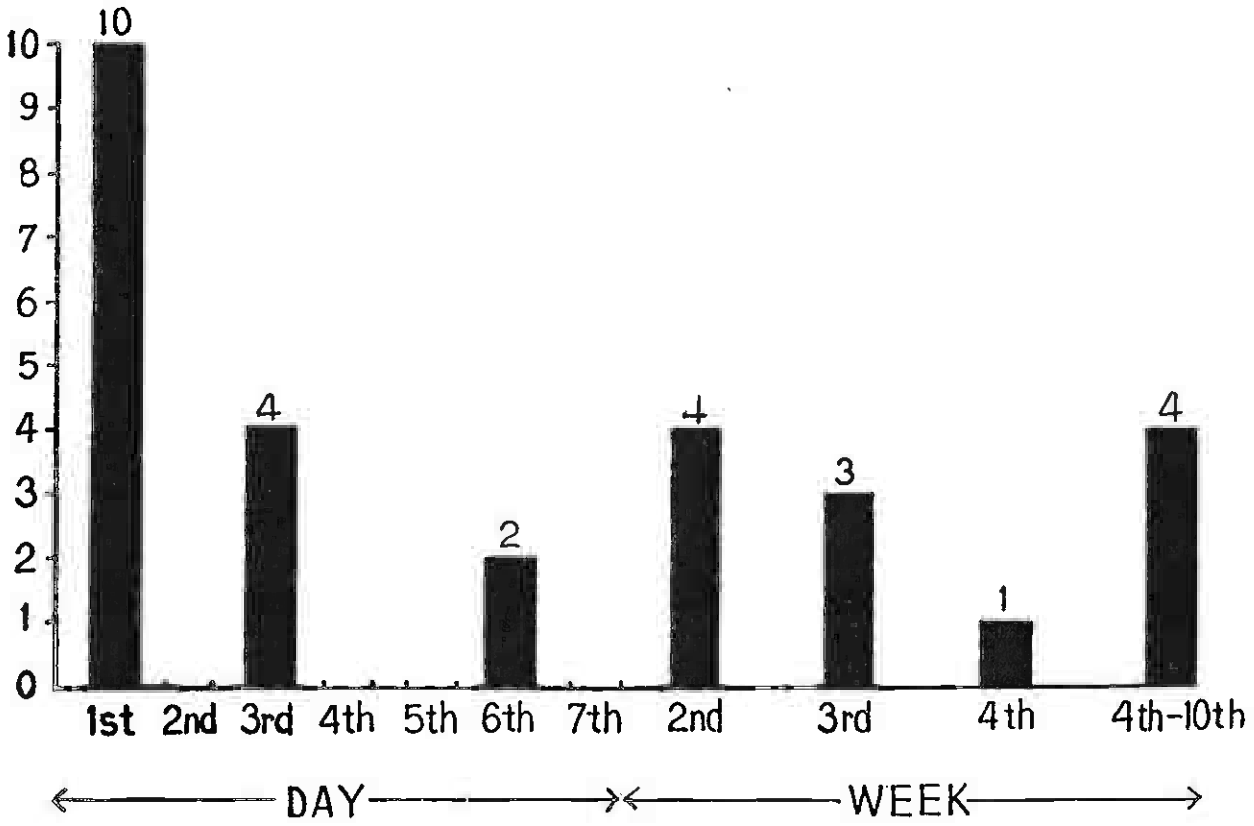


Fig 3. TREND OF MORTALITY IN PERCENTAGE

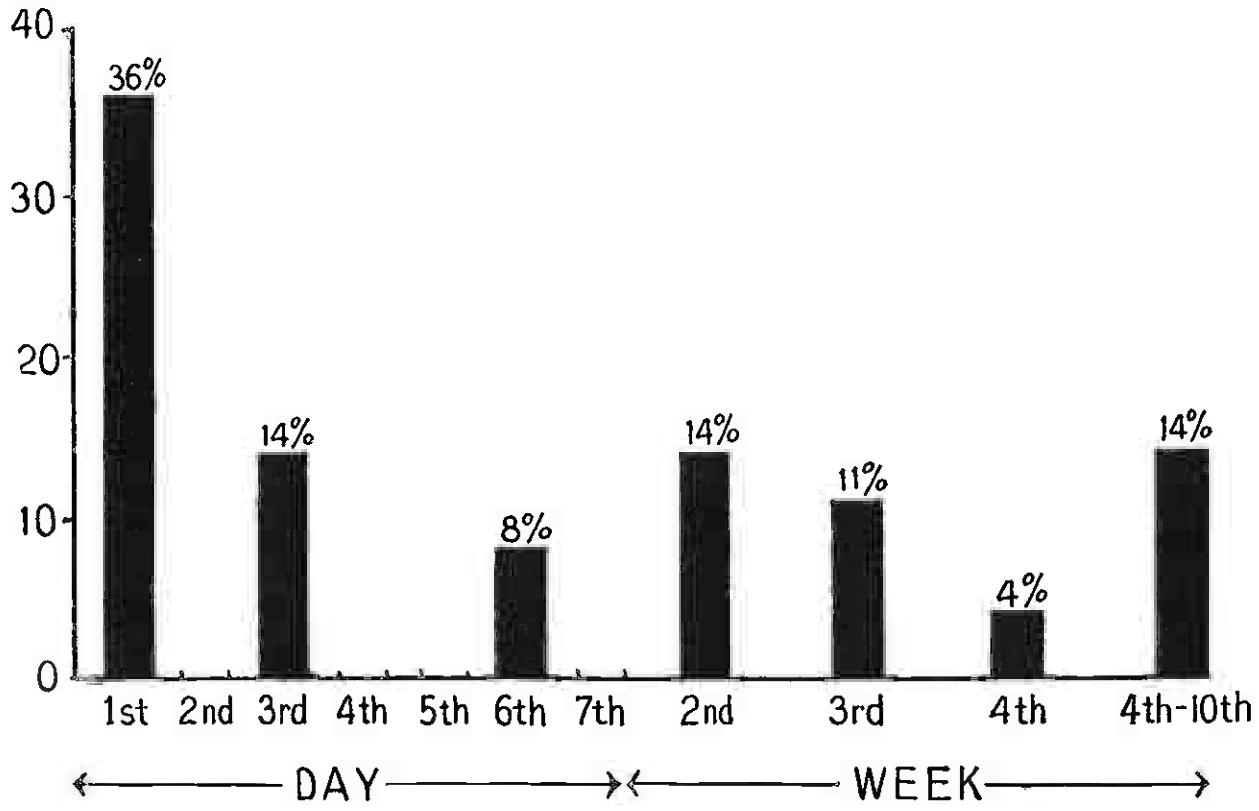


Fig 4. MORTALITY (UNCORRECTED)

