Regular Aspirin-Use Preceding the Onset of Primary Intracerebral Hemorrhage is an Independent Predictor for Death

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Background and Purpose—Hematoma volume and impaired level of consciousness are the most potent predictors of outcome after spontaneous intracerebral hemorrhage (ICH). The effect of preceding aspirin-use on outcome after ICH is poorly investigated. We investigated short-term mortality and hematoma enlargement in subjects with ICH to find the predictors for these outcomes.

Methods—This population-based study included all subjects with ICH during a period of 33 months in the population of Northern Ostrobothnia, Finland. The subjects were identified, and their clinical characteristics and outcomes were checked from hospital records or death records.

Results—Three-month mortality of the 208 identified subjects with ICH was 33%. The independent risk factors for death were regular aspirin-use at the onset of ICH (relative risks [RR], 2.5; 95% CI, 1.3 to 4.6; $P=0.004$), warfarin-use at the onset of ICH (RR, 3.2; 95% CI, 1.6 to 6.1; $P=0.001$), and ICH score higher than 2 on admission (RR, 13.8; 95% CI, 6.0 to 31.4; $P<0.001$). Regular aspirin-use preceding the onset of ICH associated significantly with hematoma enlargement during the first week after ICH ($P=0.006$).

Conclusions—We observed poor short-term outcomes and increased mortality, probably attributable to rapid enlargement of hematomas, in the subjects with ICH who had been taking regularly moderate doses of aspirin (median 250 mg) immediately before the onset of the stroke. (***Stroke***. 2006;37:129-133.)

Key Words: aspirin ■ cerebral hemorrhage ■ mortality ■ warfarin

Independent predictors of short-term mortality (30 days) after spontaneous intracerebral hemorrhage (ICH) include the size and location of the hemorrhage, a midline shift in head computed tomography (CT), intraventricular spread of the hemorrhage, low Glasgow Coma Scale (GCS) score on admission, and high blood glucose and blood pressure on admission.[1–6] Preceding medication and hematologic abnormalities may also predict the outcome, but their independent roles are less clear.

Many reports have demonstrated that patients on warfarin show a high mortality rate (52% to 68%) attributable to rapid enlargement of their hematomas.[7,8] Use of antiplatelet agents has not been shown to exert a similar effect, but as far as we know, only a few studies have been reported.[8–10] To resolve the role of aspirin, in particular, we investigated outcome and hematoma enlargement in a population-based cohort of patients with ICH.

Methods

We identified all subjects with ICH between January 1993 and September 1995 in the population of Northern Ostrobothnia, Finland. The study included all patients admitted into Oulu University Hospital for ICH during this period. Oulu University Hospital is the only hospital serving acute stroke patients in the area (population 356 026). ICH was verified by a head CT scan on admission in all cases. We excluded patients not living in the catchment area of the hospital and those with a brain tumor, aneurysm, vascular malformation, hematologic malignancy, hemophilia, or head trauma. The fatal cases of ICH in the community during the study period were identified from death records (Statistics Finland), but cases without verification of ICH at autopsy or by brain imaging were excluded. The study protocol was approved by the ethics committee of the hospital.

Information about previous diseases, blood pressure histories, medications, and smoking were extracted from the hospital records. Data were extracted from the forensic autopsy charts of those who had succumbed on the scene. Cardiac complications, infection, deep vein thrombosis, or pulmonary embolus during hospitalization were recorded, as were also neurosurgical interventions. The time of ICH onset was defined to be the acute onset of headache or a neurological deficit.

The subjects were considered to be hypertensive if their blood pressure readings preceding the index stroke had repeatedly exceeded 160/95 mm Hg, or if they were taking antihypertensive medication. The patients were recorded as having diabetes mellitus if they used oral hypoglycemic agents or insulin. Previous hemorrhagic

and ischemic strokes were recorded. Cardiac disease included myocardial infarction, coronary artery disease, heart failure, and atrial fibrillation. Gastrointestinal bleeding and hematuria in the patients' history were recorded. Subjects were categorized into current cigarette smokers and nonsmokers.

The ICH score[11] was calculated on the basis of the GCS score[12] on admission, volume, supra- or infratentorial location and ventricular extension of the hematoma, and the patient's age. The scores were classified into 3 categories: zero (0 points), low (1 to 2 points), and high (3 to 6 points). The patients' survival during the first 3 months after the onset of ICH was checked from hospital records and death records. Functional outcome at 3 months was assessed according to the Glasgow Outcome Scale[13] on scheduled control visits ≈3 months after the ICH. Those who showed good recovery at discharge were assumed to maintain this state at 3 months, unless they had been readmitted.

