Intracranial Hemorrhage in Patients with Hematologic Disorders: Prevalence and Predictive Factors

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Background: *Intracranial hemorrhage (ICH) is an uncommon complication in patients with hematologic disorders although high fatality rates have been shown in these patients. At present, no epidemiological data regarding ICH in patients with hematologic disorders has been collected and/or reported in Thailand.*
Objective: *The purpose of this study was to determine the incidence of ICH in hospitalized patients with hematologic disorders and to identify predictive factors associated with ICH in these patients.*
Material and Method: *The medical records of all patients with hematologic disorders admitted to Siriraj Hospital (Bangkok, Thailand) between January 2002 and September 2011 were reviewed. Patients with ICH were identified and factors associated with ICH were investigated using a retrospective case-control design.*
Results: *Of 9,627 patients identified with hematologic disorders, ICH was diagnosed in 106 (1.1%). The ICH rate was higher in acute myeloid leukemia (AML) patients than in patients with other hematologic malignancies (4.29% vs. 0.78%; p<0.001) and higher in aplastic anemia (AA) patients than in patients with other benign hematologic disorders (4.00% vs. 0.97%; p<0.001). Cortical hemorrhage was the main presentation in all hematologic disorders, with a single lesion in the parietal area as the most common site. The overall mortality rate was 85% with most patients succumbing within two days of onset. The independent predictors of ICH were hyperleukocytosis and a low platelet count in AML patients, and ecchymosis, upper gastrointestinal hemorrhage, hematuria, and a low platelet count in AA patients.*
Conclusion: *AML and AA patients had the highest risk of ICH compared with other hematologic disorders and several predictive factors for ICH were identified.*

Keywords: *Acute myeloid leukemia, Aplastic anemia, Hematologic disorder, Hematologic malignancy, Intracranial hemorrhage*

J Med Assoc Thai 2016; 99 (1): 15-24
Full text. e-Journal: *http://www.jmatonline.com*

Intracranial hemorrhage (ICH) is the second most common cause of morbidity and mortality in adult hematologic malignancy patients[1-5]. The pathogenesis of ICH can involve vasculopathy from tumor invasion, thrombocytopenia or platelet dysfunction, coagulopathy, disseminated intravascular coagulation, hyperfibrinolysis, and hyperleukocytosis[1-6].

Several previous ICH studies found that this condition is an uncommon complication, but found high mortality rates in hematologic malignancy patients and acute myeloid leukemia (AML) patients to have the highest incidence of ICH among hematologic disorder patients[1,3,5,7]. ICH risk factors include low platelet level, high white blood cell (WBC) count, systemic bleeding symptoms, and disseminated intravascular coagulation; however, none of the previous studies included a control group[1-5]. Intraparenchymal bleeding is the most common in hematologic malignancy patients and a higher risk of death occurs in patients with prolonged prothrombin time, subarachnoid hemorrhage, and multifocal cerebral hemorrhage[3,8].

To date, no epidemiological data regarding ICH in patients with hematologic disorders in Thailand has been collected and/or reported[9,10]. Because ICH is the major cause of death in hematologic disorder patients with bleeding complications, we designed this retrospective study to assess the prevalence of ICH in hospitalized patients with hematologic disorders and to identify ICH predictive factors in patients with hematologic disorders.

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Material and Method

We performed a retrospective hospital-based chart review of patients who were admitted to Siriraj

Hospital - the largest tertiary care hospital in Thailand, between January 1, 2002 and September 30, 2011 study period. Patients with the following hematologic disorders were reviewed: acute lymphoblastic leukemia (ALL), AML, chronic myeloid leukemia (CML), myeloproliferative neoplasm (MPN), non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), multiple myeloma (MM) or plasma cell myeloma (PCM), myelodysplastic syndrome (MDS), aplastic anemia (AA), immune thrombocytopenic purpura (ITP), and hemophilia. This study was approved by the Siriraj Institutional Review Board (SIRB) and followed the guidelines outlined in the Declaration of Helsinki and all of its subsequent amendments.

ICH patients

Adult patients with ICH were identified and the demographic characteristics, bleeding symptoms prior to ICH, initial laboratory results, ICH management, and early mortality rate were evaluated. The inclusion criteria for this study were: 1) hematologic disorder with spontaneous ICH; 2) ICH confirmed by computed tomography (CT) or magnetic resonance imaging (MRI); and 3) patient age ≥15 years. The exclusion criteria included: 1) previous ICH before the diagnosis of a hematologic disorder; 2) history of traumatic brain injury; and 3) patients taking antithrombotic drugs or other drugs with anticoagulant effects.

Factors associated with ICH

The factors associated with ICH were investigated in the hematologic malignancy group with the highest ICH rate (AML patients) and in the benign hematologic disorder group with the highest ICH rate (AA patients). For each of AML and AA, a control group was selected that consisted of patients without ICH who were diagnosed with the same hematologic condition at the same time as the patients with ICH. Group selection was determined by block randomization method. Data from the case and control groups were compared to identify the factors associated with ICH.

