Minor Head Injury in Warfarinized Patients: Indicators of Risk for Intracranial Hemorrhage

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Background: Head injury represents one of the most important and frequent traumatic pathology in the emergency department. Among the different risk factors, preinjury use of warfarin has received considerable attention in trauma literature. The aim of this study was to identify further risk indicators of intracranial hemorrhage (ICH) to improve risk stratification of warfarinized patients with minor head injuries.

Methods: Medical records of 1,554 adult patients with minor head injuries evaluated by the Emergency Department of Azienda Ospedaliera, Universitaria Careggi from January 2007 to February 2008 were analyzed retrospectively. All the patients included in the study were subjected to blood tests. The international normalized ratio (INR) measured on admission was correlated with the results of head computed tomography scan.

Results: Of the 1,410 patients included in the study, 75 (5.2%) were warfarin anticoagulated at the time of trauma. The INR measured on admission was 2.37 ± 1.04 (mean $\pm$ standard deviation), and this value was significantly associated with occurrence of ICH after head trauma ($r = 0.37$; $p < 0.005$). For 12 (of 75) patients of this group, the findings of the computed tomography scans were positive. The receiver operating characteristic curve show that the most effective INR cutoff value was 2.43, with a sensitivity of 92%, a specificity of 66%, and positive and negative predictive values of 33% and 97%, respectively.

Conclusions: This study highlights the strong relationship between INR values and the probability of ICH, as shown in previous studies. The high negative predictive value of the identified cutoff, if confirmed, could be used to exclude ICH.

Key Words: Head injury, Warfarin, Intracranial hemorrhage, Computed tomography, INR.

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Head injury represents one of the most important and frequent traumatic pathologies in an emergency department. Patients with minor head injuries (Glasgow Coma Scale (GCS) score of 14–15 and normal findings on neurologic examination) make up a substantial number of those who are acutely evaluated in the hospital.[1]

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According to the international guidelines,[2] the use of computed tomography (CT) examination for the evaluation of these patients can be safely limited to those who have certain clinical findings: severe headache, vomiting, older than 65 years, drug or alcohol intoxication, deficits in short-term memory, seizure, high-energy trauma, clinical evidence of skull fracture, loss of consciousness, and coagulopathy (clotting disorder or current treatment with warfarin).[3] Among the different risk factors, warfarin has received considerable attention in the trauma literature.

Several studies were undertaken to clarify the effect of warfarin anticoagulation on the mortality rate and risk of development of intracranial hemorrhage (ICH) in adult patients with minor head injuries.[1,4–12] Although some authors did not show that anticoagulation portends risk that requires emergency CT,[1,3,9] it is generally demonstrated that preinjury warfarin anticoagulation has a significant effect on the outcome in minor head trauma in supratherapeutically anticoagulated patients.[5,8] For this reason, 24 hours of observation and repetition of CT before hospital discharge are recommended in addition to the initial emergency CT examination.[2] The aim of this study was to identify further risk indicators of ICH to improve risk stratification of warfarinized patients with minor head injuries.

PATIENTS AND METHODS

Medical records of 1,554 adult patients with minor head injuries evaluated by the Emergency Department of Azienda Ospedaliero, Universitaria Careggi from January 2007 to February 2008 were analyzed retrospectively. The data collected from the electronic database of the Emergency Department included age, sex, Glasgow Coma Scale, clinical histories and assessments, coagulation tests (prothrombin time [PT], international normalized ratio [INR], activated partial thromboplastin time), CT scan findings, operative reports, possible therapy, and mechanism of injury. In selecting patients to enroll in the study, only those patients whose mechanism of injury was accidental were taken into account. Of the 1,554 patients with minor head injuries, 1,410 with at least one risk factor for acute intracranial lesion underwent CT examination of the head. The remaining 144 patients did not undergo CT examination and were excluded from the study. All CT scans were performed with the use of a Somatom Sensition4 scanner (Siemens). An abnormal CT examination was defined as one showing an acute intracranial hemorrhagic lesion (sunken skull fracture with relief of

hematoma following the same fracture, epidural hematoma, subdural hematoma, subarachnoid hemorrhage, parenchymal contusion, or parenchymal hematoma). All patients included in the study were subjected to blood tests. In particular, for warfarinized patients, the INR measured on admission was correlated with the results of the cranial CT examinations.

Statistical Analysis

The predictive power of INR was assessed by constructing the receiver operating characteristic (ROC) curve and evaluating sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) corresponding to a cutoff level. Odds ratios and their 95% confidence intervals were calculated. Mann-Whitney *U* tests were used for the comparison between the groups. A multiple linear regression analysis was performed to analyze the association between CT scan results and all risk factors included in the study. For all risk factors, a dummy 0/1 variable was used.

An alpha <0.05 was considered statistically significant. Statistical analyses were performed by SPSS software release 11.0 for Windows XP.

RESULTS

A total of 1,410 (male/female, 743/667) adult blunt minor head trauma patients (mean age, 57 ± 25 years; male, 52 ± 24; female, 63 ± 24) between January 2007 and February 2008, with at least one risk factor for acute intracranial lesion, were subjected to CT scanning. Of these patients, 89 showed an acute intracranial lesion. The other clinical data are presented in Table 1. At the multiple regression analysis, anticoagulant treatment and clinical evidence of skull fracture were significantly associated with a positive CT, and the results are shown in Table 2.

