Original Article

Risk factors and clinical outcomes associated with acquired hypofibrinogenemia in patients administered hemocoagulase batroxobin for hemoptysis

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Background: Hemocoagulase batroxobin is used to prevent hemostasis or bleeding in surgical and trauma patients; however, the role of batroxobin in patients with hemoptysis is not well understood. We evaluated the risk factors and prognosis of acquired hypofibrinogenemia in hemoptysis patients treated systemically with batroxobin.

Methods: We retrospectively reviewed the medical charts of hospitalized patients who were administered batroxobin for hemoptysis. Acquired hypofibrinogenemia was defined as a plasma fibrinogen level >150 mg/dL at baseline, decreasing to <150 mg/dL after batroxobin administration.

Results: Overall, 183 patients were enrolled, of whom 75 had acquired hypofibrinogenemia after the administration of batroxobin. There was no statistical difference in the median age of the patients in the non-hypofibrinogenemia and hypofibrinogenemia groups (72.0 *vs.* 74.0 years, respectively). The patients in the hypofibrinogenemia group showed a higher rate of intensive care unit (ICU) admission (11.1% *vs.* 22.7%; P=0.041) and tended to have more massive hemoptysis than those in the non-hyperfibrinogenemia group (23.1% *vs.* 36.0%; P=0.068). The patients in the hypofibrinogenemia group further showed a higher requirement for transfusion (10.2% *vs.* 38.7%; P<0.000) than those in the non-hyperfibrinogenemia group. Low levels of baseline plasma fibrinogen and a prolonged and higher total dose of batroxobin were associated with the development of acquired hypofibrinogenemia. Acquired hypofibrinogenemia was associated with increased 30-day mortality [hazard ratio (HR), 4.164; 95% confidence interval (CI), 1.318–13.157].

Conclusions: The plasma fibrinogen levels in patients who were administered batroxobin for hemoptysis should be monitored, and batroxobin should be discontinued if hypofibrinogenemia occurs.

Keywords: Hemoptysis; hemocoagulase; batroxobin; hypofibrinogenemia

Submitted May 25, 2022. Accepted for publication Nov 25, 2022. Published online Dec 09, 2022.
doi: 10.21037/jtd-22-717
View this article at: https://dx.doi.org/10.21037/jtd-22-717

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Introduction

The term hemoptysis refers to the expectoration of blood from the lower respiratory tract or lung parenchyma (1). Hemoptysis is most commonly caused by respiratory infection, bronchiectasis, lung cancer, and pulmonary tuberculosis (2-4). The majority of hemoptysis cases are self-limiting; however, massive hemoptysis can be life-threatening (5,6). Treatment for patients with massive hemoptysis requires bronchial arterial embolization or surgery, while conservative management may be considered for patients with non-life-threatening hemoptysis (5,6). Systemic hemostatic drugs, such as pituitrin, hemocoagulase, and tranexamic acid, can also be administered simultaneously (6). Tranexamic acid is used to prevent bleeding associated with traumatic injury, surgery, and congenital fibrinogen deficiency (7,8).

Hemocoagulase batroxobin is a hemostatic drug that reduces bleeding time and the need for blood transfusion in patients with trauma or those undergoing surgery (9-12). Batroxobin forms a fibrin clot by degrading fibrinogen into fibrin, which exerts a hemostatic effect (13,14). Batroxobin can be topically administered using bronchoscopy with an infusion or systemically to patients with hemoptysis (6,15-17). However, there have been reports of bleeding associated with acquired hypofibrinogenemia following batroxobin administration (12,18-20). The risk factors and prognosis related to acquired hypofibrinogenemia in hemoptysis patients treated with batroxobin are not well established. In this study, we evaluated the risk factors for and prognosis of acquired hypofibrinogenemia in hemoptysis patients treated systemically with batroxobin. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-717/rc).

Highlight box

Key findings

- Low levels of baseline plasma fibrinogen and a prolonged and higher total dose of batroxobin were associated with the development of acquired hypofibrinogenemia. Acquired hypofibrinogenemia was associated with increased 30-day mortality (hazard ratio, 4.164; 95% confidence interval, 1.318–13.157).

What is known and what is new?

- Batroxobin is used to prevent hemostasis or bleeding in surgical and trauma patients.
- Prolonged use and higher total doses of batroxobin were associated with the development of acquired hypofibrinogenemia. Acquired hypofibrinogenemia was associated with increased 30-day mortality in patients with hemoptysis.

What is the implication, and what should change now?

- The plasma fibrinogen levels in patients who were administered batroxobin for hemoptysis should be monitored, and batroxobin should be discontinued if hypofibrinogenemia occurs.

