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Abstract

Lysis of fibrin was first recognized by MORGAGNI in 1769, observing a liquid blood in a patient of acute death, and the phenomenon was named as fibrinolysis by DASTRE in 1893. In 1937, MACFARLANE recognized in a patient after cholecystectomy that the blood clot was lysed completely in the following morning. Since then, much attention has been paid clinically on fibrinolysis and it has been said to occur in case receiving a large amount of blood transfusion, shock, cancer, obstetric diseases, hemophilia, various drug poisonings, allergic diseases, after irradiation and after the operations of lung, pancreas and prostate. In our department, also, the similar phenomenon was recognized often in association with cardiac surgery using the artificial heart-lung machine, and a difficulty in hemostasis was encountered postoperatively. We have been studying, therefore, on fibrinolysis in open heart surgery.

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STUDIES ON AN ANTIFIBRINOLYTIC AGENT TRANS-AMCHA

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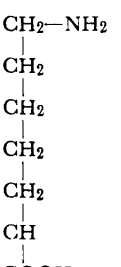
Lysis of fibrin was first recognized by MORGAGNI in 1769, observing a liquid blood in a patient of acute death, and the phenomenon was named as fibrinolysis by DASTRE in 1893. In 1937, MACFARLANE recognized in a patient after cholecystectomy that the blood clot was lysed completely in the following morning. Since then, much attention has been paid clinically on fibrinolysis and it has been said to occur in case receiving a large amount of blood transfusion, shock, cancer, obstetric diseases, hemophilia, various drug poisonings, allergic diseases, after irradiation and after the operations of lung, pancreas and prostate.

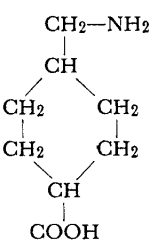
In our department, also, the similar phenomenon was recognized often in association with cardiac surgery using the artificial heart-lung machine, and a difficulty in hemostasis was encountered postoperatively. We have been studying, therefore, on fibrinolysis in open heart surgery.

For prophylaxis and treatment of fibrinolysis, various substances have been used for a long time, such as fibrinogen, fresh blood, serum albumin fraction, anti-hemophilic globulin, soy-bean inhibitor, cortisone, platelet transfusion and various hemostatics. However, in 1954, OKAMOTO introduced ε-aminocaproic acid (EACA) which was found to have a strong

Fig. 1



ε-aminocaproic acid (EACA)



Trans-1-aminomethyl-cyclohexane-4-carboxylic acid (AMCHA)

anti-fibrinolytic action, and then it has been widely used as a therapeutic agent. Then, OKAMOTO *et al.* (1965) introduced a trans-stereoisomer of 4-aminomethyl cyclohexane carboxylic acid (AMCHA) which has stronger anti-fibrinolytic activity than EACA (Fig. 1).

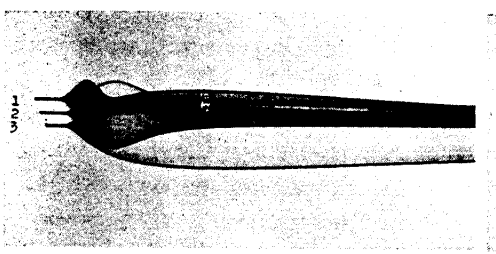
We used AMCHA both experimentally and clinically in 23 cases, and compared its activity with that of EACA.

(A) Experimental evaluation

(1) Thrombelastography

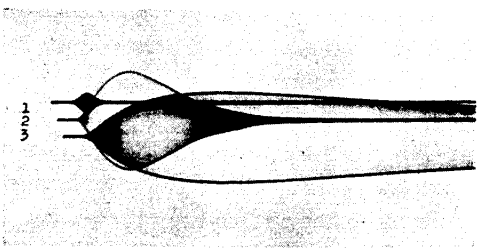
One hundred units of streptokinase (SK) was added to 1 ml of normal citrated plasma, and then calcium ion was added to observe the thrombelastograms (TEG). The plasma having 3 minutes of the lysis time was used for the experiments. EACA or AMCHA was added in various concentrations before 100 units/ml of SK was mixed to plasma for the purpose of obtaining TEG (Photographs 1, 2, Table 1).