All CT scans were reanalyzed and the locations and volumes of hematomas measured by the same neuroradiologist (J.P.) who was blind to the medications and outcomes of the patients. Hematomas were divided into categories based on their location. The volumes of the hematomas were measured following previously described principles.[14] The volumes were measured on a workstation by encircling the boundaries of each hematoma with a pointer slice by slice and thereby determining its area. The area was multiplied by slice thickness (5 mm in posterior fossa and 10 mm supratentorially) to obtain the volume. The presence of intraventricular bleeding was recorded. Possible enlargement of the hematoma was assessed in the patients who received a second CT scan within a week after the onset of ICH. For statistical analysis, relative enlargement (by percent) of hematomas were calculated. A second CT scan was always obtained if clinical deterioration occurred, except for those patients who were already moribund on admission.

Categorical variables were compared by Fisher exact 2-tailed test and the Pearson χ^2 test. Continuous variables were compared between the groups by the Mann-Whitney U-test, Student t test, and ANOVA. For life table analysis and the Cox proportional hazards regression model, each patient was followed to death or until 3 months after ICH. Cumulative survival rates were estimated by the Kaplan-Meier product-limit method, and the curves of the different groups were compared by the log-rank test. The Cox proportional-hazards model with a forward stepwise-regression procedure served to determine the significance of several variables in predicting relative risks (RR) and 95% CI for death. The following variables, which were known at the beginning of follow-up, were analyzed: age; sex; history of hypertension, ischemic or hemorrhagic stroke, cardiac disease, diabetes, and cancer; ICH score; warfarin treatment; regular aspirin-use; bleeding disorders; and current smoking. The assumption of proportionality was checked. The test for significance was based on changes in log (partial) likelihood. A 2-tailed probability value of <0.05 was considered to be statistically significant.

Results

We found altogether 208 subjects with a verified spontaneous ICH during the study period, and the crude annual incidence rate was 21/100 000. The baseline characteristics of the subjects are shown in Table 1. Two hundred and three patients were admitted into our hospital, and the diagnosis was verified by a head CT scan. Five subjects succumbed elsewhere, and their diagnoses were verified at autopsy. The aspirin users were significantly older than nonusers of aspirin/warfarin ($P=0.004$). History of cardiac disease ($P<0.01$) and ischemic stroke ($P<0.01$) were more common in the group of aspirin/warfarin users than in the nonuser group.

The clinical characteristics and outcomes are shown in Table 2. On admission, aspirin users did not have larger hematomas than nonusers of aspirin/warfarin, but warfarin users had significantly larger hematomas than aspirin users ($P=0.015$) and nonusers of aspirin/warfarin ($P=0.012$). CT scanning was performed on the day of symptom onset in 73% of aspirin users, 76% of warfarin users, and 70% of nonusers of aspirin/warfarin. The groups differed significantly by outcome at 3 months ($P<0.001$) and bleeding into the ventricles ($P=0.001$), the latter finding being most frequent in warfarin users. In the 47 patients with ICH score >2, 55% had GCS score 3 to 4, 40% had GCS score 5 to 12, 74% had hematoma volume ≥30 cm³, 89% had intraventricular and 13% had infratentorial hemorrhage, and 28% were aged ≥80 years.

The primary bleed was the cause of death in 17 (89%) of the 19 fatalities in the group of aspirin users. The 2 others died of pneumonia and pulmonary embolism. Among warfarin users, the cause of death was the primary bleed in 18 cases (95%), and 1 patient died of thrombosis of the abdominal

TABLE 1.   Baseline Characteristics of 208 Subjects With Spontaneous ICH

Characteristics	No Aspirin or Warfarin (n=138)	Aspirin Users (n=44)	Warfarin Users (n=26)*	Total (n=208)
Men, n (%)	68 (49)	22 (50)	11 (42)	101 (49)
Mean age, y (SD)	65.6 (11.1)	71.6 (11.2)	70.0 (11.1)	67.4 (11.4)
Mean BMI, kg/m² (SD)	27.4 (5.9)	27.4 (5.6)	26.8 (6.5)	27.3 (5.8)
Previous diseases, n (%)				
Hypertension	79 (57)	29 (66)	19 (73)	127 (61)
Hypertension untreated	29 (21)	7 (16)	0	36 (17)
Cardiac disease	44 (32)	26 (59)	22 (85)	92 (44)
Ischemic stroke	12 (9)	19 (43)	11 (42)	42 (20)
Hemorrhagic stroke	14 (10)	6 (14)	0	20 (10)
Gastrointestinal bleeding	9 (7)	5 (11)	5 (19)	19 (9)
Hematuria	7 (5)	3 (7)	3 (12)	13 (6)
Cancer	15 (11)	6 (14)	2 (8)	23 (11)
Diabetes mellitus	12 (9)	8 (18)	2 (8)	22 (11)
Current smoking	15/115 (13)	5/37 (14)	3/23 (13)	23/175 (13)

*One subject in the warfarin group also was regular aspirin user.

