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Clinical Article

The Outcomes of Spontaneous Intracerebral Hemorrhage in Young Adults - A Clinical Study

Gyeong O Go[1], Hyun Park[1], Chul Hee Lee[1], Soo Hyun Hwang[1], Jong Woo Han[1], In Sung Park[1,2]
[1]Department of Neurosurgery, Gyeongsang National University School of Medicine, Jinju, Korea
[2]Gyeongsang Institute of Health Sciences, Gyeongsang National University School of Medicine, Jinju, Korea

Objective : Spontaneous intracerebral hemorrhage (ICH) in young adults is rare. The purpose of this study was to investigate causes, sites and other factors affecting the prognosis of ICH in young adults aged ≤ 40 years.

Methods : We reviewed 39 consecutive patients diagnosed with spontaneous ICH between January 2001 and June 2012. Patients with primary subarachnoid hemorrhage, previously diagnosed brain tumor bleeding, or vascular malformation were excluded. We analyzed the differences in prognostic factors such as hemorrhage location and vascular structural etiology. The outcome was measured using the Glasgow outcome scale (GOS), and a good outcome was defined as a score of 4 or more.

Results : We retrospectively evaluated 39 patients (mean age, 33 years; SD = 6.4, range 17 to 40 years). The most common structural etiology was arteriovenous malformation. A statistically significantly higher proportion of patients with good outcomes had a lower initial systolic blood pressure (SBP ≤ 160 mmHg, p = 0.036), a higher initial Glasgow coma scale (GCS) (9 or more, p = 0.034), lower cholesterol levels (< 200 mg/dl, p = 0.036), and smoking history (at discharge, p = 0.008; 6 months after discharge, p = 0.019).

Conclusion : In this study, cryptogenic ICH was the leading cause of spontaneous ICH. A GCS score of 9 or more on admission, a lower serum cholesterol level (< 200 mg/dl), and a lower SBP (< 160 mmHg) predicted a good outcome.

Keywords Intracerebral hemorrhage, Outcomes, Prognostic factors, Spontaneous, Young adult

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Correspondence to In Sung Park
Department of Neurosurgery, Gyeongsang National University Hospital, Gyeongsang Institute of Health Science, 90 Chiram-dong, Jinju 660-702, Korea

Tel : 82-55-750-8112
Fax : 82-55-758-1782
E-mail : gnuhpis@nongae.gsnu.ac.kr

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INTRODUCTION

Nontraumatic spontaneous intracranial hemorrhage (ICH) causes significant morbidity and mortality throughout the world. Ten to 20% of strokes are caused by ICH in Western countries.[6] Over 45 years of age, ICH is common,[5)16)21)] but rare before then. Therefore, the goal of our study was to perform a descriptive analysis of ICH etiology and prognostic factors in patients aged ≤ 40 years.

METHODS

We analyzed patients using medical records. We selected 39 consecutive patients who were ≤ 40 years of age diagnosed between January 2001 and June 2012.

All cases of ICHs were confirmed using computed tomography (CT) or magnetic resonance imaging (MRI). Traumatic ICH, insufficient medical information, previously diagnosed intracranial tumors, arteriovenous malformation (AVM), and primary subarachnoid hemorrhage were exclusion factors for this study. For each patient, we analyzed the following prognostic factors: smoking history (the consumption of ≥ 5 cigarettes at least 2 days per week over a period of 12 months), alcohol use (the ingestion of 100 g/d or more every day for at least 20 days per month during the last 2 months or acute alcoholic intoxication during the 24 hours prior to the attack), previously diagnosed underlying disease such as hypertension or diabetes mellitus, the use of antihypertensive or antidiabetic agents, high serum cholesterol (fasting cholesterol values ≥ 200 mg/dl at admission) or low serum cholesterol (< 150 mg/dl), and bleeding tendency (prolongation of prothrombin time > 14.3 seconds or activated partial thromboplastin time > 43.5 seconds). The hematoma volume was estimated via the analysis of CT scans using the ABC/2 method.[12] The hematoma site was denoted by lobe (frontal, parietal, temporal or occipital), thalamus, basal ganglia, cerebellum, or brain stem.