The median time of ICH in AML patients in this study was day 5 of admission, and the laboratory results at time of onset of ICH in AML patients were compared with the laboratory results on day 5 of admission in the AML control group. The median time of ICH in AA patients in this study was day 2 of admission, and the laboratory results at the time of ICH in AA patients were compared with the laboratory results on day 2 of admission in the AA control group.

Statistical analysis

The clinical characteristics of each group are presented as the median and interquartile range, mean and standard deviation, or percentage. Continuous data were compared between groups using the Student's t-test or Mann-Whitney U test. Categorical data were compared between groups using the Chi-square test or Fisher's exact test. Univariate and multivariate logistic regression analyses were used to determine the relationships between variables and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Parametric and nonparametric analyses were also performed. The *p*-value of <0.05 were considered to be statistically significant.

Results

Prevalence of ICH in patients with hematologic disorders

We found 145 patients diagnosed with ICH from the 9,627 cases with hematologic disorders. We excluded 39 patients, as follows, 16 patients had a history of cerebral hemorrhage before being diagnosed with the hematologic disorder and 23 patients had symptoms of suspected ICH without imaging confirmation. We included a final 106 ICH patients (45 men and 61 women) (Fig. 1) with a median age of 43 years (range: 15-84).

The ICH patients included: 5/351 (1.42%) patients with ALL, 38/885 (4.29%) with AML, 15/498 (3.01%) with CML, 0/266 with MPN, non-CML,

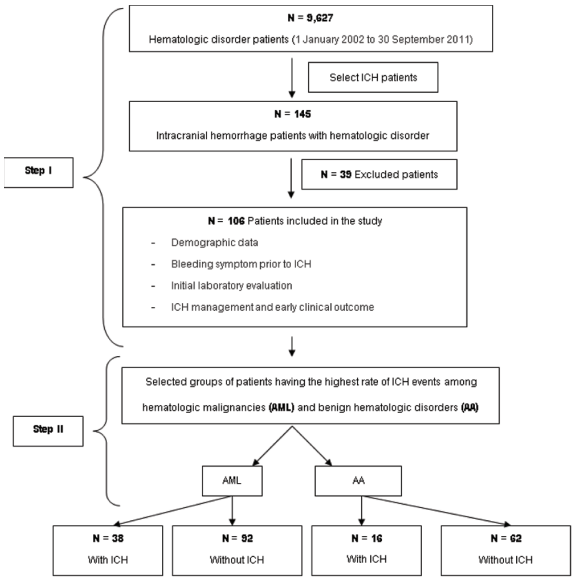

Fig. 1 Flow chart of patient recruitment.

9/3293 (0.27%) with NHL, 0/236 with HL, 3/647 (0.47%) with MM/PCM, 16/400 (4%) with AA, 16/2406 (0.66%) with ITP, 1/552 (0.18%) with MDS, and 3/93 (3.22%) with hemophilia. The overall ICH prevalence rate was 1.1% among the hematologic disorder patients, and the ICH rate in AML and AA patients was significantly higher than in other hematologic disorder patients (Table 1). AML patients had the highest rate of ICH when compared with other hematologic malignancies (4.29% vs. 0.78%, $p<0.001$; OR: 5.723, 95% CI: 3.712-8.694). Of patients diagnosed with AML, 89% were recently diagnosed, 11% were relapses, and 42% were diagnosed with AML at the time of ICH. The median time of ICH in AML patients was day 5 of admission (range: 0-51 days).

Using the French-American-British (FAB) Classification subtypes, among the 38 AML patients with ICH, we found the following number for each subtype, AML-M0: 1 patient (2.63%), AML-M1: 6 patients (15.79%), AML-M2: 13 patients (34.21%), Acute promyelocytic leukemia (APL): 6 patients (15.79%), AML-M4: 5 patients (13.16%), AML-M5: 2 patients (5.26%), and no subtype recorded in 5 (13.16%) patients. APL patients showed a higher rate of ICH events compared with other AML subgroups (6.52% vs. 4.06%, $p<0.001$; OR: 6.15, 95% CI: 2.15-14.36).

Among the 15 CML patients with ICH, nine (60%) patients were in the chronic phase, five (33.33%) patients were in the blastic phase, and one (6.66%) patient was in the accelerated phase. Among the nine NHL patients with ICH, there were four (44.44%) patients were with diffuse large B cell lymphoma, two (22.22%) patients were with follicular lymphoma, and one (11.11%) patient each was with chronic lymphocytic leukemia/small lymphocytic lymphoma, peripheral T-cell lymphoma, and follicular lymphoma.

