Secondary Intracranial Hemorrhage After Mild Head Injury in Patients With Low-Dose Acetylsalicylate Acid Prophylaxis

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Background: Low-dose acetylsalicylate acid (LDA) therapy is accepted as a major risk factor for intracranial hemorrhages (ICH) in head injuries. Coincidentally, patient admissions that might be indicated for in hospital observation of neurologic function causes increased health care costs. In the literature, there is no evidence concerning the incidence of secondary intracranial hemorrhagic events (SIHE) in patients with LDA prophylaxis that had negative primary computed tomography (CT)-scan of the head.

Methods: In this prospective study, we enrolled 100 consecutive trauma patients older than 65 years presenting in a Level I urban trauma center after a mild head injury (Glasgow Coma Scale score of 15) who had LDA prophylaxis. Patients included had a negative primary head CT-scan concerning ICH. For analysis of the incidence of SIHEs patients had routine repeat head CT (RRHCT) after 12 hours to 24 hours.

Results: Sixty-one patients were women and 39 men. Mean age was 81 years ± 10 years. Injury mechanism was a level fall in 84 cases and others in 16. In four patients (4%) an SIHE was detected in the RRHCT ($p < 0.00001$). In two patients (2%) major secondary ICH had occurred without neurologic deterioration at the time of RRHCT with fatal outcome in one patient and neurosurgical intervention in another. The remaining two patients (2%) had minor SIHE with an uneventful clinical course.

Conclusion: The incidence of SIHE has been neglected until now. The current study revealed that patients with LDA prophylaxis after mild head injury with negative primary head CT should be subjected to RRHCT within 12 hours to 24 hours to accurately identify SIHE. Alternatively to RRHCT, patients should be subjected to a prolonged in-hospital observation for at least 48 hours.

Key Words: Mild head injury, Low dose aspirin, Head computed tomography, Glasgow Coma Scale, Secondary intracranial hemorrhagic event.

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Prophylactic oral anticoagulation with low-dose aspirin is widely used for patients suffering from cardiovascular disorders, such as ischemic heart disease and cerebrovascular disease, as well as for any man aged >45 years who has at least two cardiac risk factors.[1] The pharmacological effect of aspirin in a dose of 100 mg/d is reduction of the amount of thromboxane A2[2] with consecutive diminishing platelet aggregation with prolongation of both bleeding and thrombin time.[3]

The correlation between aspirin ingestion and intracranial hemorrhages (ICHs) in patients with head injuries was reported by Reymond et al.,[4] and emphasized by Ohm et al.,[5] who observed a higher mortality in patients sustaining traumatic ICH taking antiplatelet agents as aspirin, clopidogrel, or both in combination compared with matched control patients not taking antiplatelet agents (23 vs. 9%). Thus, older patients who are already at greater risk for head injuries[6] and often taking low-dose acetylsalicylate acid (LDA) on a regular basis constitute a selected group of patients that might indicate particular attention at the emergency department. Spektor et al.[7] invalidated this theory for patients sustaining mild or moderate head injury. The authors compared patients older than 60 years of age receiving LDA prophylaxis and controls who did not received after mild or moderate head injury. The study showed that LDA did not increase surgically relevant parenchymal or meningeal bleeding in this group of patients. None of the patients in both groups with a Glasgow Coma Scale (GCS)[8] score 15 admitted to the emergency room required surgery. No data on secondary intracranial hemorrhagic events (SIHEs) are reported by the authors.

At present, there is a lack of evidence regarding the incidence of SIHEs in patients taking LDA prophylaxis and having mild head injury. At the authors' department all patients with an age more than 65 years taking regular LDA are admitted after mild head injury for at least 24 hours neurologic observance. This treatment rationale requires considerable consumption of medical resources and costs.

The purpose of the current study was to reduce the number of admissions of patients older than 65 years of age with LDA prophylaxis after mild head injury with GCS Score of 15 at the time of admission. The hypothesis was stated that patients 65 years of age and older with a negative primary head computed tomography (CT)-scan would have an uneventful course with a negative follow-up head CT-scan after a minimum of 12 hours. That is, there is no secondary hemorrhage on a follow-up head CT-scan in LDA patients that had a negative primary head CT-scan.