Methods

Study population and design

This study retrospectively evaluated the data of hospitalized patients who were administered hemocoagulase batroxobin for hemoptysis in a single tertiary hospital in South Korea from January 2020 to April 2021. Plasma fibrinogen was measured in all enrolled patients before the administration of intravenous batroxobin and at least once after receiving treatment. Patients with a baseline plasma fibrinogen level of <150 mg/dL, those without plasma fibrinogen measurements, or those aged <18 years were excluded. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Institutional Review Board at Chonnam National University Hospital, Gwangju, Republic of Korea approved the study (ID: CNUH-2022-367). The requirement for informed consent was waived because of the retrospective nature of the study.

Data collection

We reviewed the medical charts of the patients during the study period. The patients' age, sex, body mass index, smoking status and duration, underlying diseases (hypertension, diabetes, ischemic heart disease, liver disease, malignancy, and drugs associated with bleeding tendency), presence of disseminated intravascular coagulation (DIC) at admission, causes of hemoptysis (bronchiectasis, old tuberculosis, mycobacterial disease, aspergilloma, lung cancer, lung abscess, drugs associated with hemoptysis, and cryptogenic causes), initial respiratory parameters (respiratory rate, partial pressure of oxygen/fraction of inspired oxygen ratio, pH, and partial pressure of dioxide), treatment for hemoptysis (bronchial artery embolization and surgery), presence of massive hemoptysis (≥100 mL/24 hours of hemoptysis), admission to the intensive care unit (ICU), transfusions (packed red blood cells, fresh frozen plasma, and cryoprecipitates), baseline laboratory findings (fibrinogen and platelet levels, activated

partial thromboplastin time, prothrombin time, total bilirubin, aspartate transaminase, alanine transferase, and albumin levels), follow-up plasma fibrinogen levels, usage period and dosage of batroxobin, in-hospital death, and 30-day death after initiation of batroxobin were investigated.

Definitions

Acquired hypofibrinogenemia was defined as a baseline plasma fibrinogen level of >150 mg/dL, dropping to a follow-up level of <150 mg/dL after batroxobin administration (21,22). We also classified the hypofibrinogenemina as mild (100–200 mg/dL), moderate (50–100 mg/dL), and severe (10–50 mg/dL) (23). The Fibrinogen Clauss assay was used to measure plasma fibrinogen concentration. The definition of uncontrolled bleeding was hemoptysis that persisted despite treatment or recurred after treatment. Cryptogenic hemoptysis was defined as an absence of any cause after investigation of chest computed tomography and bronchoscopy for hemoptysis (1). Massive hemoptysis was defined as hemoptysis of more than 100 mL/24 h (6,24). DIC was diagnosed following the algorithm of the International Society on Thrombosis and Haemostasis (25).

Batroxobin dosage and administration route

Batroxobin was administered according to the clinician's judgment regardless of bronchial artery embolization. Batroxobin at 10–20 National Institute of Health Unit (NIHU) was diluted with 500 mL of normal saline and administered intravenously for 24 hours. Batroxobin administration was stopped after hemoptysis improved clinically.

Statistical analysis

All data were expressed as the median [interquartile range (IQR)] or number (percentage). Demographic and clinical variables were compared between the hypofibrinogenemia group and non-hypofibrinogenemia group using the chi-square test (for categorical variables) or the Mann-Whitney U test (for continuous variables). A receiver operating characteristic (ROC) curve was plotted based on baseline plasma fibrinogen levels to predict hypofibrinogenemia. The Youden index was used to calculate optimal baseline fibrinogen cut-offs, sensitivities, and specificities in the ROC curve. Factors associated with acquired hypofibrinogenemia were selected using univariate logistic regression analysis. Subsequent multivariate logistic regression analyses included variables with P values of <0.25 in the univariate analysis using a forward method. Although DIC and chronic liver disease had P values greater than 0.25 in the univariate analysis, we included both variables in the multivariate logistic regression analysis as they were associated with acquired hypofibrinogenemia. Owing to the interaction between the total dosage and the duration of batroxobin administration, two models were developed, each utilizing each variable separately. We used the Kaplan-Meier analysis to evaluate the 30-day mortality. Factors associated with acquired hypofibrinogenemia were identified using a Cox-regression analysis that included variables with P values of <0.25 in the univariate analysis using the forward method. All statistical analyses were performed using SPSS version 25.0 (IBM, Armonk, NY, USA) and MedCalc version 20.023 (Ostend, Belgium); a P value of <0.05 was considered statistically significant.

Results

During the study period, 399 patients were administered batroxobin for hemoptysis and had available plasma fibrinogen measurements (*Figure 1*). Of these, 216 were excluded for the following reasons: plasma fibrinogen level was only measured once (n=190), inconsistent timing of batroxobin use and fibrinogen measurements (n=22), and initial hypofibrinogenemia ≤150 mg/dL (n=4). Finally, 183 patients were enrolled, of whom 75 had acquired hypofibrinogenemia after the administration of batroxobin.

Mild hypofibrinogenemia occurred in 28 patients (15.3%) and moderate hypofibrinogenemia in 60 patients (32.8%) after batroxobin use. There were no cases of severe hypofibrinogenemia.