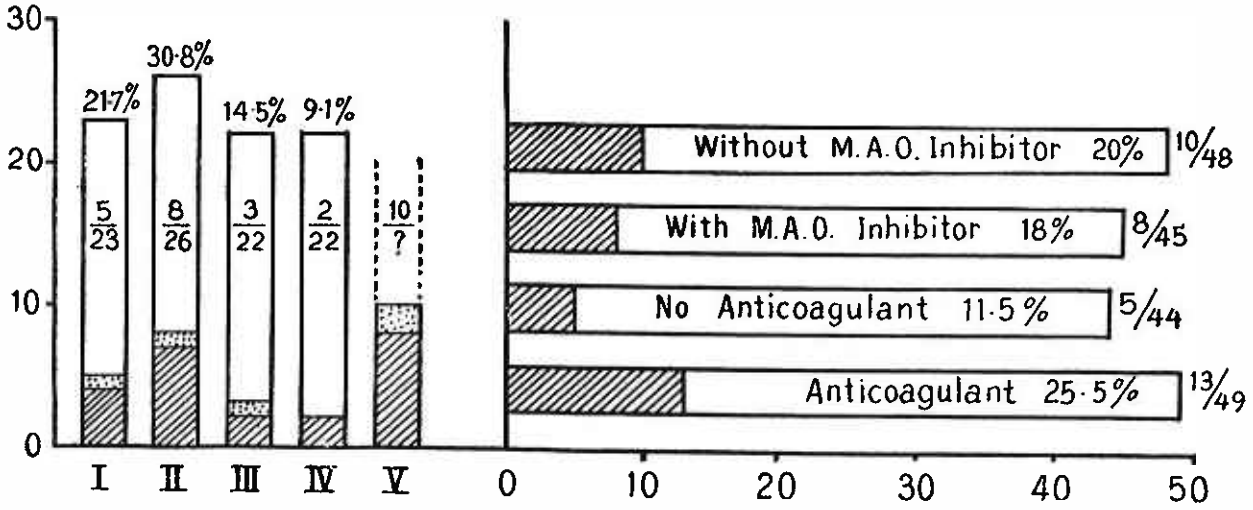


Fig 5. MORTALITY AFTER CORRECTING FOR SUDDEN DEATH AND ASSOCIATED FACTORS

(Diabetes, Previous Infarction, Hypertension, Steroids.)