The lysis time of the SK activated plasma containing 1 μg/ml of



Photograph 1

1. SK 100 u/ml + EACA 10 μg/ml added
2. SK 100 u/ml + EACA 25 μg/ml added
3. SK 100 u/ml + EACA 50 μg/ml added



Photograph 2

2. SK 100 u/ml + AMCHA 0.1 ng/ml added
2. SK 100 u/ml + AMCHA 1.0 μg/ml added
3. SK 100 u/ml + AMCHA 10.0 μg/ml added

Table 1

Solutions added to the plasma			r (min.)	k (min.)	ma (mm)	Lysis time (min.)
SK (u/ml)	EACA (μg/ml)	AMCHA (μg/ml)				
100	0	0	5.0	/	2	3.0
100	10	0	5.0	/	12	10.0
100	25	0	5.0	6.0	21	long
100	50	0	4.0	10.0	25	/
100	0	0.1	4.0	/	6	4.5
100	0	1.0	4.0	3.5	31	39.0
100	0	10.0	4.0	8.0	28	/

AMCHA (39 minutes) varies in between that of the SK activated plasma containing 10 μg/ml of EACA (10 minutes) and that of the SK activated plasma containing 25 μg/ml of EACA (immeasurably prolonged). Thus, the activity of AMCHA is 10—25 times stronger than that of EACA.

(2) Euglobulin lysis time

Euglobulin fraction was prepared from the normal citrated plasma by the method of VON KAULLA. Five units of SK was added to 1 ml of the euglobulin solution, and thrombin was added to produce the clotting. Then, the clot dissolved in a few minutes. On the next experiment, various concentrations of EACA or AMCHA were added to the euglobulin solution in advance, and then 5 units/ml of SK was added to determine the clot lysis time.

When each value was plotted on the logarithmic graphs, EACA and AMCHA showed straight lines in parallel (Fig. 2). The activity ratio of

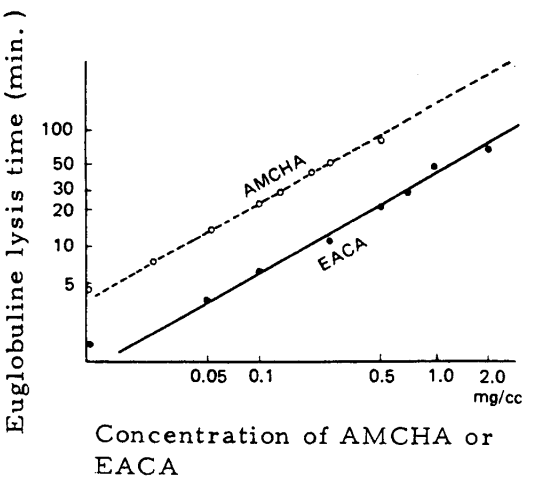


Fig. 2

AMCHA and EACA is, therefore, the same at any concentration. The ratio of normal 3 samples was 5.3, 5.3 and 5.6 times, respectively. The average value among 3 determinations was 5.4 in their activity.

(B) Evaluation on clinical cases

Among 3218 major surgical operations done in our department for the past 7 years excluding cardiac surgery, increased fibinolysis was recognized only in 8 cases (0.25% i. e. esophageal carcinoma 1, gastric carcinoma with Banti's syndrome 1, coarctation of the aorta 1, thoracic aneurysm 1, pulmonary tuberculosis 1, bronchiectasis 2, Werlhof's disease

1). On the contrary, increased fibrinolysis in open heart surgery was seen in 7 out of 29 cases (24.1%), as reported previously. Since we started to use EACA prophylactically after the completion of the extracorporeal circulation, increased fibrinolysis have been able to prevent in consecutive 250 cases. Through our various experiments, 0.25 g/kg of body weight of EACA was reported to be adequate. Instead of using EACA, AMCHA was given in two groups, receiving 1/5 dosis of EACA (0.05g/kg) and 1/10 that of EACA (0.025 g/kg) after perfusion (Tables 2, 3).