MATERIALS AND METHODS

Prospective study at a Level I trauma center between July 2007 and November 2008. All patients with 65 years of age and older taking regular LDA prophylaxis were included

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if admitted at our emergency department and indication for neurologic observation after mild head injury was set. Accordingly, patients were included in the study with routine repeat head CT (RRHCT) if they fulfilled the following criteria: (1) ≥65 years, (2) regular low-dose therapy (100 mg/d) with aspirin (independent from the indication), (3) isolated mild head injury with a GCS score of 15, (4) primary negative head CT, and (5) no hypertensive irregularities (systolic blood pressure <150 mm Hg).

Patients who received other anticoagulant medications as warfarin, coumarin, clopidogrel, or nonsteroidal anti-inflammatory drugs, and patients with hematological or oncological diseases and moderate or severe head injuries were not included in the study.

In the study period 109 patients with an age of 65 years or older sustaining mild head injury under LDA therapy had been admitted at our department. The primary head CT revealed ICH in nine patients. None of these patients required acute neurosurgery. Thus, 100 patients fulfilled the inclusion criteria with a negative primary head CT.

Usually, mild head injury is defined according a GCS score of 13 to 15.[9] However, a significantly increased overall risk for patients with GCS 13 to 14 compared with patients with GCS 15 has been reported.[10] Thus, the situation for patients with GCS 13 to 14 is more serious, which led us, for reasons of medicolegal safety, to think about a home care strategy only in patients with a GCS score of 15. These patients also constitute the vast majority with mild head injury.[11]

On admission to the emergency department, all patients underwent a general physical and neurologic examinations, a routine laboratory test with determination of the coagulation parameters and a radiologic evaluation by head CT-scan. The axial CT-scans were performed without contrast injection using a 16-slice CT scanner (Siemens Somatom Emotion 16, Siemens, Erlangen/Germany). The CT findings were reviewed without delay by an in-house attending senior radiologist. The patients were placed under observation for 24 hours with hourly control of vital signs including measurement of the blood pressure, evaluation of the consciousness and pupil function. During the next day a RRHCT scan was performed with a minimum time interval of 12 hours from index CT-scan. In case of no evidence for SIHE, patients were discharged home.

Both, initial and follow-up head CT scans from all patients were evaluated for study purposes a second time by the same senior radiologist who was blinded to the clinical status. The study was IRB approved, and all patients gave informed written consent to participate in this study.

For statistical analysis, the one-sample binomial test was used to test whether the probability for an SIHE was of statistical significance and the corresponding 95% Clopper-Pearson confidence interval was computed. A p value less than 5% indicated a statistical significant effect. All data analyses were done with StatXact 7.0 (Cytel Software Corporation in Cambridge, MA).

RESULTS

One hundred patients had RRHCT to exclude an SIHE. The mean age was 81 years ± 10 years. There were 61 women and 39 men. All patients had sustained mild head injury and presented with a GCS of 15 at the emergency room according to the inclusion criteria. Reason for the use of LDA prophylaxis included coronary artery disease (46%), cerebral vascular accident or transient ischemic attack (26%), atrial fibrillation (7%), and unknown (21%). Mechanism of head injury included level fall in 84 patients, fall from sitting or lying position in 12, car accident in 3, and bicycle crash at low velocity in one. Forty-three patients presented with superficial skull injuries to the soft-tissues including wounds and lacerations.

The time interval between head injury and initial head CT was less than 3 hours in 91 patients, and between 3 hours and 16 hours (average 6.4 ± 3.9 hours) in 9. The mean time interval between initial head CT and RRHCT was 19 hours ± 9 hours with a minimum 12 hours (range, 12–37 hours). The mean platelet count was 228.943 ± 73.512 in patients without SIHE versus 199.500 ± 59.369 in those with, which yielded not statistical significance ($p > 0.05$). Platelets were not given in any of the patients during in hospital treatment. The differences between the group without SIHEs (96 patients) and the four patients with a positive RRHCT are itemized in Table 1.

