

Original Paper

Predictors of the Intracerebral Hemorrhage Volume in Hypertensive Patients

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Key Words

Brain hemorrhage • Coagulation profile • Hemorrhage volume • Hypertension • Intracerebral hemorrhage • Warfarin

Abstract

Background: Hemorrhage volume is an important predictor of outcome in patients with intracerebral hemorrhage (ICH). It is not clear why in some patients ICH volume is larger than in others. Identification of modifiable factors responsible for large-volume hemorrhage in hypertensive patients may help to reduce ICH-related morbidity and mortality. **Objective:** The objective of this study was to identify predictors of large-volume ICH in hypertensive patients. **Methods:** At a tertiary care center in Karachi (Pakistan), 157 hypertensive patients with ICH were prospectively analyzed in 2008–2009, and hemorrhage volumes were determined using CT or MRI and various factors, including duration of hypertension, medical treatment, compliance, co-morbidity, and hematologic and coagulation profiles. Logistic regression analysis was used to identify predictors of high-volume hemorrhage. A volume $>30 \text{ mm}^3$ was defined as high-volume hemorrhage. **Results:** Of 157 patients with hypertensive ICH evaluated, 133 patients were included in the study, and 24 patients with brain stem, cerebellum and pure intraventricular hemorrhage were excluded. The mean age of the study patients was 55 years; 56 patients (70%) were male. High-volume hemorrhage ($>30 \text{ mm}^3$) was noted in 47 (35%) patients. Mortality was significantly increased in patients with high-volume ICH (32 vs. 6% in patients with low-volume ICH). In univariate analysis, factors significantly associated with large-volume ICH were male gender ($p = 0.002$), hypertension lasting >10 years ($p = 0.03$), warfarin treatment ($p = 0.05$), use of >1 anti-hypertensive agent ($p = 0.001$) and poor compliance with medication ($p = 0.001$). In multivariate analysis, use of >1 anti-hypertensive agent and poor compliance were also predictors of

large-volume ICH. **Conclusion:** High-volume hemorrhage was less common (28%) in our patients with hypertension and ICH. Use of >1 anti-hypertensive agent and poor compliance were predictors of large-volume ICH.

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Introduction

Intracerebral hemorrhage (ICH) is the cause of stroke in about 30–40% of stroke patients in Pakistan [1]. The hemorrhage volume is an important predictor of outcome in ICH patients [2], and it is well known that an increased hemorrhage volume in ICH patients is associated with increased functional disability and mortality. One study demonstrated that the predicted 30-day mortality was 93% for ICH volumes >60 mm³, 64% for those from 30 to 60 mm³ and 19% for those <30 mm³ [3]. In another study, warfarin treatment in patients with INR >3.0 was associated with larger ICH volumes [4]. Apart from anticoagulation, it is not well known why some patients have large-volume and others small-volume hemorrhage. Relationships between ICH volume and duration of hypertension, number and types of anti-hypertensive medications, drug compliance and blood pressure (BP) control 3–6 months prior to the ICH event have not been elucidated yet.

Identification of modifiable factors associated with large-volume hemorrhage in hypertensive patients may help to reduce morbidity and mortality related to ICH. Therefore, the objective of this study was to identify predictors of large-volume ICH in hypertensive patients.

Methods

We prospectively analyzed 157 consecutive hypertensive patients admitted for ICH in 2008–2009 at the Aga Khan University, a tertiary care center in Karachi, Pakistan. Their ICH volumes were assessed using CT or MRI, and various factors, including duration of hypertension, medical treatment, compliance, co-morbidity, and hematologic and coagulation profiles, were determined. An ICH volume >30 mm³ was defined as high-volume ICH, which was calculated using Broderick's method [3, 5].

Hypertension was defined as a history of hypertension, BP >140 (systolic) and/or >90 (diastolic) mm Hg on ≥3 measurements during hospitalization or treatment with anti-hypertensive drugs. Diabetes mellitus was defined as a history of diabetes mellitus and fasting serum glucose levels >110 mg/dl, or treatment with insulin or hypoglycemic drugs. Dyslipidemia was defined as a fasting total blood cholesterol ≥200 mg/dl and/or LDL cholesterol ≥100 mg/dl and/or triglycerides ≥150 mg/dl. Patients smoking ≥10 cigarettes/day for >10 years were classified as smokers. Patients or immediate family members were asked about the use of anti-hypertensive medications, compliance to these medications and quality of BP control at home prior to admission. Patients were regarded as non-compliant if they did not take half or more of their anti-hypertensive medication during the preceding month. BP control was classified as poor if BP was >140 (systolic) and/or >90 (diastolic) mm Hg on >50% of home measurements despite taking anti-hypertensive medication during the 1-month period preceding the ICH event.