Differences in baseline characteristics between the non-hypofibrinogenemia and hypofibrinogenemia groups

Table 1 summarizes the baseline characteristics of the two groups. The median age of the patients in the non-hypofibrinogenemia and hypofibrinogenemia groups was 72.0 and 74.0 years, respectively, without a statistically significant difference. Men were significantly more common in the non-hypofibrinogenemia group (73.1% *vs.* 50.7%; P=0.003). There was no significant difference in underlying diseases between the two groups. None of the patients in either group had hematologic disorders. The most common cause of hemoptysis in both groups was bronchiectasis. The

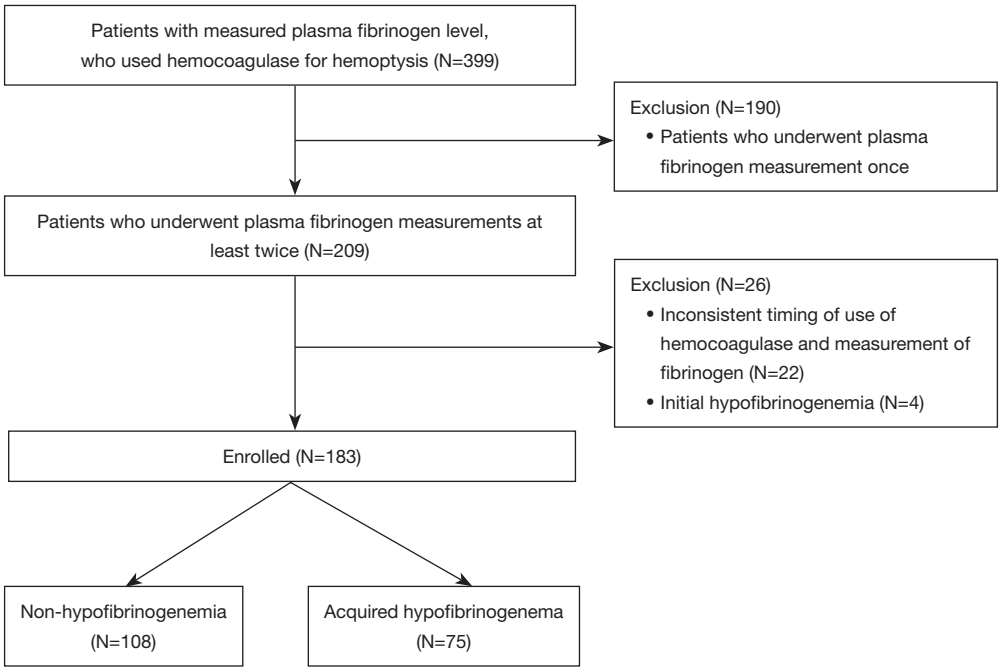


Figure 1 Flow chart of the study design.

Table 1 Baseline characteristics of patients in the non-hypofibrinogenemia and hypofibrinogenemia groups

Variables	Non-hypofibrinogenemia (N=108)	Hypofibrinogenemia (N=75)	P
Age, years	72.0 (60.0–80.0)	74.0 (64.0–82.0)	0.157
Men	79 (73.1)	38 (50.7)	0.003
Body mass index, kg/m^2	21.8 (18.8–23.7)	20.8 (18.6–23.9)	0.785
Current smoker	12 (11.2)	3 (4.0)	0.103
Pack-years	0 (0–20.0)	0 (0–0)	0.002
Hypertension	37 (34.3)	31 (41.3)	0.354
Diabetes	20 (18.5)	19 (25.3)	0.277
Ischemic heart disease	26 (24.1)	23 (30.7)	0.396
Liver disease	6 (5.6)	3 (4.0)	0.739
Malignancy	12 (11. 2)	6 (8.2)	0.617
DIC	2 (1.9)	3 (4.0)	0.402
Bronchiectasis	33 (30.6)	24 (32.0)	0.872
Old tuberculosis	26 (24.1)	19 (25.3)	0.863
Mycobacterial disease	17 (15.7)	10 (13.3)	0.679
Aspergilloma	4 (3.7)	6 (8.0)	0.321
Lung cancer	4 (3.7)	3 (4.0)	1.000
Lung abscess	6 (5.6)	3 (4.0)	0.739

