Tranexamic Acid in Patients with Hemoptysis

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Abstract

Hemoptysis is a common respiratory symptom leading to admission to hospital. The main management of hemoptysis depends on treating the underlying cause. The use of tranexamic acid is recommended by many doctors without much information available.

Material and Method : This study was a randomized double blinded placebo controlled trial in using tranexamic acid (Transamine™) in hemoptysis patients. The study period was one week. Patients with hemoptysis were separated into 3 groups depending on the amount of blood. Group 1 consisted of patients with blood streak sputum. Group 2 coughed up less than 20 ml of frank blood. Patients in Group 3 were those who coughed up 20-500 ml of blood per day. A record of the amount of bleeding and drug side effects was done.

Results : From June 1994 to May 1997, 46 patients with hemoptysis completed the study. There were 21 in the tranexamic acid group and 25 in the placebo group. The placebo group had a tendency not to have underlying lung disease and more patients who had a normal chest X-ray. The benefit of tranexamic acid in shortening the days of hemoptysis is not shown in this study. There was a low incidence of side effects of tranexamic acid in this study.

Conclusion : This randomized double blinded placebo controlled trial could not demonstrate the benefit of tranexamic acid in shortening the days of hemoptysis and confirm the low incidence of side effects of this drug.

Key word : Tranexamic Acid, Hemoptysis

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Hemoptysis is a common respiratory symptom leading to admission to hospital. There are many etiologic causes of hemoptysis and its' natural history depends largely on individual etiology[1]. Except for massive hemoptysis which is defined by bleeding more than 500 ml per day, the main management of hemoptysis depends on treating the underlying cause. In spite of this concept of management together with a thorough explanation to the patients by the doctors, patients are still concerned about the blood that they cough up. Some physicians add tranexamic acid to their treatment regimen in order to try to control the bleeding.

Tranexamic acid, (4-(aminomethyl) cyclohexanecarboxylic acid), is a synthetic derivative of the amino acid lysine and has antifibrinolytic activity in humans. The antifibrinolytic effect of tranexamic acid results from the formation of a reversible complex of the drug with plasminogen[2] and almost completely blocks the interaction of plasminogen and the heavy chain of plasmin with the lysine residues of fibrin monomer. This process retards fibrinolysis because, although plasmin is still formed, it is unable to bind to fibrinogen or fibrin monomer. Some indications for the use of tranexamic acid are in gynecological bleeding, oral surgery and acute upper gastrointestinal hemorrhage which all have evidence of increased fibrinolysis. The use of tranexamic acid in hemoptysis is very controversial and very little information is available[3-7].

This study aimed to evaluate the efficacy of tranexamic acid (Transamine™) in various degrees of hemoptysis and to study the side effects of tranexamic acid in these patients.

MATERIAL AND METHOD

Patients with hemoptysis who attended the Pulmonary and Tuberculosis Division, Department of Internal Medicine, Siriraj Hospital either as out patients or in patients on the ward were enrolled into this study. All patients gave written inform consent and were divided in to 3 groups. Patients who had blood- streaked sputum or minimal bleeding were categorized as Group 1. Group 2 were patients who had a hemoptysis of frank blood estimated at less than 20 ml per day. Group 3 included those who coughed up frank blood estimated at between 20 to 500 ml per day. The patients who had massive hemoptysis (bleeding of more than 500 ml per day) were excluded from this study because they needed emergency intervention to control the bleeding such as bronchoscopic related procedures in order to tamponade the bleeding site, bronchial artery embolization or surgery.

This study was a randomized double blinded placebo controlled study. The study period was one week. After taking a history and examining the patient, a chest X-ray was done. Blood was drawn and sent for complete blood count. Other investigations for the causes of hemoptysis such as sputum examination for acid fast bacilli, sputum culture for bacteria or bronchoscopy were done on individual patients as indicated. The patients in each group were given a pack of Transamine™ capsules (tranexamic acid 250 mg per capsule, Ouiheng Import Co., Ltd. Bangkok, Thailand) or placebo containing a week's supply of capsules, 2 capsules three times a day (1.5 gram per day). Other medication needed for the treatment of the underlying diseases of these patients were also given. The patient was given a card to record the amount of bleeding per day and any drug side effects and follow-up was arranged for day 3 and day 7.

The study end points were cessation of hemoptysis (in day), completing one week of tranexamic acid therapy or the occurrence of side effect that cannot tolerated. The drug's company had no influence or input on all processes of this study.

Statistical analysis

The patients' demographic data and the effects of treatment on their symptom of hemoptysis between the tranexamic acid and placebo groups were compared. For analysis of continuous variables, unpaired *t*-test was used. Chi-square test (χ^2 test) was used for categorical variables and Fisher's exact test was applied when the expected value was below 5. A statistically significant difference between the treatments was defined with a p value of less than 0.05.