Four patients revealed an SIHE in the RRHCT ($p < 0.00001$, Clopper-Pearson interval 95% CI: 1.1–9.9%). The pattern of SIHE included one of each massive intraparenchymal hematoma, subdural hematoma with midline shift, intracerebral hematoma with a diameter of 2 cm, and minimal subarachnoid hemorrhage. Table 2 shows data of patients suffering SIHE. None of these patients showed clinical deterioration at the time of RRHCT. The patient with massive intraparenchymal hematoma (Fig. 1) showed progression of the SIHE (Fig. 2) with neurologic deterioration after 27 hours and fatal outcome after 4 days. The patient with a subdural hematoma with a commencing midline shift (Fig. 3) deteriorated 3 hours after RRHCT and emergency craniotomy with evacuation of the subdural hematoma was performed. He was discharged after 14 days with a good outcome. Cases 3 and 4 required no intervention with discharge after 6 and 8 days, respectively. Follow-up head CT-scans showed regression of the hemorrhages with uneventful neurologic course.

TABLE 1. Patients' Characteristics with Negative vs. Positive Secondary Head CT

	Negative RRHCT	Positive RRHCT	p
No.	96 patients	4 patients	
Age (yr)	82 ± 10	78 ± 5	0.23
Gender	59 F: 37 M	2 F: 2 M	
Mechanism	Level fall 81, car accident 3, fall from sitting position 12	Fall 3, bicycle crash 1	
GCS	15	15	
LOC	42	3	0.03
PT (70–130%)	103.2 ± 17.6	93.8 ± 15.2	0.15
PTT (26–40 s)	30.8 ± 4.9	31.3 ± 3.0	0.43
Platelets	228,943 ± 73,512	199,500 ± 59,369	0.22

LOC, loss of consciousness; PT, prothrombin time; PTT, partial thromboplastin time.

TABLE 2. Patients' Data With a Positive RRHCT

	Case 1	Case 2	Case 3	Case 4
Age/gender	84 M	80 M	75 F	72 F
Trauma mechanism	Bicycle crash at low velocity	Level fall	Fall	Fall
GCS	15	15	15	15
LOC	−	+	+	+
Time (h) injury—1st CT	<3	<3	<3	<3
Time (h) 1st CT—RRHCT	22	37	14	28
Injury pattern	Massive intraparenchymal hemorrhage	Subdural hematoma with midline shift	Intracerebral hematoma Ø 2 cm	Minimal subarachnoid hemorrhage
PT (70–130%)	95	117	75	88
PTT (26–40 s)	30	27	35	33
Platelet count	108,000	248,000	256,000	186,000
Outcome	Death	Good after craniotomy	Good	Good

M, male; F, female; LOC, loss of consciousness; PT, prothrombin time; PTT, partial thromboplastin time.

Figure 1. Case 1. RRHCT after 22 hours shows an extended ICH in the right temporal region as contre-coup lesion to the primary head impact on the left fronto-temporal region.

Figure 2. Case 1. Third head CT performed 48 hours after the injury reveals progression of ICH with a second intraparenchymal hemorrhage in the left fronto-temporal region and an additional subarachnoid hemorrhage at the right hemisphere.

DISCUSSION

To the authors' best knowledge, this is the first study to focus on the incidence of secondary ICH in patients taking regular LDA after mild head injury with a negative primary head CT. The reason for admission in this specific group of patients despite a GCS score of 15 was the presence of two main risk factors for posttraumatic complications after head injuries, which are advanced age and regular taking of LDA. These factors are well documented in the literature.[5,12,13] The background for our study was an increasing number of elderly patients taking anticoagulation agents who required admission for observation despite a negative initial head CT. The primary purpose of this study was to show that regular medication of LDA does not expose patients having a negative trauma head CT-scan after mild head injury with a GCS of 15 to an increased risk for secondary ICH. We expected a negative series of RRHCT that should warrant medicolegal justification of new treatment rationale indicating immediate discharge of patients in case of a negative initial head CT and lack of loss of consciousness. Thus, the number of patients requiring admission for neurologic observation should be reduced resulting into a considerable economic relief.