Table 1. Incidence of ICH in different types of hematologic disorders

Disease		Hemorrhage		OR (95% CI)	*p*-value
		Yes, n (%)	No, n (%)		
Benign		35 (1.21)	2,864 (98.79)	1.146 (0.739-1.746)	0.512
Malignant		71 (1.06)	6,657 (98.94)		
ALL	Yes	5 (1.42)	346 (98.58)	1.313 (0.415-3.194)	0.441
	No	101 (1.09)	9,175 (98.91)		
AML	Yes	38 (4.29)	647 (95.71)	5.723 (3.712-8.694)	<0.001
	No	68 (0.78)	8,674 (99.22)		
CML	Yes	15 (3.01)	483 (96.99)	3.084 (1.645-5.408)	<0.001
	No	91 (1.00)	9,038 (99.00)		
MPN	Yes	0 (0)	266 (100)	-	0.123
	No	106 (1.13)	9,255 (98.87)		
NHL	Yes	9 (0.27)	3,293 (99.73)	0.175 (0.078-0.348)	<0.001
	No	97 (1.53)	6,228 (98.47)		
HL	Yes	0 (0)	236 (100)	-	0.117
	No	106 (1.13)	9,285 (98.87)		
MM	Yes	3 (0.46)	647 (99.54)	0.399 (0.089-1.205)	0.105
	No	103 (1.15)	8,874 (98.85)		
AA	Yes	16 (4.00)	384 (96.00)	4.230 (2.290-7.330)	<0.001
	No	90 (0.97)	9,137 (99.02)		
ITP	Yes	16 (0.66)	2,390 (99.33)	0.530 (0.290-0.911)	<0.018
	No	90 (1.24)	7,131 (98.75)		
MDS	Yes	1 (0.18)	551 (99.82)	0.155 (0.004-0.887)	0.032
	No	105 (1.16)	8,970 (98.84)		
Hemophilia	Yes	3 (3.23)	90 (96.77)	3.052 (0.608-9.458)	0.083
	No	103 (1.08)	9,431 (98.92)		

AA = aplastic anemia; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CI = confidence interval; CML = chronic myeloid leukemia; HL = Hodgkin lymphoma; ITP = idiopathic thrombocytopenic purpura; MDS = myelodysplastic syndrome; MM = multiple myeloma; MPN = myeloproliferative neoplasm; NHL = non-Hodgkin lymphoma; OR = odds ratio

AA patients showed the highest rate of ICH compared with those with other benign hematologic disorders (4.00% vs. 0.97%, $p<0.001$; OR: 4.230, 95% CI: 2.29-7.33). Among the AA patients, 75% were recently diagnosed, 43% were hospitalized because of systemic bleeding symptoms, 37% were newly diagnosed with AA at the time of ICH, 18.75% had infections at admission and subsequently developed ICH, and 12.5% were hospitalized for anti-thymocyte globulin (ATG) therapy. The median time of ICH in AA patients was day 2 of admission (range: 0-60 days).

Clinical and laboratory characteristics of ICH patients

The age, gender, and rates of anemia, hyperleukocytosis, grade 4 thrombocytopenia, prolonged prothrombin time, and prolonged activated partial prothrombin time were significantly different among ICH patients with different hematologic disorders.

The number of patients with bleeding symptoms prior to the ICH events included 32/106 (30.2%) with petechiae, 24/106 (22.6%) with ecchymosis, 22/106 (20.8%) with oral mucosal bleeding, 16/106 (15.1%) with upper gastrointestinal bleeding, 9/106 (8.5%) with hematuria, 9/106 (8.5%) with hematoma, 7/106 (6.6%) with conjunctival bleeding, 5/106 (4.7%) with menorrhagia, 4/106 (3.8%) with epistaxis, 3/106 (2.8%) with pulmonary hemorrhage, 3/106 (2.8%) with retinal hemorrhage, 2/106 (1.9%) with lower gastrointestinal bleeding, and 2/106 (1.9%) with purpura. Sixty-three of 106 patients (59.4%) presented with altered consciousness, 46/106 (43.4%) with headache, 24/106 (22.6%) with focal neurological deficits, 22/106 (20.8%) with nausea/vomiting, 14/106 (13.2%) with seizure, and 2/106 (1.9%) with fever.

Eighty-six of 106 patients (81.10%) had anemia, 27/106 (25.5%) had hyperleukocytosis, 48/82 (58.53%) had prolonged prothrombin time, 32/82 (39.02%) had prolonged activated partial prothrombin time, and 98/106 (92.45%) had platelet counts $<100x10^9$/L. Among the patients with thrombocytopenia, 75/106 (70.8%) had platelet counts $<25x10^9$/L (grade 4 thrombocytopenia).

Types and locations of ICH

The locations of intracranial bleeding included 52/106 (49.05%) patients with cortical hemorrhage, 19/106 (17.92%) with cerebellar hemorrhage, 18/106 (16.98%) with subcortical hemorrhage, 16/106 (15.09%) with intraventricular hemorrhage, 11/106 (10.37%) with brainstem hemorrhage, 10/106 (9.43%) with multiple localized hemorrhages, 10/106 (9.43%) with subarachnoid hemorrhage, 6/106 (5.66%) with subdural hematoma, and 1/106 (0.94%) with epidural hematoma. Among the 52 cortical hemorrhagic patients, ICH occurred in the frontal area in 53.84%, parietal area in 63.46%, temporal area in 21.15%, and occipital area in 19.23%. Cortical hemorrhage was the main ICH presentation in all hematologic disorders, with a single lesion in the parietal area most commonly.