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Non-hypofibrinogenemia (N=108)	Hypofibrinogenemia (N=75)	P
Cryptogenic	5 (4.6)	4 (5.3)	1.000
Medication	4 (3.7)	1 (1.3)	0.650
Initial respiratory parameters			
Respiratory rate	20 (20–20)	20 (20–20)	0.216
PaO_2/FiO_2 ratio	335 (263–403)	313 (195–426)	0.312
pH	7.43 (7.39–7.45)	7.42 (7.39–7.44)	0.168
pCO_2	38.9 (35.0–43.8)	40.0 (33.7–45.0)	0.875
Treatment			
BAE	20 (18.5)	15 (20.0)	0.850
Surgery	1 (0.9)	0 (0)	1.000
Massive hemoptysis	25 (23.1)	27 (36.0)	0.068
ICU admission	12 (11.1)	17 (22.7)	0.041
PRC transfusion	11 (10.2)	29 (38.7)	<0.000
FFP	3 (2.8)	17 (22.7)	<0.000
Cryoprecipitates	2 (1.9)	15 (20.0)	<0.000
Uncontrolled bleeding			<0.000
Continuous bleeding	4 (3.7)	16 (21.3)	
Rebleeding	1 (0.9)	8 (10.7)	
Baseline fibrinogen, mg/dL	418.0 (301.2–542.3)	332.1 (246.4–423.6)	<0.000
Platelet, /mm^3	227.5 (177.2–280.7)	209.0 (166.0–258.0)	0.210
aPTT	29.1 (26.5–32.9)	28.9 (26.1–31.1)	0.238
PT (INR)	1.07 (1.01–1.20)	1.06 (1.00–1.17)	0.533
Total bilirubin, mg/dL	0.66 (0.45–0.96)	0.60 (0.45–0.79)	0.234
ALT, U	17.0 (12.0–25.0)	20.0 (14.0–25.0)	0.950
AST, U	28.0 (22.0–39.0)	27.0 (22.0–36.0)	0.314
Albumin, mg/dL	3.6 (3.1–4.1)	3.9 (3.4–4.2)	0.121
Duration of batroxobin use, days	3.0 (2.0–4.0)	3.0 (2.0–4.7)	0.007
Total doses of batroxobin, NIH units	30.0 (20.0–30.0)	30.0 (20.0–50.0)	<0.000
In-hospital mortality, n (%)	5 (4.6)	11 (14.7)	0.030
30-day mortality, n (%)	5 (4.6)	10 (13.3)	0.057

Data are presented as the median (interquartile range) or number (%). DIC, disseminated intravascular coagulation; PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen; PCO_2, partial pressure of carbon dioxide; BAE, bronchial artery embolization; ICU, intensive care unit; PRC, packed red cell; FFP, fresh frozen plasma; aPTT, activated partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NIH, national institute of health.