(1) Appearance of fibrinolysis

Whole blood clot lysis and TEG were used for the evaluation. None of the cases receiving EACA and AMCHA showed increased fibrinolysis.

(2) Comparison of the amount of blood discharge through the intrathoracic drain

The amount of blood discharge through the drain was measured at 12 hours after the surgery and at the time of removing the drain in 18 cases without EACA and AMCHA, in 11 cases receiving 0.25 g/kg of EACA, in 12 cases receiving 0.05 g/kg of AMCHA and in 11 cases receiving 0.025g/kg of AMCHA. The amount of blood discharge decreased in the order of non-treated group, EACA group, 0.025 g/kg AMCHA group and 0.05 g/kgAMCHA group. At 12 hours after the operation, the amount of blood discharge in EACA group was 42.2% less than that of

Table 2

No.	Name	Age	Sex	Diagnosis	Operation	Perfusion time (min.)	Lowest temperature (°C)
1	M. K.	11	F	VSD	Closure of the defect	76	20.8
2	M. I.	5	F	VSD	Closure of the defect	32	27.0
3	K. O.	9	F	Aortic stenosis	Dilatation of the ostium	151	20.2
4	K. A.	19	F	VSD	Closure of the defect	13	28.6
5	M. H.	17	M	Ruptured aneurysm of Valsalva's sinus	Closure of the defect	70	21.6
6	A. H.	3	F	ASD	Closure of the defect	10	33.7
7	M. M.	6	F	VSD	Closure of the defect	16	34.0
8	T. F.	16	M	Right ventricular aneurysm	Radical operation	86	22.8
9	B. N.	17	M	Mitral stenosis	Commissurotomy	31	33.6
10	E. K.	11	F	Mitral steno-insufficiency	Valuloplasty	81	33.4
11	Y. T.	12	F	VSD	Closure of the defect	87	26.0
12	M. T.	16	M	ASD	Closure of the defect	18	33.8

Table 3

No.	Name	Age	Sex	Diagnosis	Operation	Perfusion time (min.)	Lowest temperature (°C)
13	T. A.	35	M	Mitral insufficiency	Valvuloplasty	100	30.2
14	R. A.	5	M	VSD	Closure of the defect	88	27.8
15	S. N.	16	F	ASD	Closure of the defect	16	32.0
16	Y. N.	19	M	VSD	Closure of the defect	36	27.6
17	T. I.	21	M	Aortic steno-insufficiency Mitral stenosis	Transplantation of the valve Commissurotomy	236	24.3
18	T. O.	5	F	ASD	Closure of the defect	9	33.8
19	O. O.	26	M	Aortic steno-insufficiency Mitral stenosis	Transplantation of the valve Commissurotomy	184	26.9
20	T. O.	7	M	ASD	Closure of the defect	15	33.6
21	Y. M.	14	F	ASD	Closure of the defect	7	33.5
22	A. H.	7	M	VSD	Closure of the defect	31	32.2
23	M. U.	15	M	VSD	Closure of the defect	22	34.5

non-treated group; in 0.025 g/kg AMCHA group 12.5% less than that of EACA group; in 0.05 g/kg AMCHA group 17.8% less than that of 0.025 g/kg AMCHA group. The total amountof blood discharges obtained until the removal of the drain showed the similar changes. Namely, the amount of blood discharge in EACA group was 26.3% less than that of non-treated group; in 0.025 g/kg AMCHA group 34.1% less than that of EACA group, in 0.05 g/kg AMCHA group 17.3% less than that of 0.025