Af Geijerstam and Britton[14] published a literature review concerning adverse outcomes in patients with mild head injury that had acute head CT-scans with normal findings. Out of more than 65,000 patients, they found only three cases to be deemed to have experienced an early adverse outcome within 2 days despite a normal early CT and GCS 15 on initial presentation.[15–17] One of these was a 74-year-old man taking salicylate therapy who after a fall had no loss of

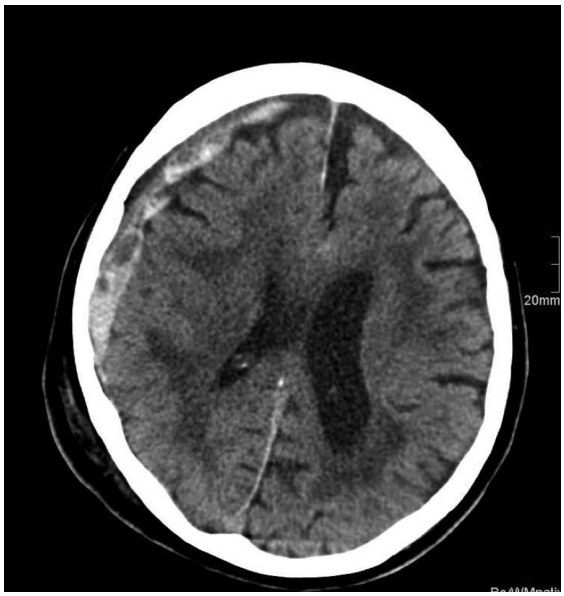

Figure 3. Case 2. RRHCT after 37 hours shows an extended subdural hematoma on the right hemisphere with small hypoechoic areas of beginning resorption of the hematoma. At the time of CT scan, the patient had a GCS of 15 without clinical signs of neurologic deterioration.

consciousness or amnesia.[17] After discharge, the patient returned 23 hours later with a GCS 3 presenting a subdural hematoma in the follow-up CT with fatal outcome. In other eight cases with incomplete descriptions, the interpretation was doubtful. The authors concluded that the strongest scientific evidence available at this time would suggest that a CT strategy is a safe way to triage patients for admission.

Velmahos et al.[18] stressed that according to the results derived from their retrospective series of 179 patients with minimal head injury that RRHCT is unnecessary. RRHCT was ordered, if the initial head CT indicated traumatic pathology. Twenty-one percent showed signs of injury evolution on RRHCT without change in management in 17%. Four percent had clinical deterioration preceding RRHCT requiring acute intervention. The authors concluded that clinical examination identifies accurately the few patients who will show significant evolution and require intervention. In that series, 20% of patients had an anticoagulation therapy at the time of admission, which was not identified as risk factor for a worse RRHCT.

The data from Spektor et al.[7] revealed no statistically significant difference in the frequency or types of ICH between patients older than 60 years of age who received aspirin prophylaxis and those who had not after minor and moderate head injury. In this prospective study including 231 patients, no information are available concerning delayed hemorrhagic complications, neither for the study group nor for the control group. However, a high percentage of patients (13.8% in the LDA group and 16.3% in the control group) presenting with excellent or good neurologic condition with an initial GCS of 15 showed some form of ICH. The most important predictor of traumatic ICH and the possible need for surgical treatment was found to be the clinical condition of the presentation in the emergency department, but without correlation to LDA therapy.

Based on the results of our study, we have to assess the clinical condition in this group of patients with caution. Both of our patients with major SIHE showed absolutely no sign of neurologic deterioration with a GCS of 15 when RRHCT was performed. If not participating to the study, patients would have been early discharged, which would have been hazardous.

Analyzing the four cases did not find a predictive factor for SIHE. According to the inclusion criteria, systolic blood pressure did not exceed 150 mm Hg, medication with other drugs influencing the coagulation cascade indicated exclusion from the study, and an additional trauma during observation can be excluded by nursing protocols. A certain role could play the mechanism of the head injury which often is of different impact. The two patients with major SIHE had superficial wounds, which may be associated with a higher impact at injury. Three patients had initial short loss of consciousness, which has been reported to be a strong predictor of mortality in the anticoagulated trauma patient.[19] Loss of consciousness has to be interpreted as an expression of increased grade of brain injury and might be valued as possible risk factor for SIHEs. Case 1 with the fatal outcome showed mild thrombocytopenia, which could be a further possible co-factor for the development of SIHE.

