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Tranexamic acid and upper gastrointestinal haemorrhage—a double-blind trial

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SUMMARY The efficacy of antifibrinolytic therapy in the management of acute upper gastrointestinal haemorrhage has been investigated in a double-blind clinical trial. Two-hundred patients were studied using tranexamic acid, a potent antifibrinolytic agent. Of these, 103 were in the treatment group and 97 in the control group. Patients were analysed to determine severity of initial blood loss, transfusion requirements, together with the incidence of recurrent bleeding, surgical intervention, and death. Final diagnosis as to the site of bleeding was arrived at using endoscopy, barium studies, and the findings at operation and necropsy. The groups were well matched as regards severity of initial haemorrhage, age, sex, aetiological diagnosis, and precipitating factors. A significant difference was observed in the requirement for surgical intervention to control continuing or recurrent haemorrhage. Twenty-three of 97 in the control group and seven of 103 in the treatment group required surgery. There appeared to be a reduction in the transfusion rate after the first three days of hospitalization in the treatment group. There were no significant differences in mortality or in side-effects between the two groups.

Upper gastrointestinal haemorrhage is a common occurrence and may be of life-threatening severity. Although the haemorrhage frequently ceases with conservative therapy, management is often difficult and surgical intervention may be required. Fibrinolytic activity has been demonstrated in the mucosa of patients with peptic ulceration and free plasmin had been found in the gastric venous blood of such patients (Cox *et al.*, 1967; 1969). Therefore, it seemed appropriate to investigate the use of antifibrinolytic therapy in a double blind trial, to assess its effectiveness in the management of acute haemorrhage from the gastrointestinal tract.

Tranexamic acid (amino-methylcyclohexanecarboxylic acid) was chosen as the antifibrinolytic agent, as it has been shown to be a potent drug with an action similar to epsilon amino caproic acid, but has the advantage of greater potency and fewer side-effects (Dubber *et al.*, 1964; Andersson *et al.*, 1968; Andersson, 1972).

[1]Each ampoule and tablet of tranexamic acid contained 0.5g. The placebo was identical in appearance. The tablet contained cellulose-lactate, while the ampoule contained normal saline, supplied, by Kabi, A. B. Stockholm.

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Methods

PATIENTS

Patients entering the trial presented consecutively to the accident and emergency centre of St. Vincent's Hospital. Haemorrhage was observed by a medical officer or confirmed by gastric aspiration and examination of the faeces for melaena. Only patients who required admission to hospital entered the trial. Patients who were pregnant, had chronic renal impairment, previous vascular surgery, or a history of a thromboembolic episode during the preceding 12 months were excluded.

Therapy was given on a double blind, randomized basis. Two ampoules[1] intravenously and two tablets[1] orally were administered eight hourly for 48 hours, followed by two tablets orally, eight hourly for an additional 72 hours. The intravenous agent was given slowly as a single injection into the drip tubing. The period of study was until the end of the seventh hospital day.

HAEMATOLOGICAL PARAMETERS

Using standard methods, blood was taken on admission for full blood count, platelet count, partial thromboplastin time, prothrombin time,

euglobulinl ysis time, and other investigations when appropriate. These tests were repeated on day 2 and day 4.

ASSESSMENT OF PATIENT'S PROGRESS
Patients were seen daily and a clinical assessment was made of the amount of further haemorrhage. A record was kept of transfusion requirements, morbidity, surgical intervention, and mortality.

CAUSE OF HAEMORRHAGE
An effort was made to determine the site of haemorrhage in all patients on a basis of history, physical signs, endoscopy, barium studies, surgical and necropsy findings where appropriate.

ASSESSMENT OF SEVERITY
The severity of blood loss was assessed at the time of presentation on clinical grounds. Three categories were defined: trivial (up to 200 ml), moderate 200-1000 ml), and massive (more than 1000 ml).

Results

Two hundred patients entered the trial and of these 103 were found to be in the treatment group, while 97 received a placebo only.

AGE AND SEX
The distribution of the patients' age is shown in Fig. 1. It will be noted that the majority of patients were in the fifth decade or beyond. The sex distribution was similar in both groups with 73% being males in the treatment group and 83% males in the placebo group.

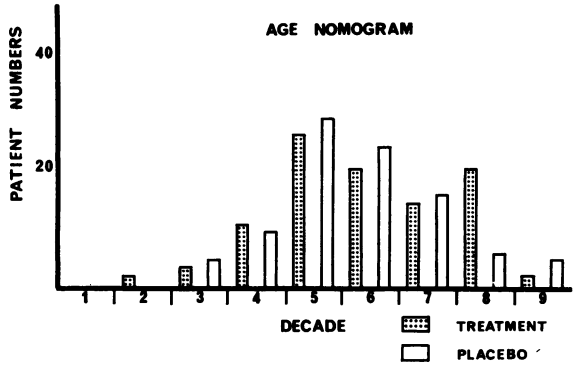

Fig. 1 *Age of patients in decades.*

CLINICAL SEVERITY OF HAEMORRHAGE
The clinical severity of each patient's condition was assessed on presentation to the accident service. When placed in the categories defined above, it can be seen that both groups were well matched, with most patients falling into the category associated with moderate blood loss (Fig. 2).