RESULTS

From June 1994 to May 1997, sixty four patients with hemoptysis were enrolled in the study. Of these patients, 46 completed the study and 18 were lost to follow-up. There were 21 in the tranexamic acid group and 25 in the placebo group. There were 13 patients in Group 1, 14 in Group 2 and 19 in Group 3. The patients' demographic data is shown in Table 1.

Table 1. Patients' demographic data.

	Tranexamic acid	Placebo
Number of cases (total)	21	25
Group 1	4	9
Group 2	7	7
Group 3	10	9
Gender		
Male : female	2.5 : 1	2.57 : 1
Age (years)		
Mean ± SD	45.38 ± 15.43	40.46 ± 13.67
Hemoptysis before study (days)	3.8 ± 7.2	7.3 ± 18.2
Associated symptoms before the study (number of cases)		
No	3	7
History of TB treatment	7	8
Fever	8	4
Dyspnea	7	5
Underlying diseases (number of cases)		
No	9	17
Tuberculosis	6	7
Others	7	1
Complete blood count		
White blood count (/mm^3)	9,482 ± 3,433	8,340 ± 4,098
Hematocrit (%)	37.3 ± 7.2	40.4 ± 4.3
Platelet count	All adequate	All adequate
Chest X-ray		
Normal	1	6
Abnormal	20	19
Associated drugs used		
No other drug used	5	13
Antituberculous drugs	6	5
Antibiotics	7	4
Others (antitussis, expertorant etc.)	3	3

As shown in Table 1, the gender distribution, age, duration of hemoptysis before the study and associated symptoms were not different between the two groups. The patients who used placebo seemed not to have any underlying disease compared to the tranexamic acid group. Most of the studied patients had abnormal chest X-ray that explained the cause of their hemoptysis. Other drugs used along with the studied drug showed no difference between the two groups.

Out of the total of 46 patients, there were 4 patients (19.04%) taking tranexamic acid and 7 patients (28%) taking placebo who still had hemoptysis at the end of the study (day 7) with no statistically significant difference ($p = 0.514$). In the majority of patients, the bleeding stopped on average on day 2.29 (range day 1 to day 6) in the tranexamic acid group and day 2.94 (range day 1 to day 6) in the placebo group with a p value of 0.21. For all degrees of hemoptysis, there was no statistically significant difference in the time course of bleeding between the tranexamic acid and placebo groups (Table 2).

There were three patients in the tranexamic acid group who reported minor symptoms during the study period. These symptoms were mild headache, slight chest discomfort and nausea. In the placebo group, there was one report of a minor skin rash which was thought to be from allergy to antituberculous drugs. None of the complications lead to discontinuation of the study drugs.

DISCUSSION

Hemoptysis is the common respiratory symptom leading to admission to the hospital. Because of various underlying causes, the treatment of hemoptysis is basically dependent on its' etiology. The prognosis of the bleeding is not related to the amount of blood per se and mostly runs a benign course except in cases of massive active bleeding

Table 2. Number of cases who had hemoptysis on day 7 and cases who had no hemoptysis on day 7.

	Hemoptysis at day 7 (cases)	No hemoptysis at day 7 (cases)	P-value
Group 1			
Transamine™	0	4	0.33
Placebo	2	7	
Group 2			
Transamine™	2	5	0.23
Placebo	0	7	
Group 3			
Transamine™	2	8	0.13
Placebo	5	4	
All			
Transamine™	4	17	0.48
Placebo	7	18	

defined by a quantity of blood of more than 500 ml per day and the consequences of a compromised respiratory system which requires interventions such as bronchial artery embolization, surgery or bronchoscopic local treatment in order to stop the bleeding. Even though most hemoptysis stops spontaneously, the patients are frustrated by it and their doctors look for management that can reduce the bleeding time. Many interventions have been used in conjunction with other treatments in patients with hemoptysis such as bed rest, lying with the bleeding side down to prevent aspiration of blood to the other side and some medications such as cough suppressant, intravenous estrogen, vasopressin, light sedation which all have controversial indications. Tranexamic acid is another drug which has been used for treating hemoptysis in adults from a variety of etiologic causes, including tuberculosis, aspergilloma, bronchiectasis and carcinoma[3]. The general indications for using tranexamic acid are as an adjuvant treatment in blood dyscrasia and as prophylaxis for rebleeding in intracranial aneurysms[8]. It is also used in the treatment of hereditary angioneurotic edema and menorrhagia[9] and peri-operatively in urological, orthopedic[10], and cardiothoracic procedures[11]. Information about the use of tranexamic acid in hemoptysis has been published as case reports [4-7]. Because most hemoptysis has a benign clinical course it requires a double blinded placebo controlled trial to evaluate the efficacy of tranexamic acid in controlling of hemoptysis. This study was design as a double blinded placebo controlled trial.