Hypertensive ICH was defined as hemorrhage into the brain parenchyma in the absence of causal trauma or a structural disease process on a macroscopic level, such as a tumor, aneurysm, vascular malformation, or arteriovenous fistula, in patients treated for hypertension (or who were previously diagnosed with hypertension), as well as the absence of another cause of ICH. AVM, venous angioma and other vascular malformations were confirmed using CT angiography, conventional cerebral angiography, or magnetic resonance angiography. If there was no explanatory underlying disease or abnormal structural lesion in the image workup, the ICH was defined as cryptogenic ICH.

Patients with an ICH volume greater than 30 ml in the basal ganglia or thalamus received surgical treatment, with the exception of 4 patients. One patient was a high surgical risk because of disseminating intravascular coagulopathy associated with acute mye-

Table 1. Patients characteristics

	Number	Mean
Gender		
Male	28 (71.8%)	
Female	11 (28.2%)	
Age	33.2 ± 6.4	
Etiology		
AVM	10 (25.6%)	
HTN	9 (23.1%)	
Aneurysm	2 (5.1%)	
Venous angioma	2 (5.1%)	
Cryptogenic	16 (41.0%)	
Smoking history	21 (53.38%)	
Alcohol use	26 (66.7%)	
Hypertension	28 (71.8%)	
Cholesterol		
< 150 mg/dl	12 (30.8%)	130.2 ± 16.9
150 – 199 mg/dl	18 (46.1%)	153.0 ± 24.1
≥ 200 mg/dl	9 (23.1%)	236.9 ± 32.3
Bleeding tendency		
Absent	33 (84.6%)	
Present	6 (15.4%)	
SBP		
< 160 mmHg	26 (66.7%)	130.0 ± 16.5
≥ 160 mmHg	13 (33.3%)	182.3 ± 21.3
DBP		
< 90 mmHg	18 (46.2%)	74 ± 8.9
≥ 90 mmHg	21 (53.8%)	97.7 ± 9.1
IVH		
Absent	21 (53.8%)	
Present	18 (46.2%)	
Direction		
Left	20 (51.3%)	
Right	19 (48.7%)	
GCS		
≤ 8	14 (35.9%)	5.8 ± 1.1
> 8	25 (64.1%)	13.8 ± 1.9
Volume		
< 30 ml	16 (41.0%)	10.7 ± 7.9
≥ 30 ml	23 (59.0%)	63.8 ± 29.0

AVM= arteriovenous malformation; HTN= hypertension; SBP/DBP= systolic/diastolic blood pressure; IVH= intraventricular hemorrhage; GCS= Glasgow coma scale.

locytic leukemia, and the others showed no definite neurological deterioration and tolerated the event with conservative management. For the patients with an ICH volume of less than 30 ml, conservative management was indicated. However, for the patients with an ICH volume of less than 30 ml, if progressive acute hydrocephalus due to intraventricular hemorrhage and neurological deterioration was present, external ventricular drainage was performed. In cerebellar ICH, regardless of the hemorrhage volume, a decompressive craniectomy with hematoma removal was performed if the patient showed progressive neurological deterioration.

We defined the final outcome by the Glasgow outcome scale (GOS). A good outcome was defined as a GOS score ≥ 4, and a poor outcome was defined as a GOS score < 4.

We analyzed data using the SPSS software (version 18; SPSS Inc., Chicago, IL, USA). A cross-tabulation test identified significant factors associated with ICH prognosis. Fisher's exact test was applied to assess statistical significance, and null hypotheses of no difference were rejected if p values were less than 0.05.

RESULTS

Thirty-nine young patients were diagnosed with non-traumatic spontaneous ICH. The mean age was 33.21 ± 6.42 years (range 15-40 years), and there were 11 females and 28 males. The characteristics of the study subjects by outcome at discharge and 6 months after discharge are described in Table 1. The prognostic factors are summarized in Table 2. We assessed outcomes by reviewing the GOS of medical record at discharge and 6 months after discharge.

Based on the outcomes at discharge and 6 months after discharge, smoking history was significantly associated with prognosis. Alcohol use, previously diagnosed hypertension and bleeding tendency were not statistically significantly associated with outcome. Fasting serum cholesterol at the time of admission was also a prognostic factor. Patients in the hypercholesterolemia group were more likely to experience a poor prognosis. All of the patients with cholesterol levels less than 200 mg/dl had good outcomes at 6 months after discharge; this finding was statistically significant ($p = 0.047$).