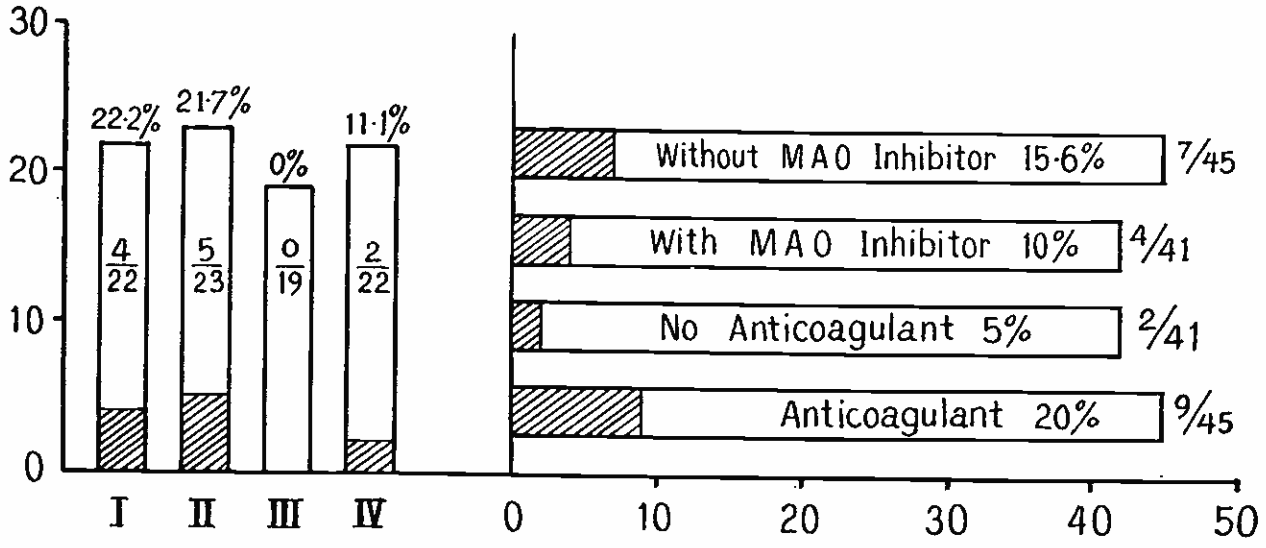
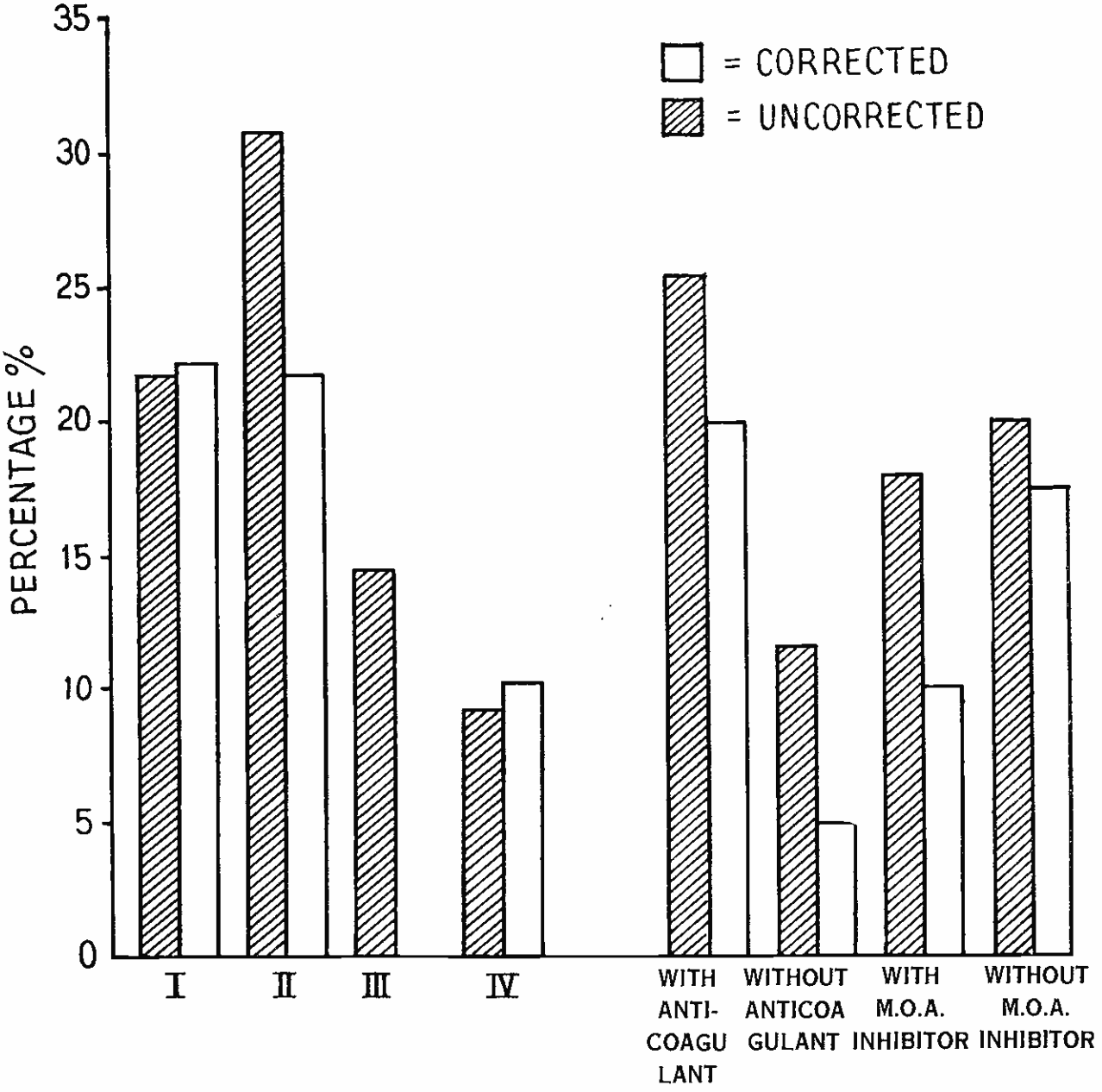