PRECIPITATING FACTORS
A precipitating factor for the haemorrhage was sought by questioning each patient and results are listed in Table 1.

COAGULATION AND FIBRINOLYTIC PARAMETERS
Of the 200 patients only 19 had abnormal tests on presentation. The prothrombin time was prolonged in four patients in the treatment group and in three patients in the placebo group. The partial thromboplastin time was prolonged in eight patients in the tranexamic group and 10 patients in the placebo. Thrombocytopaenia was observed in four and six patients respectively and no patient showed evidence of systemic fibrinolysis as assessed by euglobulin lysis and fibrin plate assay. These abnormalities were observed almost exclusively in patients with a history or physical signs suggestive of excessive alcoholic intake. There was no significant difference between the groups in this regard.

SITE OF HAEMORRHAGE
Table 2 shows the lesions responsible for haemorrhage. The efficacy of endoscopy and upper gastrointestinal contrast radiology in these patients is shown in Tables 3 and 4. It will be noted that endoscopy was more helpful in the diagnosis of gastric ulcer, acute gastric erosions, and Mallory-Weiss tear. However, radiology was equally effective in the diagnosis of duodenal and pyloric ulceration and oesophageal varices. Early in the trial the duodenoscope was unavailable because of a technical failure, so duodenal visualization was not possible in 30 patients; 17 of these had gastroscopy only. But all patients with gastric or duodenal ulcer had the diagnosis confirmed by barium studies, endoscopy, or surgery (Table 4).

TRANSFUSION REQUIREMENTS
The total transfusion requirements in both groups were not significantly different (Table 5); 25·2% did not require transfusion in the treatment group and 26·8% were not transfused in the placebo group. On analysing the subgroups of gastric ulcer, gastric erosions, and duodenal ulcer there was no difference in the total transfusion requirements. The other subgroups were too small for significant analysis.