Patients with an initial systolic blood pressure (SBP) < 160 mmHg had better outcomes (good outcomes in 65.4% of patients), while those patients with an SBP ≥ 160 mmHg had poorer prognoses (poor outcomes in 69.2% of patients); this result was statistically significant ($p = 0.044$). The level of diastolic blood pressure (DBP) upon admission showed similar results ($<$ 90 mmHg: 66.7% experienced good outcomes; $\geq$ 90 mmHg: 57.1% experienced poor outcomes) although, these results were not significant.

The ICH location, as well as the presence or absence of intraventricular hemorrhage (IVH), had no significant effect on outcome ($p = 0.451$). There were also no statistically significant findings associated with ICH direction (left or right).

The initial Glasgow coma scale (GCS) score significantly predicted results and outcomes. In particular, patients with GCS ≤ 8 had a higher proportion of poor outcomes, compared to patients with GCS $>$ 8; this finding was statistically significant ($p = 0.02$ via Fisher's exact test).

Variations in the volume of the hematoma showed no significant difference ($p = 0.051$) in GCS score. Lobar hemorrhage was the most common location of ICH in young adults, and there were no statistically significant findings associated with hematoma location (Table 3).

DISCUSSION

In our institution, 280 patients were diagnosed with ICH during the investigation period; of these patients, 39 (13.9 %) were aged ≤ 40 years. In Western countries, only 3-5% of ICH patients were younger than 45 years.[14)24)] The distribution of ICH reflects the charac-

Table 2. Outcome prognostic factors

Factors	Discharge		6 Months		*p* value	
	Good	Poor	Good	Poor	Discharge	6 Months
Smoking history						
No	6	12	6	12		
Yes	16	5	15	6	0.008*	0.019*
Alcohol use						
No	7	6	7	6		
Yes	15	11	14	12	0.543	0.632
HTN history						
No	17	11	5	6		
Yes	5	6	16	12	0.305	0.38
Cholesterol						
< 150 mg/dl	7	5	7	5		
150 – 199 mg/dl	12	6	13	5		
≥ 200 mg/dl	2	7	2	7	0.086	0.047*
Bleeding tendency						
No	18	15	17	16		
Yes	4	2	4	2	0.465	0.41
SBP						
< 160 mmHg	18	8	17	9		
≥ 160 mmHg	4	9	4	9	0.026*	0.044*
DBP						
< 90 mmHg	12	6	12	6		
≥ 90 mmHg	10	11	9	12	0.192	0.122
Location						
Infratentorial	5	3	5	3		
Supratentorial	17	14	16	15	0.508	0.442
IVH						
Absent	13	8	12	9		
Present	9	9	9	9	0.336	0.451
Direction						
Left	10	10	9	11		
Right	12	7	12	7	0.307	0.208
GCS						
≤ 8	4	10	4	10		
> 8	18	7	17	8	0.011*	0.02*
Volume						
< 30 ml	12	4	12	4		
≥ 30 ml	10	13	10	13	0.051	0.051

*Statistically significant value. HTN= hypertension; SBP/DBP= systolic/diastolic blood pressure; IVH= intraventricular hemorrhage; GCS= Glasgow coma scale.

teristics of the population (ethnic/racial groups and the criteria of a young adult) although these studies were not standardized.[4] In this study, 11 (28.2%) of the patients diagnosed with ICH had also been diagnosed with hypertension. In young adults, hypertension is a primary cause of ICH, and this hypertension/ICH ratio varies from 11 to 15%.[2][3][23] As with other published literature, our study showed that a

poor prognosis is more likely in patients with hypercholesterolemia. This finding was statistically significant in our study. In this and other studies, hypercholesterolemia is associated with poor prognosis and a risk factor for ICH. Many studies describe serum cholesterol level and smoking history as risk factors for ICH.[2)18)20)22)23)] In our study, the serum cholesterol level and smoking history were also prognostic factors.