Fig 6. CORRECTED AND UNCORRECTED MORTALITIES IN PERCENTAGE



b.d. by intramuscular route. Prothrombin time was assessed daily so that dosage of Dindevan might be adjusted when the occasion arose. Electrocardiogram was done soon after admission and serum glutamic oxaloacetic transaminase was also estimated. In addition, serum cholesterol was estimated once on admission and again at least 4 weeks after admission. The patient was kept as an inpatient for at least 2 weeks but not more than 4 weeks—this varying period was due to the bed shortage which became acute from time to time. Mortality figures were computed at the end of the trial which lasted 4 weeks, but for long term results, cases were called up again so as to render it possible to compute the survival rate at the completion of 1 year follow up. This latter study is continuing.

RESULTS

The intention was to have 25 cases in each group but a number had to be rejected at the end of the trial, because they were proved to be wrongly diagnosed as coronary thrombosis. These cases were picked out early so that no further treatment along the line for myocardial infarction was given, but in order not to interfere with the serial nature of alloting cases to groups, no adjustment was made so as to eliminate personal conscious or subconscious bias as far as possible.

During the trial, a number of deaths occurred amongst cases not diagnosed as myocardial infarction, but were found to be so when analysed at the "death round". These cases—silent infarcts—were grouped together as Group V, and at least half of them was admitted moribund and died before much could be done. It was not possible in this study to estimate the number of silent infarcts that survived but an attempt was being made to assess the figure. When the results were studied, it became apparent that although the distribution was reasonably even, the smallness of the numbers made any difference assume a more significant importance, hence an attempt was also made to make some corrections statistically so as to reduce the bias. Also in Group V where the cases were not diagnosed, 5 of them were found to be fatal within a few hours of admission, and had the survival been a little bit longer, they would have been allotted on to one of the four series. Assuming a random distribution, these cases were divided up so that each of the four in the series would get a mortality more, whether these procedures were valied would always remain arguable, but it was thought that a comparison of uncorrected and corrected figures would be an interesting venture. In any case, both the sets of figures suggested the same conclusion, the difference being only a matter of degree.

DISCUSSION OF RESULTS

The assessment of the result of any therapy in a disease is open to many sources of errors.

Firstly, a disease entity may have a widely varying natural history, in which case, a correct assessment of the response to therapy may be impossible.