Treatment and mortality of patients with ICH

ICH patient management included: surgery in 14/106 (13.20%) patients, transfusion support in 92/106 (86.79%) patients, hyperventilation in 75/106 (70.80%) patients, antihypertensive drugs in 7/106 (6.60%) patients, intravenous dexamethasone in 7/106 (6.60%) patients, and therapeutic leukapheresis in 3/106 (2.80%) patients. Patients receiving surgical management had better survival rates than those receiving conservative treatment (50% vs. 12%, respectively; $p = 0.034$; OR: 7.074, 95% CI: 1.164-43.000). The overall mortality was 83%, with most patients expiring within two days of ICH onset. Among 106 patients, seven (6.60%) partially recovered and 11 (10.40%) completely recovered. Fourteen (13.31%) of 106 patients had surgery, nine (8.49%) had craniectomy, three (2.83%) had ventriculostomy, one (0.94%) underwent burr-hole craniostomy, and eight (7.54%) had splenectomy.

Univariate and multivariate analysis showed that female gender ($p = 0.013$; OR: 11.909, 95% CI: 1.670-84.906), normal prothrombin time ($p = 0.048$; OR: 0.214, 95% CI: 0.047-0.987), and surgical treatment ($p = 0.034$; OR: 7.074, 95% CI: 1.164-43.000) were associated with independent good predictive outcomes (Table 2).

Factors associated with ICH

The clinical characteristics of the AML patients, including age, gender, history of alcohol use, co-morbidities, baseline blood pressure, and initial laboratory findings were not statistically significantly different between case and control groups. However, a history of smoking was statistically significantly different between cases and controls (7/30 (23.33%) vs. 8/92 (8.69%), respectively; $p = 0.034$).

Univariate analysis revealed that smoking, ecchymosis, upper gastrointestinal hemorrhage,

hyperleukocytosis (WBC >50x10^9/L), and platelet count <10x10^9/L were associated with a high likelihood of developing ICH in AML patients. In multivariate analysis adjusting for all risk factors that were significantly associated with ICH events, patients with hyperleukocytosis and platelet count <10x10^9/L had an increased probability of ICH (Table 3).

The clinical characteristics of AA patients were similar between cases and controls for age, gender, history of smoking, history of alcohol use, co-morbidities, baseline blood pressure, and initial laboratory findings; but the initial platelet count was statistically significantly different between cases and controls (median platelet count 4x10^9/L vs. 13x10^9/L, respectively; $p = 0.003$).

In univariate analysis, ecchymosis, upper gastrointestinal hemorrhage, and platelet count <10x10^9/L were associated with high likelihood of ICH developing in AA patients. In multivariate analysis adjusting for all risk factors that were significantly associated with ICH events, patients with ecchymosis, upper gastrointestinal hemorrhage, hematuria, and platelet count <10x10^9/L increased the probability of ICH (Table 4).

Table 2. Univariate and multivariate analysis of factors associated with 7-day mortality after ICH in all patients with hematologic disorders

Characteristics	Dead	Alive	Univariate			Multivariate		
			OR	95% CI	*p*-value	OR	95% CI	*p*-value
Sex								
Male	42	3	1.0			1.0		
Female	46	15	4.505	1.234-16.890	0.023	11.909	1.670-84.906	0.013
WBC count >50x10^9/L								
No	62	17	1.0			-		
Yes	26	1	0.140	0.018-1.110	0.063			
Prolonged PT								
No	23	11	1.0			1.0		
Yes	45	3	0.139	0.035-0.555	0.005	0.214	0.047-0.987	0.048
Prolonged aPTT								
No	38	12	1.0			-		
Yes	30	2	0.211	0.944-1.016	0.052			
Platelet count <10x10^9/L								
No	48	9	1.0			-		
Yes	39	9	1.231	0.446-3.399	0.689			
Surgery								
No	11	81	1.0			1.0		
Yes	7	7	7.364	2.169-25.001	0.001	7.074	1.164-43.000	0.034
Subcortical hemorrhage								
No	71	17	1.0			-		
Yes	17	1	0.246	0.031-1.976	0.187			
Cortical hemorrhage								
No	45	9	1.0			-		
Yes	43	9	1.047	0.380-2.885	0.930			
Brainstem hemorrhage								
No	78	17	1.0			-		
Yes	10	1	0.459	0.055-3.888	0.472			
Cerebellar hemorrhage								
No	74	13	1.0			-		
Yes	14	5	2.033	0.025-6.610	0.238			
Multiple hemorrhages								
No	80	16	1.0			-		
Yes	8	2	1.250	0.243-6.443	0.790			

aPPT = activated partial thromboplastin time; CI = confidence interval; OR = odds ratio; PT = prothrombin time; WBC = white blood cell

Table 3. Univariate and multivariate analysis of potential risk factors for ICH in AML patients