A major limiting factor of the present study represents the lack of a control group taking no anticoagulation therapy. But as mentioned above, the primary study design yielded on the analysis of the incidence of SIHE in a selected collective of patients. Further prospectively controlled studies have to be performed to focus on a matched control group. In the literature, a certain percentage of aspirin nonresponsiveness has been reported.[20,21] We did not analyze the study group regarding the effectiveness of LDA prophylaxis. Admittedly, this could influence the results in a certain way.

Another argument to discuss about could be the time interval between initial and RRHCT. But, considering the very strict inclusion criteria with only mild head injury and a GCS score of 15, no hypertensive irregularities and no clinical signs of deterioration, a minimum 12 hours from injury to detect an SIHE seems to be fairly sufficient. From a pathomorphogenetic view, the vascular lesion should occur at the time of injury with immediate or delayed hemorrhage. Of course, several co-factors have to be considered as platelet count, blood pressure, or co-existing unknown coagulopathies. However, if after 12 hours no SIHE could be revealed by RRHCT, in our opinion, there is no reasonable explanation for a later onset of secondary hemorrhage.

Following the current study, we were facing a very striking result that indicated institutional consequences concerning the treatment rationale for patients 65 years and older with mild traumatic head injuries taking LDA prophylaxis. The primary purpose to reduce hospital admissions of this selected collective of patients must be rejected. The decision to perform RRHCT or not should be adapted to the local infrastructures and possibilities of each emergency depart-

ment. In our study group, secondary ICH occurred slowly and neurologic deterioration in the two patients with major SIHEs developed after 27 hours and 40 hours, respectively. Thus, the meaningful incidence of SIHE in these patients should be kept in mind and, if an RRHCT is not performed, clinical in-hospital observance should be extended from 24 hours to at least 48 hours alternatively for performance of RRHCT after 12 hours.

CONCLUSION

The incidence of SIHE in elderly patients taking regular LDA after mild head injury was underestimated, so far. The primary hypothesis that in this group of patients no secondary ICH after a negative initial head CT occurs was not confirmed in the current study. In contrast, our data show an incidence of SIHEs of 4% with 1% mortality. Therefore, for this selected group of patients admission for neurologic observation with RRHCT after 12 hours to 24 hours is recommended. If RRHCT is not possible, extended in-hospital observation for at least 48 hours seems indicated.

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EDITORIAL COMMENT

As people continue to live longer and the population ages, the volume of cases of minor head injury among the elderly will continue to increase. These patients can be challenging to treat because of their significant comorbidities and lack of functional, neurologic, and cardiorespiratory reserve function. In addition, a higher percentage of this age group is taking antiplatelet or anticoagulants at the time of their injury. These medications can increase progression of even minor injuries or lead to a higher rate of delayed hemorrhages. However, various views on the management of these patients exist without a clear consensus.

Tauber et al. performed a prospective analysis of 100 elderly patients with mild closed head injury who were taking low-dose aspirin (85 mg) at the time of admission and had negative computed tomography (CT) scans in the emergency department. They found a 4% rate of delayed hemorrhage on repeat CT scan with one mortality. As a result of these findings, they rejected their hypothesis that it would be safe to discharge these patients from the emergency room and recommend longer periods of observation with repeat CT scanning.

As measures to decrease the cost of health care continue to propagate neurosurgeons, trauma surgeons and emergency room physicians are going to find themselves at the crosshair of arguments regarding appropriate length of stay after such minor trauma in patients on such medications. I concur with the authors and feel that either prolonged observation with a repeat CT scan while the patient is in the emergency department or an overnight hospitalization with repeat CT scan is appropriate for most of these patients. In addition, it is important to avoid extrapolation of these results to patients who might be on higher doses of aspirin or other antiplatelet agents as the effect of these medications on the risk of either delayed hemorrhage or injury progression are unknown and could possibly be even higher.

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