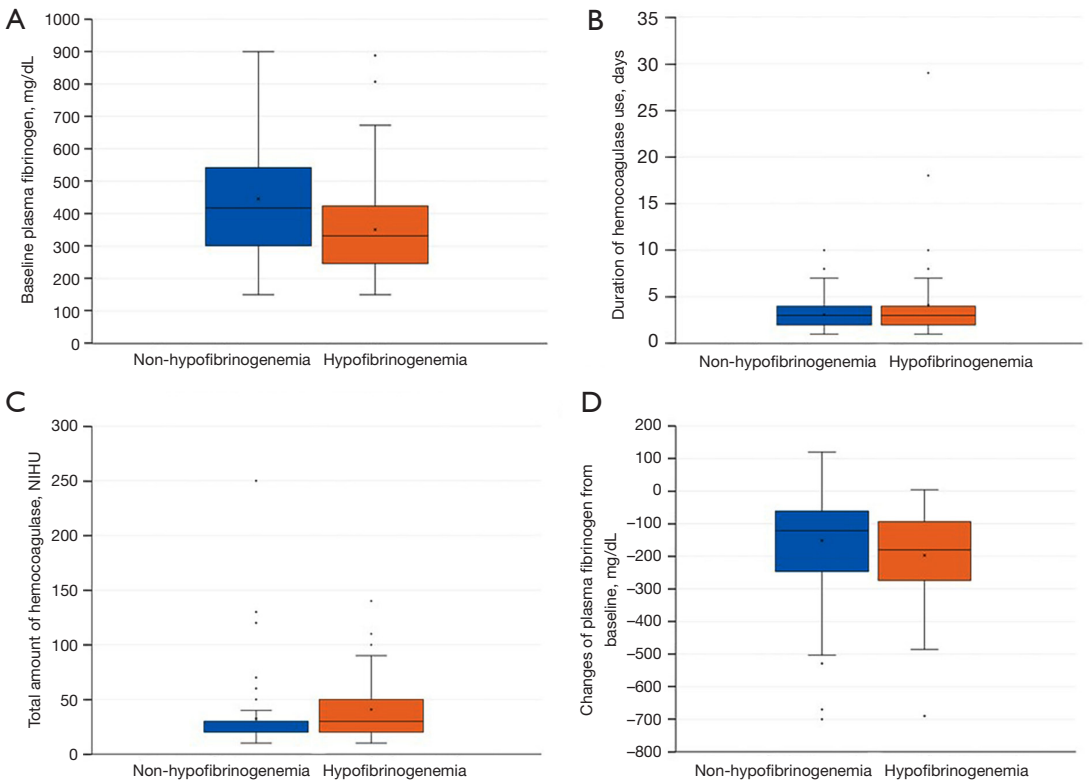


Figure 2 Comparisons between the non-hypofibrinogenemia and acquired hypofibrinogenemia groups. (A) Median baseline plasma fibrinogen levels, 418.0 (IQR 301.2–542.3) *vs.* 332.1 (246.4–423.6) mg/dL (P<0.000); (B) median duration of batroxobin use, 3.0 (2.0–4.0) *vs.* 3.0 (2.0–4.7) days (P=0.007); (C) total dosages of batroxobin, 30.0 (20.0–30.0) *vs.* 30.0 (20.0–50.0) NIHUs (P<0.000); and (D) changes in plasma fibrinogen levels from baseline, −121.5 *vs.* −180.0 mg/dL (P=0.011). IQR, interquartile range; NIHUs, National Institute of Health Units.

proportions of patients who underwent bronchial artery embolization were similar in the non-hypofibrinogenemia and hypofibrinogenemia groups (18.5% *vs.* 20.0%, respectively). The patients in the hypofibrinogenemia group showed more ICU admissions (11.1% *vs.* 22.7%; P=0.041) and tended to have more massive hemoptysis than those in the non-hyperfibrinogenemia group (23.1% *vs.* 36.0%; P=0.068). The patients in the hypofibrinogenemia group required more transfusions of packed red blood cells, frozen fresh plasma, and cryoprecipitates than those in the non-hyperfibrinogenemia group. Moreover, the number of patients with persistent or recurrent hemoptysis was higher in the hypofibrinogenemia group than in the non-hyperfibrinogenemia group. The baseline plasma fibrinogen levels were significantly lower in the hypofibrinogenemia group than in the non-hypofibrinogenemia group (332.1 *vs.* 418.0 mg/dL; P<0.000). The patients in the hypofibrinogenemia group received batroxobin at significantly higher total doses and for longer periods of time than those in the non-hypofibrinogenemia group (shown in *Figure 2*). The decrease in plasma fibrinogen level from baseline was greater in the hypofibrinogenemia group than in the non-hypofibrinogenemia group (−121.5 *vs.* −180.0 mg/dL; P=0.011) (shown in *Figure 2*). In-hospital mortality was also significantly higher in the hypofibrinogenemia group than in the non-hyperfibrinogenemia group (4.6% *vs.* 14.7%; P=0.030).

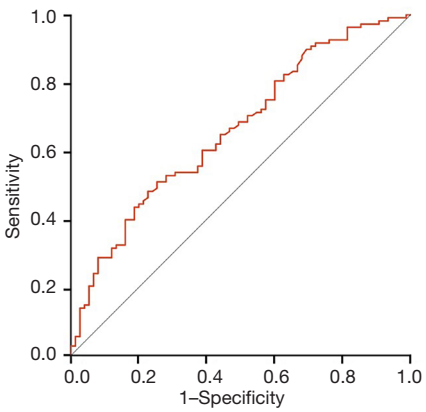
Risk factors associated with acquired hypofibrinogenemia

Risk factors for acquired hypofibrinogenemia are shown in *Table 2*. Because the duration of batroxobin use and total dose of batroxobin were significantly different between the non-hypofibrinogenemia and hypofibrinogenemia groups, two models, including each variable, were used. In the multivariate analysis with logistic regression, age, male sex and low levels of baseline plasma fibrinogen were associated

Table 2 Risk factors associated with acquired hypofibrinogenemia in both models

Variables	Model 1[a]				Model 2[b]			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age	1.016 (0.994–1.038)	0.153	1.025 (1.000–1.051)	0.043	1.016 (0.994–1.038)	0.153	1.026 (1.001–1.051)	0.043
Men	2.652 (1.425–4.937)	0.002	3.277 (1.633–6.579)	0.001	2.652 (1.425–4.937)	0.002	2.329 (1.095–4.956)	0.028
Current smoker	0.330 (0.090–1.212)	0.095			0.330 (0.090–1.212)	0.095		
Pack-years	0.967 (0.944–0.991)	0.008			0.967 (0.944–0.991)	0.008		
DIC	0.453 (0.074–2.778)	0.392			0.453 (0.074–2.778)	0.392		
Massive hemoptysis	1.867 (0.975–3.577)	0.060			1.867 (0.975–3.577)	0.060		
Baseline fibrinogen	0.996 (0.994–0.998)	<0.000	0.996 (0.994–0.999)	0.002	0.996 (0.994–0.998)	<0.000	0.996 (0.994–0.999)	0.001
Platelet	0.998 (0.995–1.001)	0.153			0.998 (0.995–1.001)	0.153		
PT (INR)	0.575 (0.221–1.496)	0.257			0.575 (0.221–1.496)	0.257		
aPTT	0.961 (0.906–1.018)	0.177			0.961 (0.906–1.018)	0.177		
Duration of batroxobin use	1.201 (1.015–1.421)	0.033	1.244 (1.019–1.519)	0.032				
Total doses of batroxobin					1.012 (1.000–1.024)	0.057	1.014 (1.000–1.029)	0.049

[a], model 1 include duration of batroxobin use; [b], model 2 include total doses of batroxobin. OR, odds ratio; CI, confidence interval; DIC, disseminated intravascular coagulation; PT, prothrombin time; INR, international normalized ratio.