Characteristics	Controls	Cases	Univariate			Multivariate		
			OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age	92	38	0.989	0.964-1.101	0.366	-		
Sex								
Male	33	13	1.0			-		
Female	59	25	1.076	0.486-2.380	0.857			
Smoking								
No	65	23	1.0			-		
Yes	8	7	3.213	1.007-9.781	0.041			
Alcohol								
No	66	25	1.0			-		
Yes	7	5	1.886	0.548-6.494	0.315			
Co-morbidities								
No	84	33	1.0			-		
Yes	8	5	1.591	0.485-5.217	0.444			
Anemia								
No	8	3	1.0			-		
Yes	84	35	1.111	0.278-4.435	0.881			
WBC count >50x10^9/L								
No	86	24	1.0			1.0		
Yes	6	14	8.461	2.903-24.085	<0.001	11.522	3.563-37.776	<0.001
Platelet count <10x10^9/L								
No	73	24	1.0			1.0		
Yes	17	14	2.574	1.103-6.092	0.028	3.108	1.149-8.861	0.038
Prolonged PT								
No	13	19	1.0			-		
Yes	24	12	1.137	0.414-3.127	0.803			
Prolonged aPTT								
No	25	19	1.0			-		
Yes	12	12	1.316	0.485-3.570	0.590			
sBP	92	38	0.989	0.960-1.019	0.471	-		
dBP	92	38	1.017	0.976-1.060	0.420	-		
Conjunctiva								
No	87	33	1.0			-		
Yes	5	5	2.636	0.717-9.700	0.145			
Oral mucosa								
No	82	30	1.0			-		
Yes	10	8	2.187	0.789-6.061	0.133			
UGIB								
No	88	32	1.0			-		
Yes	4	6	4.125	1.093-15.570	0.037			
LGIB								
No	87	38	1.0			-		
Yes	5	0	-	-	-			
Menorrhagia								
No	78	36	1.0			-		
Yes	14	2	0.310	0.067-1.434	0.134			
Hematuria								
No	90	35	1.0			1.0		
Yes	2	3	3.857	0.618-24.076	0.149	7.012	0.975-55.852	0.066
Petechiae								
No	57	28	1.0			-		
Yes	35	10	0.582	0.252-1.342	0.204			
Purpura								
No	90	37	1.0			-		
Yes	2	1	1.216	0.107-13.826	0.875			
Ecchymosis								
No	81	28	1.0			-		
Yes	11	10	2.630	1.009-6.856	0.048			
Hematoma								
No	92	34	1.0			-		
Yes	0	4	-	-	-			

aPTT = activated partial thromboplastin time; CI = confidence interval; dBP = diastolic blood pressure; LGIB = lower gastrointestinal bleeding; OR = odds ratio; PT = prothrombin time; sBP = systolic blood pressure; UGIB = upper gastrointestinal bleeding; WBC = white blood cell

Table 4. Univariate and multivariate analysis of potential risk factors for ICH in AA patients

Characteristics	Controls	Cases	Univariate			Multivariate		
			OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age	55	16	0.980	0.947-1.014	0.239	0.965	0.927-1.004	0.079
Sex								
Male	19	6	1.0			-		
Female	36	10	0.880	0.277-2.791	0.828			
Smoking								
No	52	13	1.0			-		
Yes	3	0	-	-	-			
Alcohol								
No	52	12	1.0			-		
Yes	3	1	1.444	0.138-15.125	0.759			
Co-morbidities								
No	52	13	1.0			-		
Yes	3	3	4.000	0.722-22.156	0.112			
Anemia								
No	11	3	1.0			-		
Yes	44	13	1.083	0.262-4.476	0.912			
Platelet count <10x10^9/L								
No	42	3	1.0			1.0		
Yes	13	12	12.923	3.156-52.922	<0.001	17.132	2.780-110.749	0.003
Prolonged PT								
No	5	10	1.0			-		
Yes	4	1	0.125	0.011-1.434	0.095			
Prolonged PTT								
No	7	11	1.0			-		
Yes	2	0	-	-	-			
sBP	55	16	1.029	0.999-1.060	0.058	-		
dBP	55	16	1.054	0.998-1.112	0.059	-		
Conjunctiva								
No	53	14	1.0			-		
Yes	2	2	3.786	0.489-29.306	0.202			
Oral mucosa								
No	44	12	1.0			-		
Yes	11	4	1.333	0.360-4.943	0.667			
UGIB								
No	52	12	1.0			1.0		
Yes	3	4	5.778	1.140-29.290	0.034	17.302	1.823-160.835	0.013
LGIB								
No	55	15	1.0			-		
Yes	0	1	-	-	-			
Menorrhagia								
No	47	14	1.0			-		
Yes	8	2	0.839	0.160-4.416	0.836			
Hematuria								
No	53	13	1.0			1.0		
Yes	2	3	6.115	0.925-40.449	0.060	37.505	2.695-531.183	0.007
Petechiae								
No	19	10	1.0			-		
Yes	36	6	0.317	0.100-1.005	0.051			
Purpura								
No	46	16	1.0			-		
Yes	9	0	-	-	-			
Ecchymosis								
No	53	12	1.0			1.0		
Yes	2	4	8.833	1.447-53.940	0.018	21.905	1.871-248.000	0.013

aPTT = activated partial thromboplastin time; CI = confidence interval; dBP = diastolic blood pressure; LGIB = lower gastrointestinal bleeding; OR = odds ratio; PT = prothrombin time; sBP = systolic blood pressure; UGIB = upper gastrointestinal bleeding

Discussion

Our 10-year retrospective review of patients with hematologic disorders found that these patients had a higher ICH rate than the general population[11-15]. In this study, AML patients, particularly APL patients, had a higher ICH rate than other patients with hematologic malignancies, a finding consistent with results reported by previous studies[1-5]. APL patients have elevated levels of urokinase-type plasminogen activator and tissue plasminogen activator, resulting in low levels of plasminogen and α2-antiplasmin, all of which leads to a hyperfibrinolytic state and thrombocytopenia with a high rate of bleeding complications[16-18].