The χ^2 test and Student's t test were used to compare both groups regarding baseline characteristics and outcome. Based on the findings in univariate analysis, a logistic regression model was built to identify predictors of high-volume ICH.

The study protocol was approved by the local ethical review committee of the hospital.

Table 1. Predictors of high-volume (>30 ml) hemorrhage in univariate analysis

Patient characteristics	Patients, n (%)		Odds ratio (95% confidence interval)	p value
	ICH ≤30 ml	ICH >30 ml		
Patients evaluated	86 (65)	47 (35)		
Age <60 years	50 (58)	34 (72)	0.53 (0.24–1.14)	0.10
Male gender	48 (55.8)	38 (80.9)	3.34 (1.44–7.75)	0.005
Duration of hypertension				
>10 years	43 (50)	13 (27.7)	0.39 (0.16–0.92)	0.07
Anti-hypertensive treatment				
1 anti-hypertensive agent	34 (40.5)	16 (35.6)	0.39 (0.17–0.90)	0.069
≥2 anti-hypertensive agents	7 (8)	24 (51)	14.92 (3.46–45.57)	<0.001
Poor compliance	8 (9.3)	17 (36.2)	10.09 (2.57–39.60)	0.001
BP control				
Regular home monitoring	74 (86)	35 (74.5)	0.47 (0.19–1.15)	0.10
Poor during the last month	64 (74.4)	40 (85.1)	0.50 (0.19–1.30)	0.15
By a physician during the last 3 months	10 (11.6)	8 (17)	1.55 (0.57–4.26)	0.38
Diabetes mellitus	16 (19)	7 (15)	0.73 (0.35–1.96)	0.09
Duration >10 years	5 (6)	2 (4)	0.51 (0.22–0.97)	0.098
Blood glucose >150 mg/dl on admission	14 (16)	5 (10)	0.97 (0.35–2.13)	0.63
Dyslipidemia	8 (9)	3 (6)	0.55 (0.11–1.19)	0.11
Statin treatment at home	3 (4)	1 (2)	0.21 (0.09–0.87)	0.22
Smoking status	13 (15)	7 (15)	0.47 (0.11–1.25)	0.9
Medication				
Anti-platelets	35 (41)	14 (30)	1.02 (0.54–3.15)	0.06
Warfarin	2 (2)	6 (13)	7.55 (1.24–19.55)	0.05
Platelet count <50,000 on admission	8 (9)	3 (6)	0.83 (0.31–2.01)	0.09
INR >3.0 on admission	1	5 (10)	10.50 (2.25–31.45)	0.04

Results

Of the 157 hypertensive patients with ICH analyzed, 133 patients were included in the study. We excluded 24 patients with brain stem, cerebellum and pure intraventricular hemorrhage, because the volume-outcome relationship of ICH in these brain areas could be different from basal-ganglia, thalamic or lobar ICH.

Mean age of the patients was 55 years (range 19–85 years), and 56 patients (70%) were male. Diagnosis of hypertension was known in 119 (89%) patients, while 14 (11%) were unaware of their diagnosis. Duration of hypertension was >10 years in 56 (42%) patients. Only 81 patients (61%) were on any anti-hypertensive medication: 50 (38%) were treated with 1 anti-hypertensive drug while 31 (23%) were on ≥2 anti-hypertensive drugs. We were able to retrieve the history of compliance with anti-hypertensive medication for the 1-month period preceding ICH in 46 patients (35%), and 25 (19%) were poorly adherent to their medication.

Other co-morbidities included diabetes (23; 17%), dyslipidemia (11; 8%) and cigarette smoking (20; 15%). Anti-platelet medication was taken by 49 (37%) patients, while 8 (6%) patients were on warfarin.

CT scans were performed within 24 h of symptom onset in all patients. ICH were located in the basal ganglia and thalamus in 98 (74%) patients, and lobar ICH was noted in 35 (26%) patients. The mean ICH volume was 26 mm³ (range 8–96 mm³), ranging from 23 mm³ in basal ganglia/thalamus to 29 mm³ in lobar areas. This difference was not statistically significant (p = 0.09). ICH volume was <30 mm³ in 86 (65%) patients, while 47 (35%) patients had high-volume ICH (> 30 mm³). Mortality was significantly higher (32%) in patients with high-volume ICH compared to patients with low-volume ICH (6%).