AUC	95% CI	P value	Cut-off	Sensitivity	Specificity
0.662	0.583–0.741	<0.000	413	74.7%	50.9%

Figure 3 Receiver operating characteristic curve of baseline plasma fibrinogen levels to predict hypofibrinogenemia. AUC, area under the curve; CI, confidence interval.

with acquired hypofibrinogenemia. In addition, prolonged batroxobin use and higher total doses of batroxobin increased the risk of acquired hypofibrinogenemia.

The ROC curve to predict acquired hypofibrinogenemia based on baseline plasma fibrinogen levels. The area under the curve was 0.662, with statistical significance (P<0.000) (shown in *Figure 3*). The sensitivity and specificity for the cut-off value of 413 mg/dL of the baseline plasma fibrinogen level were 74.7% and 50.9%, respectively. The patients with baseline fibrinogen levels of 413 mg/dL showed a high risk of acquired hypofibrinogenemia [odds ratio (OR) 4.276, P<0.000] (*Table 3*).

Risk factors for 30-day mortality

In the Kaplan-Meier survival analysis, 30-day mortality was higher in the hypofibrinogenemia group than in the non-hypofibrinogenemia group (log lank P=0.045) (shown in *Figure 4*). In the Cox proportional hazard model, a low levels of baseline plasma fibrinogen [hazard ratio (HR), 1.004; 95% confidence interval (CI), 1.001–1.007; P=0.006], total bilirubin (HR, 1.916; 95% CI, 1.322–2.777; P=0.001), DIC (HR, 5.271; 95% CI, 1.458–19.059; P=0.011), and acquired hypofibrinogenemia (HR, 4.164; 95% CI, 1.318–13.157; P=0.015) were associated with increased 30-day mortality (*Table 4*).

Table 3 Baseline fibrinogen levels predicting hypofibrinogenemia

Variables	OR	95% CI	P
Baseline plasma fibrinogen <413 mg/dL			
Unadjusted	2.854	1.511–5.389	0.001
Adjusted[a]	3.005	1.543–5.839	0.001
Adjusted[b]	4.137	1.909–8.965	<0.000
Adjusted[c]	4.181	1.903–9.186	<0.000
Adjusted[d]	4.276	1.943–9.410	<0.000

[a], age, and sex; [b], age, sex, smoking status, pack-years, hypertension, diabetes, ischemic heart disease, liver disease, bronchiectasis, old tuberculosis, mycobacterial diseases, aspergilloma, lung cancer, lung abscess, cryptogenic, medication, and disseminated intravascular coagulation; [c], age, sex, smoking status, pack-years, hypertension, diabetes, ischemic heart disease, liver disease, bronchiectasis, old tuberculosis, mycobacterial diseases, aspergilloma, lung cancer, lung abscess, cryptogenic, medication, disseminated intravascular coagulation, and dose of batroxobin; [d], age, sex, smoking status, pack-years, hypertension, diabetes, ischemic heart disease, liver disease, bronchiectasis, old tuberculosis, mycobacterial diseases, aspergilloma, lung cancer, lung abscess, cryptogenic, medication, disseminated intravascular coagulation, and duration of batroxobin. OR, odds ratio; CI, confidence interval.

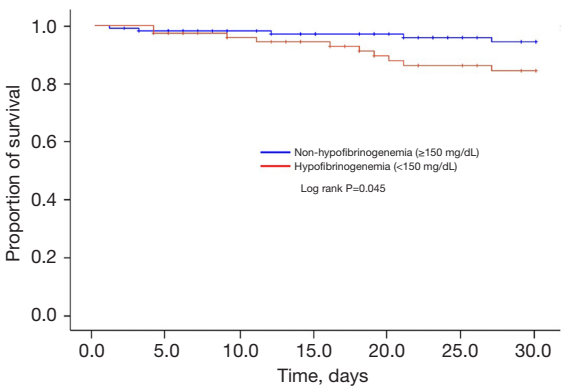


Figure 4 Kaplan-Meier curve for 30-day survival after the initiation of batroxobin administration.