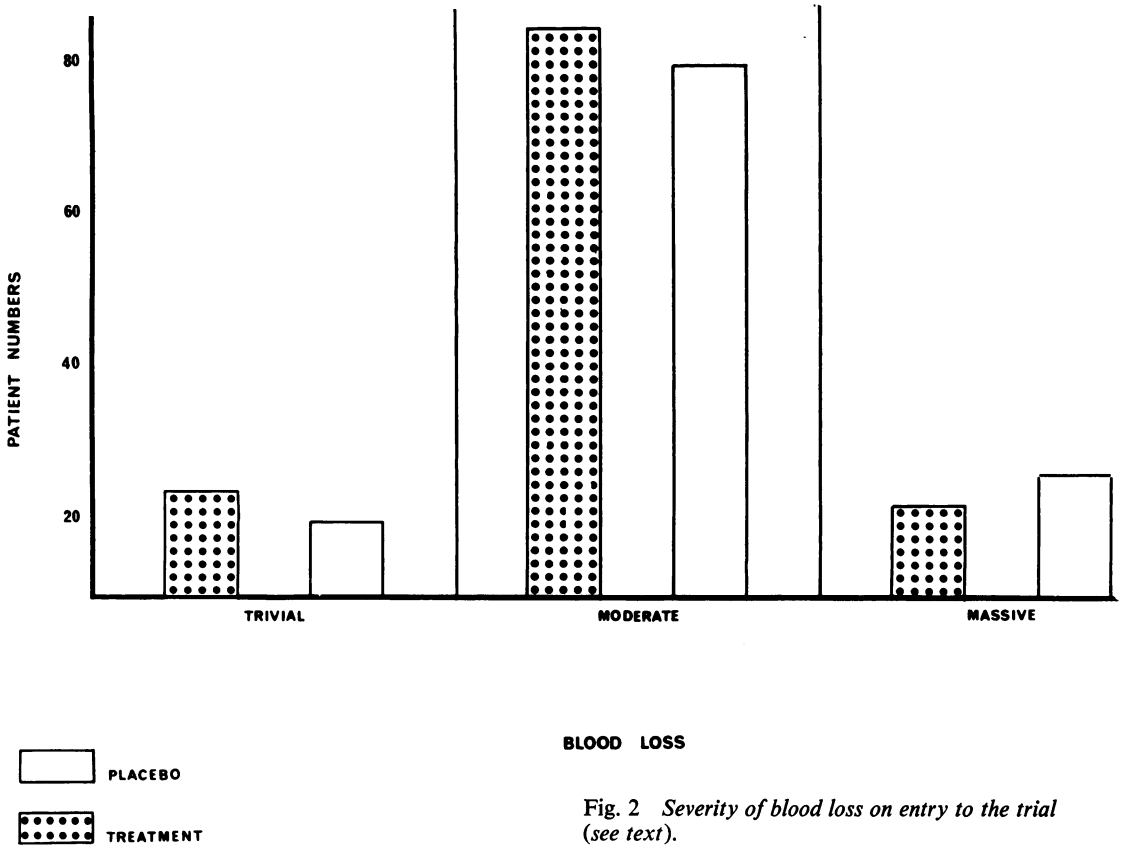

Fig. 2 *Severity of blood loss on entry to the trial (see text).*

Table 1 *Drugs ingested by patients before entry to trial*

Precipitating factors	*Tranexamic acid*	*Placebo*
Aspirin	15	10
Aspirin and alcohol	7	13
Alcohol	28	41
Corticosteroids	1	3
Indomethacin	5	3
Butazolidin	0	3

Table 2 *Causes of haemorrhage in all patients arrived at by history, barium studies, endoscopy, surgery, and necropsy*

Lesions causing blood loss	*Tranexamic acid*	*Placebo*
Duodenal and pyloric ulcer	35	40
Gastric ulcer	20	13
Acute gastric erosions	19	27
Oesophageal varices	5	7
Mallory-Weiss tear	4	4
Oesophagitis	5	1
Not determined	14	5
Other	1	0
Totals	103	97

The mean transfusion rate was calculated by dividing the total blood transfused to the group on each day by the number of patients in the trial on that day. As the period of study progressed the number of patients decreased as a result of withdrawal caused by surgical intervention or death. The transfusion rate was similar in both groups on days one, two, and three, but appeared higher in the placebo group on days four, five, and six. This difference was significant ($P < 0.05$) on two of the three days, using a non-parametric analysis (Willcoxon), despite the withdrawal of a greater number of patients in the placebo group because of surgical intervention for continued haemorrhage (Fig. 3). When the transfusion rate of the subgroups was analysed, the numbers were too small for significant analysis.

SURGICAL INTERVENTION

Twenty-one of the 97 patients in the placebo group and seven of the 103 in the treatment group required surgery within the period of study. The indications for surgery were usually continuing or re-

Table 3 *Endoscopy findings in all patients*

	Upper gastrointestinal endoscopy		
	Positive	*Negative*	*Not performed*
Duodenal and pyloric ulcer (75)†	45	17*	13†
Gastric ulcer (33)†	29	1	3
Acute gastric erosions (46)	43	2	1
Oesophageal varices (12)	11	0	1
Mallory-Weiss tear (8)	8	0	0

*Duodenoscopy was not available early in the trial and these patients had only gastroscopy performed.
†All patients with a diagnosis of gastric or duodenal ulcer were confirmed on either barium meal, endoscopy, or surgery.

Table 4 *Results of barium meal examination*

	Upper gastrointestinal barium studies		
	Positive	*Negative*	*Not performed*
Duodenal and pyloric ulceration (75)	50	12	13
Gastric ulceration (33)	15	12	6
Acute gastric erosions (46)	1	25	20
Oesophageal varices (12)	9	2	1
Mallory-Weiss tear (8)	0	5	3

Table 5 *Total blood transfusion requirements*

Blood replacement (litres)	*Tranexamic acid (no.)*	*Placebo (no.)*
None	26	26
1-2	16	15
3-4	18	15
5-6	18	12
7-8	9	7
9-10	4	5
> 10	12	17

current haemorrhage, although two patients in the placebo group were treated in this way because of a long history of duodenal ulceration (Table 6). This difference in operation rate was significant ($P < 0.005$; chi-squared = 9·153). The timing of such intervention was also of interest (Fig. 4). After the first three days surgical intervention was required in only one patient in the treatment group and in nine patients in the placebo group. The lesions found at operation largely reflected the distribution of lesions in the overall group (Table 7).