TABLE 2. Clinical Characteristics and Outcome in 208 Subjects With Spontaneous ICH

Characteristics	No Aspirin or Warfarin (n=138)	Aspirin Users (n=44)	Warfarin Users (n=26)	Total (n=208)
Median volume of ICH, mL (25th and 75th percentiles)	20 (7, 39)	16 (6, 48)	50 (16, 112)	21 (7, 45)
Intraventricular hemorrhage (%)	54 (39)	11 (25)	18 (69)	83 (40)
Mean MAP*, mm Hg (SD)	126 (24)	127 (21)	132 (22)	127 (23)
Mean blood glucose on admission, mmol/L (SD)	8.0 (3.7)	8.9 (4.7)	9.9 (8.6)	8.4 (4.8)
Mean platelet count on admission, $10^3/\mu$L (SD)	264.4 (79.0)	261.8 (68.7)	247.4 (63.0)	262.0 (75.0)
Location of hematoma, n (%)				
Subcortex	44 (32)	10 (23)	9 (35)	63 (30)
Basal ganglia (and combined†)	59 (43)	20 (45)	11 (42)	90 (43)
Thalamus	15 (11)	6 (14)	3 (12)	24 (12)
Cerebellum and pons	20 (14)	8 (18)	3 (12)	31 (15)
ICH Score, n (%)				
0	38/132 (29)	14/43 (33)	4/24 (17)	56/199 (28)
1 to 2	69/132 (52)	20/43 (47)	7/24 (29)	96/199 (48)
>2	25/132 (19)	9/43 (21)	13/24 (54)	47/199 (24)
Glasgow Outcome Scale at 3 mo, n (%)				
Good recovery	39 (28)	11 (25)	2 (8)	52 (25)
Moderate disability	24 (17)	2 (5)	1 (4)	27 (13)
Severe disability or vegetative state‡	45 (33)	12 (27)	4 (15)	61 (29)
Dead	30 (22)	19 (43)	19 (73)	68 (33)
Enlargement of hematoma§, n (%)	6/78 (8)	4/21 (19)	1/5 (20)	11/104 (11)
Mean enlargement of hematoma, % (SD)	4.8 (16.1)	12.8 (22.6)	10.6 (16.8)	6.7 (17.7)

*Mean arterial blood pressure on admission; †Extension of putaminal hematoma into thalamus and subcortical white matter; ‡Noone remained in a vegetative state; §By ≥33%.

aorta. Thirty nonusers of aspirin/warfarin died within 3 months, the causes of death being the primary bleed in 24 cases (80%) and pneumonia, myocardial infarction, and gastrointestinal bleeding in 3, 2, and 1 cases, respectively.

A second CT scan was available for 104 patients. Median time interval between the baseline and the second CT scan was 7 days (25th and 75th percentiles, 4 and 9). Regular aspirin-use preceding the onset of ICH associated significantly with relative hematoma growth (by percent; P=0.006; Mann-Whitney U-test). We also dichotomized hematoma enlargement as previously reported (≥33%).[9,15] In this analysis, the association of aspirin-use with hematoma enlargement did not reach statistical significance, probably attributable to the limited number of aspirin users with a second CT scan. A nearly significant correlation between hematoma enlargement and mortality was observed (P=0.087). However, 8 aspirin users (18%) died within 4 days after the onset of ICH without a second CT scan. Most warfarin users had large hematomas on admission already, and 16 (62%) of them died within the first 4 days without a second CT scan. Because of the small number of warfarin users with a second CT scan, the association between warfarin-use and hematoma enlargement did not reach statistical significance (P=0.082). The 4-day mortality of non-users of aspirin/warfarin was 11% (15 patients).