Secondly, the effect of therapy may be delayed and not readily perceptible, and thirdly, the personal bias of the observers may alter the significance of the observation. The use of double-blind trial with control has been popularly accepted as being capable of overcoming the personal bias to a large extent, and thereby productive of more reliable results but this would only reduce one of the three principal errors.

In myocardial infarction, the natural history of the disease is subject to wide variations, and unless the exact state of the patient's coronary circulation and myocardial damage is known (not possible at present) comparison of cases over a long term must be accepted with caution. Further, the aetiology of coronary occlusion is still a controversial issue, and without definite understanding of the aetiology and its part in the progress of the disease, it is difficult to see how long term studies can be accepted without very wide qualifications. The immediate mortality, however, of myocardial infarction seems to be much more predictable, and hence can be more readily studied with some degree of reliability.

From the results tabulated above, it can be seen that the distribution has been fairly even, and this is further shown by the fact that there is very little real difference when additional corrective factors based on expected mortality in relation to sudden death and associated diseases are introduced. It can be seen from the series that there is really no significant difference between cases receiving M.A.O. inhibitors and those not receiving M.A.O. inhibitors. There is, however, a distinct difference between cases receiving anticoagulants and those not on anticoagulants in that there is a greater number of deaths occurring in cases receiving anticoagulants. This confirms the previous observation that locally more deaths occurred when cases of myocardial infarction are placed on anticoagulants—a finding which would be quite contrary to the majority findings elsewhere.

This may suggest that there is some basic geographical difference in patients so that the mortality pattern is really different between local and foreign cases. On the other hand, another explanation is possible. It may be that Western patients are being treated with too much bed rest and too strictly, so that in addition to the risk of myocardial infarction, they have also the danger of strict bed rest, and hence the real mortality becomes more, being the sum total of the risk of myocardial infarction and that of strict bed rest. If this were so, then what the anticoagulant is benefitting would be to reduce the risk of bed rest only.

It is interesting to note also that the mortality in cases receiving anticoagulants is reasonable when compared to those reported elsewhere. This would mean that the result of cases not on anticoagulants would be very much different from similar cases elsewhere. In other words, a local patient on strict bed rest for myocardial infarction will fare much better than his counterpart elsewhere—a benefit probably attributable to the fact that local patients are unwilling to be confined to absolute bed rest even when instructed and enjoined to do so.

Table I shows a mortality of 21% in the first 4 weeks of the acute attack, and from Figures I, II and III, it can be seen that 10 out of 28 deaths (36%) occurred in the first 24 hours, and that 16 deaths were in the first week (57%), and 24 deaths within the first month (86%).

Table 2 shows that 22 deaths in 28 (79%) were males with ages ranging from 37 to 71 and the racial distribution of fatal cases was Malay: Chinese: Indian: others = 1: 15: 7: 6.

In Table 3, it can be seen that the racial distribution of total cases was Malay: Chinese: Indian: Others = 12: 35: 36: 11 and the male incidence is 75 out of 93 (83%). Since the population incidence in Singapore of Malay: Chinese: Indian: Others = 1: 7.5: 1: 0.5, this would suggest that incidence of myocardial infarction is lowest in Chinese and highest in Indians since the expected figure should be 12: 90: 12: 6. This racial bias as regards Indian predilection is in agreement with previous findings (Gwee 1961). Of the 74 cases with known serum cholesterol findings, 26 (35%) have readings below 200 mg.%, whereas 40 out of 80 cases (50%) have S.G.O.T. readings below 45 units. The former is confirmatory of local findings that a low serum cholesterol is no great insurance against myocardial infarction, and the latter merely affirms the fact that only 46 cases in 93 (50%) were admitted within the first 2 days of onset, as shown in Table 5.

Table 6 shows how some of the corrective factors were applied and the rest of the graphs are self-explanatory.

SUMMARY

A double-blind study with control was done to assess the effect of mono-amine-oxidase inhibitors and anticoagulant therapy in the mortality of acute myocardial infarction, in the first 4 weeks.

The results show that no effect whether beneficial or adverse was seen with the use of mono-amine inhibitor. On the other hand, there is a distinct decrease in mortality amongst cases not on anticoagulants.

It is believed that the rarity of phlebothrombosis in local patients is the cause of the difference between local and foreign results so far as anticoagulant therapy goes. It is postulated too that one of the reasons for the difference may be due to the fact that patients are not on so strict a bed rest as elsewhere.

There appears to be a definite increase of incidence in Indians, and also at least a third of myocardial infarction cases had low normal serum cholesterol readings.

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