Table 2. Predictors of high-volume (>30 ml) hemorrhage in multivariate analysis

Patient characteristics	Adjusted odds ratio (95% confidence interval)	p value
Male gender	2.85 (0.99–8.23)	0.06
Treatment with ≥ 2 anti-hypertensive agents	19.55 (3.01–54.43)	0.002
Poor compliance with anti-hypertensive medication	17.85 (3.17–43.86)	0.005
Warfarin use	9.67 (2.53–37.87)	0.02
INR >3.0 on admission	12.59 (2.94–44.89)	0.01

Male gender ($p = 0.005$), use of warfarin ($p = 0.05$), INR >3.0 on admission ($p = 0.04$), use of >1 anti-hypertensive agent ($p = 0.001$) and poor compliance with medication ($p = 0.001$) were associated with large-volume ICH in univariate analysis (table 1).

In multivariate analysis, predictors of large-volume ICH were use of >1 anti-hypertensive agent and poor compliance (table 2).

Discussion

These findings indicate that more than one third of patients in this tertiary hospital referral setting had high-volume ICH, and use of ≥ 2 anti-hypertensive agents and poor compliance with anti-hypertensive medication were the strongest predictors of high-volume hemorrhage. Patients treated with ≥ 2 anti-hypertensive drugs most likely represent aggressive forms of hypertension, and non-compliance is probably associated with sustained uncontrolled BP. These findings may also be a sign of more careful management of hypertension (despite lesser compliance) by doctors. They may also suggest that during acute bleeding, the presence of more vasoplegic medication triggers a longer and more intense hemorrhage, or that a lower BP in the acute phase is associated with lower intracranial pressure (compared with patients with higher BP), resulting in prolonged and larger bleeding. Poor compliance with warfarin, in addition to anti-hypertensive medication, may be associated with an increased risk of hemorrhage.

Morbidity and mortality related to high-volume ICH could be reduced by interventions aiming to lower hemorrhage volume among these patients. It is well known from non-randomized subgroup evaluation in randomized trials (e.g. PROGRESS) and extrapolation from observation studies that aggressive BP control is associated with a lower incidence of ICH, suggesting that aggressive BP control may lead to smaller-volume hemorrhage with lower mortality. Our study confirms previous reports of a correlation between warfarin treatment and high INR and large-volume ICH [6].

A limitation of this study is its small number of study patients and limited available information regarding some aspects of BP control and medication compliance. Larger multi-center studies are required to confirm our findings.

Acknowledgment

The results of this study have been presented in preliminary form at the Annual Meeting of the American Academy of Neurology in Toronto, Ont. Canada (April 2010).

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Disclosure Statement

The authors have nothing to disclose.

References

- 1 Khealani BA, Wasay M: The burden of stroke in Pakistan. *Int J Stroke* 2008;3:293–296.
- 2 Qureshi AI, Tuhim S, Broderick JP, Batjer HH, Hondo H, Hanley DF: Spontaneous intracerebral hemorrhage. *N Engl J Med* 2001;344:1450–1460.
- 3 Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G: Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. *Stroke* 1993;24:987–993.
- 4 Flaherty ML, Tao H, Haverbusch M, Sekar P, Kleindorfer D, Kissela B, Khatri P, Stettler B, Adeoye O, Moomaw CJ, Broderick JP, Woo D: Warfarin use leads to larger intracerebral hematomas. *Neurology* 2008;71:1084–1089.
- 5 Kothari RU, Brott T, Broderick JP, Barsan WG, Sauerbeck LR, Zuccarello M, Khoury J: The ABCs of measuring intracerebral hemorrhage volumes. *Stroke* 1996;27:1304–1305.
- 6 Stead LG, Jain A, Bellolio MF, Odufuye AO, Dhillon RK, Manivannan V, Gilmore RM, Rabinstein AA, Chandra R, Serrano LA, Yerragonda N, Palamari B, Decker WW: Effect of anticoagulant and antiplatelet therapy in patients with spontaneous intra-cerebral hemorrhage: does medication use predict worse outcome? *Clin Neurol Neurosurg* 2010;112:275–281.