The cumulative survival rates are shown in the Figure. Overall mortality within 3 months was 32.7%. The mortality rates of aspirin users, warfarin users and nonusers of aspirin/warfarin were 43.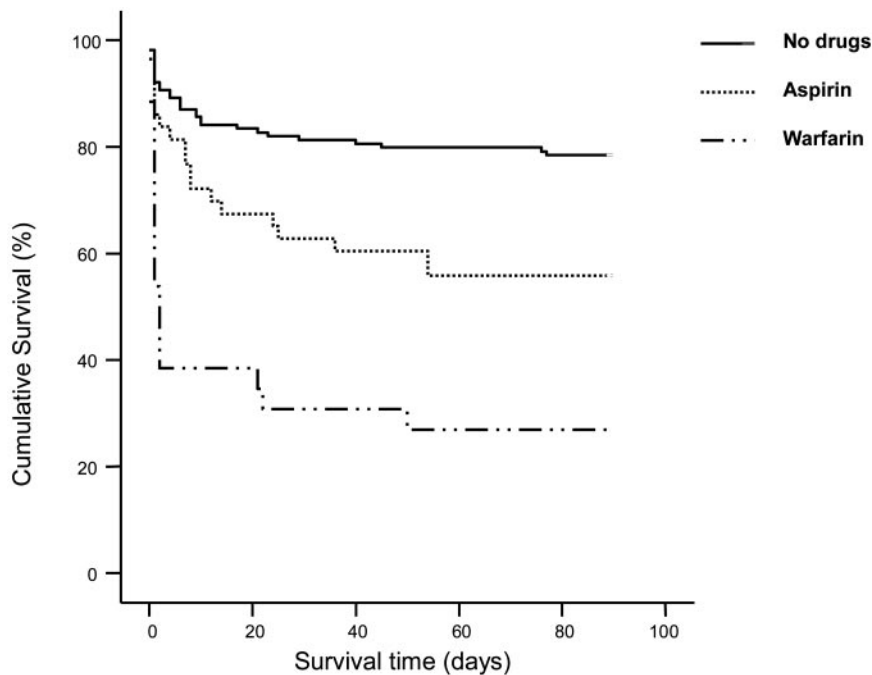2%, 73.1% and 21.7%, respectively. The log-rank test revealed significant differences between the survival curves of aspirin users and nonusers of aspirin/warfarin (P=0.0048) as well as between warfarin users and nonusers of aspirin/warfarin (P<0.0001) and between aspirin users and warfarin users (P=0.0026). Univariate and multivariate RRs of the significant predictors of death during the first 3 months after the onset of ICH are shown in Table 3.

The median daily dose of aspirin used was 250 mg (range, 50 to 500). There was no significant difference in the aspirin doses of the patients who died within 3 months after their ICH and of those who survived (P=0.58). Nor were there significant differences in mean platelet count between the study groups or between the survivors and those who died. The mean international normalized ratio (INR) of warfarin users on admission was 3.8±1.8 (range 1.5 to 7.8). The difference between the INRs of the warfarin users who died within the first 3 months after ICH and of the survivors was not significant (P=0.43).

Discussion

This population-based study indicated that regular aspirin use before the onset of primary ICH was a significant independent predictor for death within the first 3 months after the index stroke. This is a novel finding. Other significant predictors for death were warfarin-use and a high ICH score on admission.

We found 2-fold 3-month-mortality in aspirin users compared with nonusers of aspirin/warfarin. The deaths of aspirin

Three-month survival of 208 subjects with ICH according to use of aspirin or warfarin (nonusers of aspirin/warfarin, n=138; aspirin users, n=44; warfarin users, n=26).

users were attributable to ICH, except in 2 cases. On admission, aspirin-related hemorrhages were of the same size as those seen in nonusers of aspirin/warfarin. Other investigators have also reported that the baseline hematoma size in patients using platelet-inhibiting drugs is no greater than that in patients not using such drugs.[9] In our study, aspirin-use significantly associated with hematoma growth, which has been shown to be an independent factor increasing mortality after ICH.[16]

We believe that the untoward effect of aspirin-use on short-term outcome was attributable to early enlargement of hematomas in aspirin users. However, we were unable to prove this hypothesis because a second CT scan was available for only 104 patients. On the other hand, mortality during the first 4 days after the onset of ICH was higher (18%) in aspirin users than in nonusers of aspirin/warfarin (11%), despite the fact that aspirin users did not have larger hematomas on admission than nonusers of aspirin/warfarin. The cause of death in these cases may have been early hematoma growth. Alternatively, use of aspirin may have emerged as a risk factor for death after ICH attributable to a proxy effect of several factors associated with its use, like patient age,

diabetes and history of cardiac disease and ischemic stroke, although these were not solitary independent risk factors.