The results of this study did not confirm the benefit of tranexamic acid in shortening the duration of hemoptysis in all degrees of bleeding. In each of the groups defined by the degree of bleeding, there was still no demonstrable benefit. The reasons for this finding were probably that the true effect of tranexamic acid cannot control bleeding in the lung which may not depend as much on increased fibrinolysis as in other organs, and the various underlying causes of hemoptysis in the patients who may not only have differences in the causes of bleeding but also received definitive treatment of the underlying causes at the same time as tranexamic acid so the bleeding stopped because of the definitive treatment. The other weakness of this study was the small number patients studied and the large percentage of patients who were lost to follow-up although there was no difference in the characteristics of the patients in either group. A systematic study of the efficacy of tranexamic acid in hemoptysis caused by specific causes such as cystic fibrosis needs to be done to reconfirm individual case reports.

This study also confirmed the benign natural history of nonmassive hemoptysis in that most of the hemoptysis (76.08%) stopped in the one week of the study period and the duration of bleeding was between 2-4 days. The most common causes of hemoptysis were still tuberculosis and bronchiectasis. The treatment of the underlying causes responsible for the hemoptysis is the priority in the management of these cases of nonmassive bleeding. The main side effects of tranexamic acid therapy are gastrointestinal irritation with nausea, vomiting, and diarrhea. Retinal changes have been observed in

experimental animals but have not been observed in human subjects. Thrombotic events are another devastating complication so the contraindications to the use of tranexamic acid include the presence of an increased coagulopathic state, microscopic hematuria[12], and retinopathy. The incidence of these side effects in this study was low including mild headache, nausea, and slight chest discomfort which required no discontinuation of the drug so confirmed its' safety.

In conclusion this double blinded placebo controlled trial of the use of tranexamic acid in treating patients with hemoptysis could not confirm its' efficacy in hastening the duration of bleeding. The efficacy in some etiologic causes especially if no other noninvasive treatment is available needs to be further confirmed by a larger scale study. This study also confirmed the low incidence of side effects of this drug in these patients.

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TRANEXAMIC ACID ในผู้ป่วยที่มีอาการไอออกเลือด

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ภาวะไอออกเลือดเป็นภาวะที่สำคัญทางระบบการหายใจที่นำผู้ป่วยมาพบแพทย์ การรักษาภาวะนี้ส่วนใหญ่ขึ้นกับการรักษาสาเหตุที่ทำให้เกิดมีเลือดออกซึ่งถ้าปริมาณเลือดที่ออกไม่มากกว่า 500 ซีซีต่อวันแล้วมักจะหยุดได้เองหลังรักษาสาเหตุแล้ว มีผู้นิยมใช้ tranexamic acid ในกรณีนี้โดยหวังว่าจะทำให้เลือดหยุดเร็วขึ้น การศึกษานี้เป็นการศึกษาชนิด double blinded placebo controlled trial เพื่อดูสมรรถภาพของยา tranexamic acid (Transamine™) ในผู้ป่วยที่ไอออกเลือด

ผลการศึกษา : มีผู้ป่วยจำนวน 46 คนเข้ารับการศึกษาโดยอยู่ในกลุ่มที่ได้รับยา tranexamic acid 21 คน ได้รับยาหลอก 25 คน ผู้ป่วยที่ได้ยาหลอกมีแนวโน้มที่จะไม่มีโรคพื้นฐาน และมีภาพรังสีทรวงอกที่ปกติมากกว่ากลุ่มที่ได้รับยา tranexamic acid โดยไม่พบความแตกต่างอย่างอื่น การศึกษานี้ไม่พบประโยชน์ของการใช้ยา tranexamic acid ในการลดจำนวนวันของการที่มีอาการไอเป็นเลือด ไม่พบผลข้างเคียงที่รุนแรงของการใช้ยาในการศึกษานี้ ผู้วิจัยแนะนำให้มีการศึกษาเพิ่มเติมโดยมีจำนวนผู้ป่วยที่มากขึ้น และในผู้ป่วยบางโรคที่เคยมีรายงาน

สรุป : การศึกษานี้ไม่พบว่าการใช้ tranexamic acid ในขนาด 1.5 กรัมต่อวันเป็นเวลา 7 วันสามารถลดเวลาของอาการไอออกเลือดในผู้ป่วยได้ แต่ก็ไม่พบผลข้างเคียงที่สำคัญของการใช้ยาในขนาดนี้ในผู้ป่วย

คำสำคัญ : Tranexamic Acid, อาการไอออกเลือด

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