According to Ruiz-Sandoval and coworkers,[18)] AVM contributes to 33% of ICH cases, cavernous angioma contributed to 16% of cases, and hypertension contributed to 11% of cases (all under the age of 40 years), similar to our study results. However, among the elderly, hypertension was the most common cause of ICH, and the putamen was the most common location.[11)20)] Our results indicate that the most common causes of ICH were cryptogenic cases (n = 16, 41.03%) and the most common structural etiology of ICH was AVM. Lobar ICH was the most common location in young adults.

We found that an initial SBP greater than 160 mmHg indicated a poor prognosis, and patients with a SBP less than 160 mmHg were more likely to have a good prognosis. These results were statistically significant. Some authors reported a low (< 130 mmHg) or high (≥ 200 mmHg) initial SBP as a prognostic factor that was independently associated with mortality.[9)] Smoking, alcohol, and bleeding tendency in younger patients were determined to be prognostic factors of ICH.[13)18)]

Regarding the serum cholesterol, the patients with levels < 200 mg/dl (63.3%) showed a good prognosis, and patients with levels ≥ 200 mg/dl (77.8%) showed a poor prognosis. Six months after discharge, this difference was statistically significant and suggests that serum cholesterol levels can be a prognostic factor, as seen in the literature.[1)] Ruiz-Sandoval and coworkers[19)] reported that hypertension and hypercholesterolemia are 2 main risk factors for ICH. Some authors reported that hypocholesterolemia can cause ICH and that the interaction between high diastolic blood pressure and low cholesterol levels weakens the endothelium of the intracerebral arteries, resulting in a hemorrhagic stroke in the presence of hypertension.[10)] However, in that study, the association between low cholesterol levels and the prognosis was not clearly presented. A study to investigate the association between serum low-density lipoprotein cholesterol (LDL-C) and mortality in ICH found that lower LDL-C levels were associated with higher mortality rates.[17)] In our study, 7 patients (58.3%) with LDL-C levels < 150 mg/dl had good outcomes and statistically significant improvements 6 months after discharge. However, the sample size was limited in our study, age was limited to ≤ 40 years, and cholesterol was the only factor used to assess the outcome via lipid profile.

A statistically significant difference in outcomes (p = 0.034 by the t-test) by the initial GCS score was observed. An initial GCS score over 8 predicted a good prognosis. In another study, a score of 8 or less

Table 3. Outcomes by hematoma location*

Location	Number	%	At discharge		6 months later	
			Good	Poor	Good	Poor
Basal ganglia	5	12.8	1	4	1	4
Cerebellum	6	15.4	5	1	5	1
Lobe	24	61.5	14	10	15	9
Pons	2	5.1	0	2	0	2
Thalamus	2	5.1	1	1	1	1
Total	39	100.0	21	18	22	17

*p value at discharge: 0.351, 6 months later: 0.261, by cross tabulation.

predicted a higher risk of death within 2 days (odds ratio, OR = 3.9).[7] Among patients with a pre-hospital neurological decline, the GCS score was lower by an average of 6 points, and the mortality rate was 75%.[15] The usefulness of surgical treatment of ICH is still under debate.[8] In this study, there was no statistically significant difference in prognosis between patients who did or did not receive surgical treatment (p = 0.109).

ICH is rare in young adults aged ≤ 40 years; thus, the existing large-scale studies are not sufficient for studying either etiology or prognosis in this group of patients. Due to the small number of patients and limited study period, it is difficult to obtain statistically significant data for this group. More accurate and reliable outcome results could be obtained be comparative analysis of across several institutions and groups in the regional community. In this study, smoking, serum cholesterol, SBP on admission, and the initial GCS were significant prognostic factors. Some of these factors are modifiable in young patients through changes in daily habits. Therefore, efforts to control these factors could be helpful.

CONCLUSION

Cryptogenic ICH was the most common cause of ICH in this study. AVM was the most common structural etiology of non-traumatic spontaneous ICH in the patients aged ≤ 40 years. Eight points or more on the initial GCS, SBP < 160 mmHg, serum cholesterol < 200 mg/dl, and low initial SBP indicated a good prognosis. A history of smoking was associated with a good prognosis in this study, although, the initial GCS score influenced this result.

Our study had some limitations, including its retrospective nature, its involvement of a single institution, the small number of cases, and the relatively short follow-up periods. Thus, longer follow-up periods in prospective, multi-institutional studies that include large numbers of patients are necessary to better understand the prognosis of ICH in young adults.

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