The median age of patients with hematologic disorders and ICH was 43 years (range: 15-84), with the ICH rate being higher in males than in females. In contrast, the mean age of patients with ICH in the general population is 65 years, with a slightly higher rate in females than in males[15]. The most common bleeding symptom prior to ICH was petechiae, followed by ecchymosis and oral mucosal bleeding. The most common clinical presentation of ICH was a decreased level of consciousness, which occurred in 60% of the patients. Similar to previous studies, the most common pattern of ICH was a single cortical hemorrhage in the parietal area[1-5]. Subcortical and cerebellar hemorrhages were much less frequent. In contrast, the most common pattern in hypertensive ICH is basal ganglia hemorrhage[11-16].

Most of our patients with hematologic disorders and ICH had a poor outcome. The 7-day mortality rate was 83%, which is significantly higher than the reported rate of 34.6% in patients with ICH who do not have hematologic disorders[15]. The higher fatality rate in patients with hematologic disorders may be due to different mechanisms underlying the bleeding, including hypertensive hemorrhage, profound thrombocytopenia, and coagulopathy, any or all of which could lead to massive intracranial bleeding[1-5].

In this study, female gender, normal prothrombin time, and surgical treatment were independent predictors of survival after ICH. In subgroup analysis, patients with idiopathic thrombocytopenic purpura or AML who received surgical treatment tended to have better outcomes than patients with other disorders; but the numbers in each group were small and the differences were not statistically significant[19-24]. Similar to previous studies[1-5], hyperleukocytosis and a platelet count of $<10x10^9$/L were significantly associated with ICH in AML patients. In AA patients, ecchymosis, upper gastrointestinal hemorrhage, hematuria, and a platelet count of $<10x10^9$/L were associated with an increased risk of ICH.

This study is limited by the relatively small number of ICH patients, which may have affected the outcomes of statistical significance tests. However, our results are valuable because the factors associated with ICH in Thai patients with hematologic disorders have not been well-studied. Our results can be compared with patients with the same disorders in different countries and geographical areas and may be useful for predicting and preventing ICH in patients with hematologic conditions.

In conclusion, ICH occurred infrequently in Thai patients with hematologic disorders and was associated with a high short-term mortality rate. AML and AA patients had the highest risk for ICH, as compared with other hematologic disorders. In AML patients, a WBC count of $>50x10^9$/L and a platelet count of $<10x10^9$/L were independent predictors of ICH. In AA patients, ecchymosis, upper gastrointestinal hemorrhage, hematuria, and a platelet count of $<10x10^9$/L were independent predictors of ICH.

What is already known on this topic?

There were only a few previous studies related to this topic. For example, Choi et al[4] in 2004 showed that 42 hematologic patients who had intracranial hemorrhages were diagnosed as aplastic anemia, acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, myelodysplastic syndrome, multiple myeloma, and polycythemia vera. Eighty-six percent of patients had a platelet level less than $100x10^9$/L. Significant risk factors for ICH were low platelet level, high WBC count, and disseminated intravascular coagulopathy. However, most studies were small series and did not have a control group.

What this study adds?

To date, no epidemiological data regarding ICH in patients with hematologic disorders in ASEAN countries has been collected and/or reported. Furthermore, none of the previous studies included a control group for risk factor determination. In this study, a control group was selected and consisted of patients without ICH who were diagnosed with the same hematologic diseases as the patients with ICH.

Acknowledgments

The authors gratefully acknowledge Dr. Yingyong Chinthammitr and all residents and fellows at the Department of Medicine, Faculty of Medicine Siriraj Hospital for their valuable contributions to the success of this study.

Authors' contributions

Owattanapanich W participated in the design of the study, performed the statistical analysis, and drafted the manuscript. Auewarakul CU supervised the project and made critical revisions to the manuscript. Both authors read and approved the final manuscript.

Funding disclosure

This study was funded by grants from the Siriraj Chalermprakiate Fund, Faculty of Medicine, Siriraj Hospital and the Thai Society of Hematology.

Potential conflicts of interest

None.