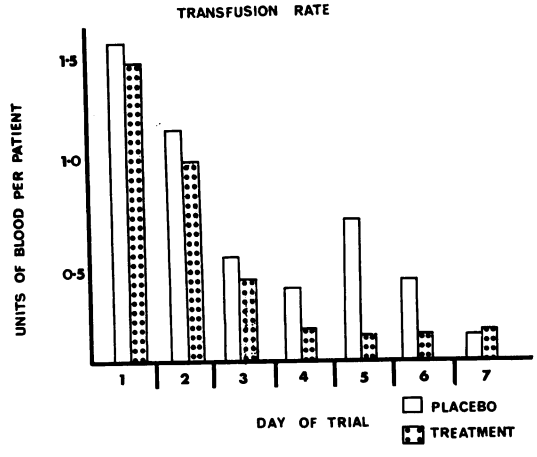

Fig. 3 *Transfusion rate in both groups (see text).*

Table 6 *Indications for surgery*

Indications for surgery	*Tranexamic acid*	*Placebo*
Continued bleeding	4	14
Recurrent bleeding	3	5
Other	0	2

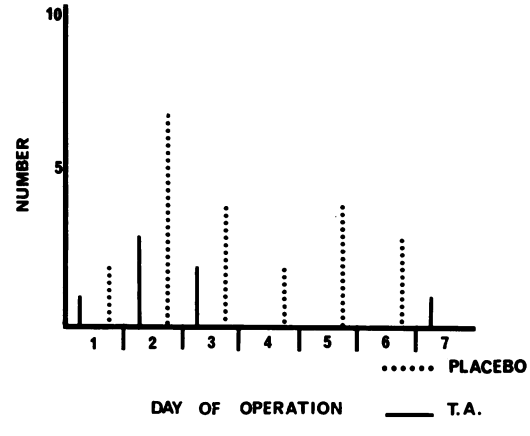

Fig. 4 *Days on which surgical intervention was required.*

SIDE-EFFECTS

There were no major side-effects of therapy. Minor side effects encountered were similar in both groups and are listed in Table 8.

MORTALITY

The overall mortality in both groups was 3%. The

Table 7 *Findings at surgery*

Lesions	*Operative group*	
	Tranexamic acid	*Placebo*
Duodenal and pyloric ulcer	1	8
Gastric ulcer	3	5
Gastric erosions	2	4
Mallory-Weiss	1	1
Oesophageal varices	0	3

Table 8 *Complications attributed to tranexamic acid*

Complications of therapy	*Tranexamic acid*	*Placebo*
Nausea	3	1
Headache	1	4
Fever	0	2
Thrombophlebitis at IV site	3	2

Table 9 *Necropsy findings in all patients who died during period of trial*

Necropsy findings	
Tranexamic acid	*Placebo*
1. Massive blood loss, duodenal ulceration, disseminated bronchial carcinoma (surgery withheld)	1. Massive blood loss, gastric ulceration, continuous bleeding postoperation
2. Massive blood loss, Mallory-Weiss tear, postoperative pneumonia	2. Massive blood loss, oesophageal varices, gastrotomy only
	3. Massive blood loss, oesophageal varices hepatic failure postoperation, cardiac arrest
	4. Massive blood loss, oesophageal varices, perforated oesophagus

causes of death are shown in Table 9. The difference in mortality between the two groups was not significant.

Discussion

Antifibrinolytic therapy has already been proven useful in controlling haemorrhage in a number of conditions—for example, menorrhagia and haemorrhage after prostatic surgery (Sack *et al.*, 1962; Andersson *et al.*, 1965; Callender *et al.*, 1970). A number of studies have suggested benefit in patients with subarachnoid haemorrhage (Gibbs and Corkill, 1971; Tovi *et al.*, 1972).

The results of this trial show that continuing haemorrhage from lesions in the upper gastrointestinal tract can be reduced, resulting in less frequent surgical intervention. It seemed theoretically likely that the effect of antifibrinolytic therapy would be most beneficial in patients with small superficial lesions such as gastric erosions and also in oesophageal varices, because of the not-uncommon association of mild fibrinolysis with the latter condition. However, the results indicate that the beneficial effect was not particularly related to these two conditions. Furthermore, the effect was not related to correction of systemic fibrinolysis as this was not demonstrated in any patient. It is possible that the beneficial effect is due to inhibition of local fibrinolysis in the gastroduodenal mucosa. This has been demonstrated *in vitro* with low concentrations of tranexamic acid (Dodds *et al.*, in preparation). It seems possible that tranexamic acid may have an effect also on the fibrinolytic activity of the gastric secretions in some circumstances (Nilsson *et al.*, 1975).

In 1973, Cormack and his colleagues published the results of a smaller trial suggesting that tranexamic acid produced a significant benefit in patients with gastrointestinal haemorrhage who had a negative barium meal examination. It was assumed that these patients had gastric erosions, but endoscopy was not performed. Continued or recurrent bleeding and surgical intervention were said to be significantly greater in those patients with peptic ulcer or gastric erosions who had received a placebo in the trial reported by these authors.

The concept of aborting sustained local haemorrhage by blocking fibrinolytic activity is attractive in theory and might be of significant therapeutic benefit in a variety of conditions. It is suggested that further studies of this type are warranted to assess the value of such agents in the control of gastrointestinal bleeding.

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