Discussion

To the best of our knowledge, this is the first study to evaluate the risk factors for and prognosis of acquired hypofibrinogenemia associated with batroxobin administration to treat hemocoagulase in patients with hemoptysis. We found that the administration of batroxobin for a prolonged period and with high total doses and lower baseline plasma fibrinogen levels were associated with acquired hypofibrinogenemia in patients with hemoptysis. The patients in the acquired hypofibrinogenemia group had a higher rate of ICU admission, transfusion, and in-hospital mortality than those in the non-hypofibrinogenemia group. Acquired hypofibrinogenemia was associated with increased 30-day mortality in patients with hemoptysis.

Hemocoagulase batroxobin is a thrombin-like serine protease extracted from snake venom (26). Thrombin forms fibrin monomers by degrading the alpha and beta chains of fibrinogen, whereas batroxobin only degrades the alpha chain of fibrinogen (13,14). Batroxobin has a 10-fold higher affinity for fibrinogen than thrombin (27). Batroxobin reduces the bleeding time and the need for blood transfusion in patients with trauma or those undergoing surgery (2,9-12). Bronchoscopy with the bronchial infusion of batroxobin was also effective in treating patients with massive hemoptysis (15-17). Additionally, batroxobin can be administered systemically to patients with hemoptysis to control bleeding (2,6,20,28). Patients with massive hemoptysis are also recommended to be administered batroxobin systemically in combination with bronchial artery embolization or surgery (6). However, the use of batroxobin leads to a reduction in plasma fibrinogen levels due to increased fibrinogen consumption (27). In this study, plasma fibrinogen levels decreased from baseline in both the patients from the hypofibrinogenemia and non-hypofibrinogenemia groups after batroxobin administration. Previous studies also reported a decrease in plasma fibrinogen after the administration of hemocoagulase batroxobin (12,18-20). Plasma fibrinogen decreased significantly more in the acquired hypofibrinogenemia group than in the non-hypofibrinogenemia group in this study.

Our study found that more uncontrolled bleeding was observed in the patients in the hypofibrinogenemia group than in those in the non-hypofibrinogenemia group, suggesting that the development of acquired hypofibrinogenemia following batroxobin administration is associated with a bleeding tendency. Wei *et al.* found that patients with postoperative hypofibrinogenemia had a higher incidence of intracranial hematomas and received more blood and plasma transfusions (29). A positive correlation between the consumption of plasma fibrinogen

Table 4 Risk factors associated with 30-day mortality after the administration of batroxobin

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age	1.023 (0.981–1.066)	0.296		
Men	1.379 (0.490–3.882)	0.543		
Baseline fibrinogen levels	1.002 (1.000–1.005)	0.076	1.004 (1.001–1.007)	0.006
Platelet	0.993 (0.987–1.000)	0.036		
aPTT	0.999 (0.964–1.035)	0.946		
PT (INR)	1.098 (0.694–1.737)	0.689		
Total bilirubin	1.676 (1.179–2.383)	0.004	1.916 (1.322–2.777)	0.001
ALT	1.000 (0.997–1.003)	0.907		
AST	1.000 (0.999–1.001)	0.904		
Albumin	0.345 (0.185–0.645)	0.001		
Body mass index	0.957 (0.840–1.090)	0.506		
Current smoker	0.994 (0.131–7.567)	0.995		
Pack-years	1.012 (0.982–1.044)	0.438		
Uncontrolled bleeding	2.745 (0.937–8.043)	0.066		
Hypertension	2.010 (0.729–5.543)	0.178		
Diabetes	1.525 (0.485–4.793)	0.470		
Ischemic heart disease	1.650 (0.587–4.638)	0.342		
Liver disease	1.215 (0.159–9.252)	0.851		
Malignancy	1.486 (0.332–6.640)	0.604		
DIC	9.664 (2.725–34.280)	<0.000	5.271 (1.458–19.059)	0.011
Massive hemoptysis	0.576 (0.162–2.041)	0.393		
Bronchiectasis	0.334 (0.075–1.479)	0.148		
Old tuberculosis	0.448 (0.101–1.984)	0.290		
Mycobacterial diseases	0.039 (0.000–17.579)	0.297		
Aspergilloma	1.208 (0.159–9.192)	0.855		
Lung cancer	0.047 (0.000–4532.678)	0.601		
Lung abscess	0.3961 (0.888–17.668)	0.071		
Cryptogenic	0.047 (0.000–5,064.288)	0.605		
Medication	0.048 (0.000–6,257.979)	0.672		
BAE	0.654 (0.148–2.900)	0.577		
Dose of batroxobin	1.001 (0.985–1.017)	0.889		
Duration of batroxobin use	1.029 (0.900–1.177)	0.674		
Hypofibrinogenemia	2.851 (0.974–8.341)	0.056	4.164 (1.318–13.157)	0.015

HR, hazard ratio; CI, confidence interval; aPTT, activated partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DIC, disseminated intravascular coagulation; BAE, bronchial artery embolization.