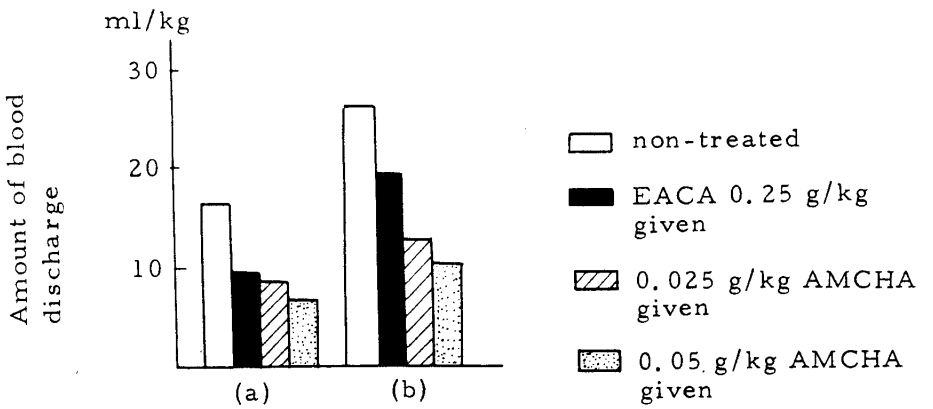


Fig. 3 Amount of blood discharge after operation
(a): 12 hours
(b): until the removal of drain

g/kg AMCHA group. Thus, AMCHA appeared to be more effective than EACA, and 0.05 g/kg AMCHA was the most adequate dose (Fig. 3).

(3) Comparison of englobulin lysis time

Hypothermia with extracorporeal circulation was used more in 0.05 g/kg AMCHA group than in 0.025 g/kg AMCHA group. Therefore, the former group showed shortening of the lysis time before the administration of AMCHA. On the administration of AMCHA, it varied from 30 min. to 60 min. in 0.05 g/kg AMCHA group, and from 82 min. to 114 min. in 0.025 g/kg AMCHA group. However, they all returned to normal value 1 hour after the operation (Fig. 4).

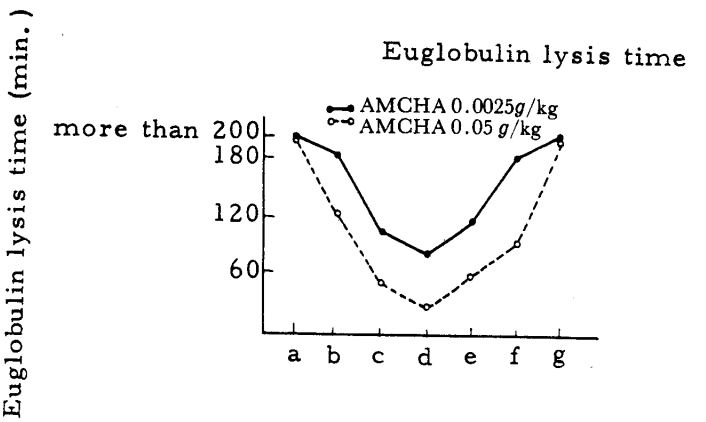


Fig. 4

a : preoperative
b : post-thoracotomy
c : during extracorporeal circulation
d : after extracorporeal circulation
e : after AMCHA given
f : after protamine given
g : 1 hour after operation

DISCUSSION AND CONCLUSION

On comparing the effects of EACA and AMCHA on fibrinolysis in this experiment, TEG showed that AMCHA was 10—25 times more than EACA. While in measuring the euglobulin lysis time it revealed that AMCHA was 5.4 times more effective than EACA. In thrombelastography, the plasma was used, in which inhibitors for fibrinolysis were also included. In euglobulin lysis time test, however, it was measured with euglobulin fraction which contained no inhibitors. Besides such a

difference of methods, there are some differences in the mechanism of their actions, so their effect might have been different with methods used. Other authors also reported that AMCHA was 5—26 times more effective than EACA.

When AMCHA was used in a dose of 1/5 that of EACA (0.05 g/kg) or 1/10 (0.025 g/kg) on cardiac surgery using artificial heart-lung machine, the amount of blood discharge through the intrathoracic drain was less than in the group receiving EACA. Euglobulin lysis time became shortened more in 0.05 g/kg AMCHA group than in 0.025 g/kg AMCHA group, probably due to hypothermia combined with extracorporeal circulation, while the amount of blood discharge was decreased in the former group. This appeared to be due to a large dose of AMCHA used after extracorporeal circulation.

Thus, through the experimental results and clinical experiences, it is concluded that AMCHA is very strong anti-fibrinolytic agent which inhibits the increased fibrinolytic activity after extracorporeal circulation and the dose of AMCHA being 1/5—1/10 that of EACA is adequate.

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