Previous studies have not found recent use of antiplatelet agents to associate with an increased risk of hematoma expansion[9] or higher mortality.[8-10] However, in the 2 hospital-based studies,[8,9] the most potent antiplatelet drug, aspirin, was not distinguished from other nonsteroidal anti-inflammatory drugs (NSAIDs). In the population-based study by Nilsson et al,[10] a nonsignificant trend for aspirin to predict mortality may be seen after omitting warfarin users. In the Swedish Aspirin Low-dose Trial (SALT), there was a significant increase in the risk of fatal hemorrhagic strokes among the aspirin (75 mg/day) users.[17] A plausible explanation for the increased mortality of aspirin users would be more frequent hematoma enlargement caused by impaired hemostasis during the first few days after the onset of ICH. We recently observed prolonged bleeding times on admission in ICH patients who had been using aspirin, and even after the discontinuation of aspirin, the effect of the drug on hemostasis continued for a few days.[18] The high 3-month mortality in warfarin users reflects the facts that most of them showed large hematomas on admission and no effective measure to reverse the anticoagulant effect was used.

Hematoma volume is a potent predictor of mortality and functional outcome.[2,4,5,11] Decreased blood coagulability,[19,20] increased blood pressure,[8] liver disease,[20] thrombocytopenia,[20] insufficient thrombin generation,[19] and elevated INR value[20] may all foster hematoma enlargement. This list may also include insufficient platelet function induced by aspirin, but the risk of aspirin-use should be weighed against each individual's need for medication and the possible risks of alternative medications. It has been suggested that ongoing enlargement of ICH might be detected on the basis of extravasation of radiographic contrast into the hematoma after CT angiography.[21]

TABLE 3. Predictors for Death Within the First 3 Months After ICH

Variable	Univariate RR (95 % CI)	Multivariate RR* (95% CI)
ICH Score >2 on admission	14.5 (6.5–32.5)†	13.8 (6.0–31.4)†
Warfarin use preceding ICH	3.9 (2.1–7.2)†	3.2 (1.6–6.1)‡
Regular aspirin use preceding ICH	2.5 (1.4–4.6)‡	2.5 (1.3–4.6)‡
Diabetes	2.4 (1.2–4.8)§	2.1 (0.99–4.3)

*RRs have been adjusted for age, sex, and the variables listed in the table; †$P<0.001$; ‡$P<0.01$; §$P<0.05$.

Our findings suggest that prevention of hematoma growth may be needed if aspirin has been used by the ICH patient. In patients on warfarin, emergent reversal of anticoagulation is needed as quickly as possible.[7] In aspirin-associated ICH, reversal of the antiplatelet effect of aspirin by platelet transfusions could be attempted. Platelet transfusion has been recommended in life-threatening ICH attributable to autoimmune thrombocytopenia.[22] However, we need further studies to prove that early hematoma growth leads to increased mortality in aspirin users and that platelet transfusion is efficient and safe as a preventive measure.

The strength of our study is that it was based on a defined population. We included all patients admitted into our hospital because of ICH during the study period, without selection based on, for example, the delay before CT scanning. Because there are no other hospitals in the area admitting acute stroke patients, and such patients are recommended to be immediately referred to our hospital, we believe we were able to avoid selection bias. In addition, we identified the subjects with ICH who died during the study period without ever reaching the hospital. Of these, we included only the patients with ICH confirmed at autopsy. However, the strict inclusion criteria may result in underestimation of the real incidence rate of spontaneous ICH in the population. The lack of systematic second CT scanning of the patients who died soon after the index stroke is a limitation of the study. Those with only a single CT scan had significantly higher mortality (79.4% versus 20.6%) than those with several CT scans. This is likely to result in underestimation of the frequency of hematoma expansion in the cohort. Also, the delay between symptom onset and the first CT scan was rather crudely estimated. The use of 10 mm CT sections in the supratentorial region introduces a degree of measurement error. On the other hand, the imaging protocol was the same in all primary and repeat scans, which are thus comparable. We did not record occasional use of aspirin, which is another limitation. Consequently, some patients classified as nonusers of aspirin/warfarin may have ingested aspirin just before the stroke, which may have worsened their outcome. Such misclassification might underestimate aspirin-associated mortality.

In conclusion, aspirin doubled the 3-month mortality of ICH patients compared with nonusers of aspirin/warfarin. Aspirin-use also associated with early hematoma growth. The observations allow us to hypothesize that aspirin-use may predispose to hematoma enlargement. Whether the benefits of interventions such as platelet transfusion outweigh the risks in aspirin-associated ICH requires further study.

Acknowledgments

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