References

1. Gonzalez-Duarte A, Garcia-Ramos GS, Valdes-Ferrer SI, Cantu-Brito C. Clinical description of intracranial hemorrhage associated with bleeding disorders. J Stroke Cerebrovasc Dis 2008; 17: 204-7.
2. Kim H, Lee JH, Choi SJ, Lee JH, Seol M, Lee YS, et al. Risk score model for fatal intracranial hemorrhage in acute leukemia. Leukemia 2006; 20: 770-6.
3. Rogers LR. Cerebrovascular complications in cancer patients. Neurol Clin 2003; 21: 167-92.
4. Choi YJ, Rha HK, Park HK, Lee KJ, Joo WI, Kim MC. Intracranial hemorrhage in patients with hematologic disorders. J Korean Neurosurg Soc 2004; 36: 302-5.
5. Chen CY, Tai CH, Cheng A, Wu HC, Tsay W, Liu JH, et al. Intracranial hemorrhage in adult patients with hematological malignancies. BMC Med 2012; 10: 97.
6. Streletz LJ, Terzic D, Salem K, Raza A, Deleu DT. CNS lymphoma masquerading as hemorrhagic stroke. Clin Neurol Neurosurg 2012; 114: 262-4.
7. Pagano L, Larocca LM, Vaccario ML, Masullo C, Antinori A, Pierconti F, et al. Acute hemorrhagic leukoencephalitis in patients with acute myeloid leukemia in hematologic complete remission. Haematologica 1999; 84: 270-4.
8. Stein E, McMahon B, Kwaan H, Altman JK, Frankfurt O, Tallman MS. The coagulopathy of acute promyelocytic leukaemia revisited. Best Pract Res Clin Haematol 2009; 22: 153-63.
9. Poungvarin N, Viriyavejakul A. Spontaneous supratentorial intracerebral haemorrhage: a prognostic study. J Med Assoc Thai 1990; 73: 206-11.
10. Lowprukmanee N. Clinical outcome of the patients treated surgically for spontaneous intracerebral hematoma at Sawanpracharak Hospital. J Med Assoc Thai 2013; 96: 669-77.
11. Choy DK, Wu PH, Tan D, Yeo TT, Chou N. Correlation of the long-term neurological outcomes with completeness of surgical evacuation in spontaneous supratentorial intracerebral haemorrhage: a retrospective study. Singapore Med J 2010; 51: 320-5.
12. Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. Lancet 2005; 365: 387-97.
13. Proust F, Leveque S, Derrey S, Tollard E, Vandhuick O, Clavier E, et al. Spontaneous supratentorial cerebral hemorrhage: role of surgical treatment. Neurochirurgie 2007; 53: 58-65.
14. Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. Lancet 2009; 373: 1632-44.
15. Sacco S, Marini C, Toni D, Olivieri L, Carolei A. Incidence and 10-year survival of intracerebral hemorrhage in a population-based registry. Stroke 2009; 40: 394-9.
16. Choudhry A, DeLoughery TG. Bleeding and thrombosis in acute promyelocytic leukemia. Am J Hematol 2012; 87: 596-603.
17. Ichikawa S, Suzuki T, Kimura J, Harigae H. Successful treatment of acute promyelocytic leukemia accompanied by serious subdural hematoma. Intern Med 2012; 51: 2209-12.
18. He B, Hu S, Qiu G, Gu W. Clinical characteristics of acute promyelocytic leukemia manifesting as early death. Mol Clin Oncol 2013; 1: 908-10.
19. Panicker JN, Pavithran K, Thomas M. Management of subdural hematoma in immune thrombocytopenic purpura: report of seven patients and a literature review. Clin Neurol Neurosurg 2009; 111: 189-92.

20. Barnes C, Blanchette V, Canning P, Carcao M. Recombinant FVIIa in the management of intracerebral haemorrhage in severe thrombocytopenia unresponsive to platelet-enhancing treatment. Transfus Med 2005; 15: 145-50.
21. Nosari A, Caimi TM, Zilioli V, Molteni A, Mancini V, Morra E. Cerebral hemorrhage treated with NovoSeven in acute promyelocytic leukemia. Leuk Lymphoma 2012; 53: 160-1.
22. Hess EP, Sztajnkrycer MD. Images in emergency medicine. Acute leukemia with blast crisis, disseminated intravascular coagulation, and intraparenchymal hemorrhage. Ann Emerg Med 2005; 46: 314, 322.
23. Rajput R, Marwah N, Chitkara N, Singh S, Meena. Acute myeloid leukemia manifested as intracerebral hemorrhage. Indian J Pathol Microbiol 2003; 46: 535-6.
24. Kim H, Lee JH, Choi SJ, Kim WK, Lee JS, Lee KH. Analysis of fatal intracranial hemorrhage in 792 acute leukemia patients. Haematologica 2004; 89: 622-4.