and the use of batroxobin has also been reported (29). Zhou *et al.* further reported 7 patients who developed hypofibrinogenemia after batroxobin administration for bleeding prevention following colon polyp excision. Among them, 3 developed lower gastrointestinal bleeding; however, there was no decrease in plasma fibrinogen in 13 patients who did not use batroxobin (18). In a case report, a patient with hemoptysis who had been treated with long-term batroxobin also developed a bleeding tendency due to acquired hypofibrinogenemia (20). In this study, the development of acquired hypofibrinogenemia was associated with the total dose of batroxobin and duration of batroxobin use. The decrease rate of plasma fibrinogen levels according to the daily dose of batroxobin was not different between the acquired hypofibrinogenemia and non-hypofibrinogenemia groups. The risk of acquired hypofibrinogenemia after batroxobin administration was also high in patients with low baseline plasma fibrinogen levels. The odds of acquired hypofibrinogenemia were four times higher if the plasma fibrinogen level was less than 413 mg/dL, even in the normal range of plasma fibrinogen levels (P<0.000). Therefore, plasma fibrinogen levels should be measured before administration of batroxobin, and patients with low hypofibrinogen levels or on long-term or high-doses of batroxobin should have their plasma fibrinogen levels monitored closely. There has been a recent increase in the use of functional fibrinogen assays such as thromboelastography and rotational thromboelastometry, allowing for the identification of fibrinogen deficiency and transfusion more quickly in trauma and surgical bleeding cases (30). Further research is needed on the effectiveness of measuring baseline and follow-up fibrinogen levels with these functional fibrinogen assays in patients receiving batroxobin for hemoptysis.

This study found that the patients in the acquired hypofibrinogenemia group had significantly higher in-hospital mortality rates than the patients in the non-hypofibrinogenemia group. Acquired hypofibrinogenemia was also associated with increased 30-day mortality. Hypofibrinogenemia is a well-known prognostic factor for patients with trauma or those undergoing surgery (31-34). Plasma fibrinogen levels of less than 2 g/L are associated with an increased 3-month mortality rate in patients with traumatic brain injury (34). The minimum hemostatic fibrinogen level is 50 mg/dL at bleeding. For unprovoked hemorrhage, suggested fibrinogen concentrations are >100 mg/dL until hemostasis is normalized and >50 mg/dL until the bleeding surface is entirely restored (35). However, 30-day mortality was not correlated with the duration of batroxobin use or total doses of batroxobin. Therefore, patients administered batroxobin for hemoptysis should undergo monitoring for plasma fibrinogen levels and discontinue batroxobin if hypofibrinogenemia develops (12,20). In hypofibrinogenemic patients, thrombotic events can occur when thrombotic factor risks are present, so bleeding risk and thrombotic risk must be managed jointly (36).

This study had several limitations. First, this was a retrospective study conducted in a single center, which limits the generalizability of our findings. Second, we enrolled patients whose plasma fibrinogen levels were measured before the administration of intravenous batroxobin and at least once after receiving treatment. However, there is a possibility that some patients with hypofibrinogenemia were excluded as plasma fibrinogen was not measured every day. Third, the possibility of other factors affecting the reduction in plasma fibrinogen levels could not be excluded completely. Hemodilution and DIC are common causes of acquired hypofibrinogenemia. The medical charts in this study were thoroughly reviewed, and no hemodilution conditions were found. However, hemodilution could not be completely excluded from hydration because of the retrospective study design. The effect of DIC on hypofibrinogenemia and 30-day mortality was also evaluated in univariate and multivariate analyses. Fourth, because most hemoptysis patients in our institution receive batroxobin, we could not evaluate hypofibrinogenemia and prognosis based on batroxobin use. Additional studies are needed to investigate the hemostatic effect, hypofibrinogenemia occurrence, and prognosis of batroxobin in hemoptysis patients. Fifth, to avoid missing important variables in the multivariate analysis, we selected variables with a P value within 0.25 in the univariate analysis. However, the possibility of missing some important variables cannot be completely ruled out.

Conclusions

High-dose or long-term batroxobin use for hemoptysis is associated with the development of hypofibrinogenemia. Hypofibrinogenemia is associated with poorer outcomes and higher 30-day mortality in patients. Thus, the plasma fibrinogen levels of patients administered batroxobin for hemoptysis should be monitored, and batroxobin should be discontinued if hypofibrinogenemia occurs.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-717/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-717/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-717/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-717/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Institutional Review Board at Chonnam National University Hospital, Gwangju, Republic of Korea approved the study (ID: CNUH-2022-367). The requirement for informed consent was waived because of the retrospective nature of the study.

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Cite this article as: Lee JK, Yoon CS, Na YO, Park HK, Oh HJ, Kho BG, Park HY, Kim TO, Shin HJ, Kwon YS, Kim YI, Lim SC. Risk factors and clinical outcomes associated with acquired hypofibrinogenemia in patients administered hemocoagulase batroxobin for hemoptysis. J Thorac Dis 2023;15(1):65-76. doi: 10.21037/jtd-22-717