การศึกษาความชุกของเกิดเลือดออกในสมองและปัจจัยที่มีผลต่อการเกิดเลือดออกในสมองในผู้ป่วยโรคเลือด

วีรภัทร โอวัฒนาพานิช, จิรายุ เอื้อวรากุล

ภูมิหลัง: *ภาวะเลือดออกในสมองเป็นภาวะแทรกซ้อนที่พบไม่บ่อยในผู้ป่วยโรคเลือด แต่เป็นภาวะแทรกซ้อนที่มีโอกาสเสียชีวิตได้มาก สำหรับในประเทศไทยนั้น ยังไม่มีข้อมูลชัดเจนทางระบาดวิทยาในผู้ป่วยโรคเลือดที่เกิดเลือดออกในสมอง ดังนั้นการศึกษานี้จัดทำเพื่อศึกษาความชุกของการเกิดเลือดออกในสมองในผู้ป่วยโรคเลือด และศึกษาปัจจัยที่มีผลต่อการเกิดเลือดออกในสมอง*

วัตถุประสงค์: *เพื่อศึกษาความชุกของการเกิดเลือดออกในสมองผู้ป่วยโรคเลือด ที่มารับการตรวจรักษาตั้งแต่วันที่ 1 มกราคม พ.ศ. 2545 ถึง 30 กันยายน พ.ศ. 2554 ที่โรงพยาบาลศิริราช และเพื่อศึกษาปัจจัยที่มีผลต่อการเกิดเลือดออกในสมองในผู้ป่วยโรคเลือด พิจารณาจากผลการศึกษาข้างต้น โดยเลือกโรคเลือดชนิดไม่ใช่มะเร็ง 1 โรค และโรคเลือดที่เป็นมะเร็ง 1 โรคมาศึกษาต่อ*

วัสดุและวิธีการ: *การศึกษาครั้งนี้ทำการศึกษาในผู้ป่วยโรคเลือดดังต่อไปนี้ คือ มะเร็งเม็ดเลือดขาวชนิดเฉียบพลัน lymphoid มะเร็งเม็ดเลือดขาวชนิดเฉียบพลัน myeloid มะเร็งเม็ดเลือดขาวชนิดเรื้อรัง myeloid มะเร็งเม็ดเลือดชนิด myeloproliferative มะเร็งต่อมน้ำเหลืองชนิด non-Hodgkin มะเร็งต่อมน้ำเหลืองชนิด Hodgkin มะเร็งเม็ดเลือดขาวชนิด multiple myeloma ไขกระดูกฝ่อ โรคเกล็ดเลือดต่ำไม่ทราบสาเหตุ myelodysplastic syndrome และ hemophilia โดยแบ่งการศึกษาเป็น 2 ระยะ คือ ระยะที่ 1 เพื่อศึกษาความชุกของการเกิดเลือดออกในสมองในผู้ป่วยโรคเลือด และระยะที่ 2 เพื่อศึกษาปัจจัยที่มีผลต่อการเกิดเลือดออกในสมองของ ผู้ป่วยโรคเลือดชนิดที่พบผู้ป่วยมากที่สุด ในผู้ป่วยโรคเลือดที่ไม่ใช่มะเร็ง และผู้ป่วยโรคเลือดที่เป็นมะเร็ง*

ผลการศึกษา: *จากการศึกษาพบผู้ป่วยเลือดออกในสมองทั้งสิ้น 106 ราย จากผู้ป่วยโรคเลือดทั้งหมด 9,627 ราย อัตราการเกิดเลือดออกในสมองในผู้ป่วยโรคเลือดคิดเป็นร้อยละ 1.1 โดยพบว่าผู้ป่วยมะเร็งเม็ดเลือดขาวชนิดเฉียบพลัน myeloid มีอัตราการเกิดเลือดออกในสมองร้อยละ 4.29 ($p<0.001$) และผู้ป่วยไขกระดูกฝ่อมีอัตราการเกิดเลือดออกในสมองร้อยละ 4 ($p<0.001$) ซึ่งมากที่สุดเมื่อเปรียบเทียบกับผู้ป่วยโรคเลือดที่เป็นโรคมะเร็ง และไม่ใช่มะเร็งตามลำดับ อัตราการเสียชีวิตสูงถึงร้อยละ 85 ปัจจัยเสี่ยงต่อการเกิดเลือดออกในสมองของผู้ป่วยมะเร็งเม็ดเลือดขาวชนิดเฉียบพลัน myeloid คือ ระดับเม็ดเลือดขาวในเลือดสูง และระดับเกล็ดเลือดต่ำ ส่วนปัจจัยเสี่ยงต่อการเกิดเลือดออกในสมองของผู้ป่วยไขกระดูกฝ่อคือ จ้ำพรายย้ำ เลือดออกทางเดินอาหารส่วนต้น เลือดออกทางเดินปัสสาวะ และระดับเกล็ดเลือดต่ำ นอกจากนี้พบว่าผู้ป่วยที่มีพยากรณ์โรคดีหลังจากเกิดเลือดออกในสมอง คือ เพศหญิง ระดับ prothrombin time อยู่ในเกณฑ์ปกติ และผู้ป่วยที่ได้รับการผ่าตัด*

สรุป: *ภาวะเลือดออกในสมองในผู้ป่วยโรคเลือดพบได้บ่อยกว่าประชากรทั่วไป โดยพบว่าผู้ป่วยมะเร็งเม็ดเลือดขาวชนิดเฉียบพลัน myeloid และไขกระดูกฝ่อมีอัตราการเกิดเลือดออกในสมองมากที่สุด และการศึกษาครั้งนี้พบปัจจัยเสี่ยงที่มีผลต่อการเกิดออกในสมองในผู้ป่วยโรคเลือด*