Of the 1,410 patients included in the study, 75 (5.2%) were warfarin anticoagulated at the time of trauma (Table 3). The INR measured on admission was 2.37 ± 1.04 (mean ± standard deviation), and this value was significantly associated with occurrence of ICH after head trauma ($r = 0.37$; $p < 0.005$). For 12 patients of this group, the findings of the CT scan were positive (4 for subdural hematoma, 1 for sunken skull fracture, 4 for parenchymal hematoma, and 3 for contusion), and the main characteristics are shown in Table 4.

Preinjury warfarin anticoagulation was significantly associated with a positive CT scan (12 of 75, 16%; $p < 0.005$); the other clinical finding and their relative risks are shown in Table 5.

The INR values were analyzed using ROC curve (Fig. 1). The most effective INR cutoff value was 2.43, with a sensitivity of 92%, a specificity of 66%, and a PPV and NPV of 33% and 97%, respectively.

TABLE 1. Clinical Findings at Presentation of Patients With Minor Head Injury

Risk Factor	No. of Patients (n = 1,410)	Odds Ratio (95% CI)	*p*
TAO	75	2.69 (1.36–5.3)	<0.005
Deficits in short-term memory	100	1.80 (0.92–3.50)	NS
Severe headache	189	0.41 (0.18–0.96)	NS
High-energy trauma	366	0.65 (0.38–1.10)	NS
Drug/alcohol intoxication	56	1.37 (0.53–3.53)	NS
Seizure	7	0.99 (0.99–0.99)	NS
Loss of consciousness	44	1.81 (0.69–4.72)	NS
Vomiting	8	0.994 (0.990–0.998)	NS
Clinicals evidences of skull fracture	5	9.40 (1.55–56.98)	<0.005
Age >65 yr	560	0.92 (0.60–1.41)	NS

TABLE 2. Multiple Linear Regression Results and Coefficients

Dependent Variable CT Scan Results	Independent Variables Risk Factors	Coefficient Beta	*t*	*p*
	High-energy trauma	−0.026	−0.903	0.366
	Deficits in short-term memory	0.047	1.693	0.091
	Severe headache	−0.044	−1.555	0.120
	TAO	0.078	2.841	0.005
	Drug/alcohol intoxication	0.019	0.717	0.473
	Age >65 yr	0.049	1.868	0.062
	Seizure	−0.018	−0.679	0.497
	Loss of consciousness	0.034	1.267	0.205
	Vomiting	−0.019	−0.726	0.468
	Clinical evidences of skull fracture	0.080	3.004	0.003

For all risk factors, a dummy 0/1 variable was used.

TABLE 3. Demographic Data, Evaluation Results, and Outcomes in Anticoagulated Patients With Minor Traumatic Brain Injury

Characteristic	Positive CT Scan	Negative CT Scan	*p*
Number	12	63	—
Male	7	5	NS
Female	5	7	NS
Age (yr)	79.75 ± 14.83	78.16 ± 8.35	NS
INR	3.55 ± 1.92	2.35 ± 0.60	<0.001
Clinical outcome			
Mortality	0	0	
Vegetative	3	0	
Good recovery	9	63	

Data are expressed as mean ± SD.
NS, not significant.

DISCUSSION

Several studies have addressed the risk factors useful in risk stratification for ICH in trauma patients with minor head injuries. In particular, the study of Haydel et al.[3] has demonstrated that anamnestic, objective, clinical, and therapeutic data are important predictive factors for positivity in cranial CT scans. The results of this study demonstrate the importance of obtaining CT scan in patients with at least one risk

TABLE 4. Characteristics of the Anticoagulated Patients With Minor Traumatic Brain Injury Positive at CT Scan

CT Positive Patient No.	Age (yr)	Initial GCS	Initial INR	Outcome
1	80	15	2,66	Good recovery
2	84	15	2,45	Good recovery
3	72	15	2,54	Good recovery
4	82	15	5,08	Good recovery
5	76	15	2,56	Good recovery
6	82	14	8,09	Comatose state
7	92	15	3,37	Good recovery
8	38	15	1,95	Good recovery
9	78	15	3,28	Good recovery
10	86	15	3.82	Good recovery
11	95	15	2.45	Comatose state
12	92	15	2,48	Comatose state

TABLE 5. Clinical Findings at Presentation of Anticoagulated Patients With Minor Head Injury

Risk Factor	Patients	Odds Ratio (95% CI)
Age >65 yr	70/75	1.02 (0.85–1.22)
Loss of consciousness*	3/75	0.95 (0.9–1.01)
Clinical evidences of skull fracture	0/75	—
Seizure	0/75	—
Severe headache	8/75	0.32 (0.09–1.17)
Vomiting*	2/75	0.97 (0.92–1.01)
Drug/alcohol intoxication	0/75	—
Deficits in short-term memory	8/75	0.32 (0.09–1.17)
High-energy trauma	9/75	0.68 (0.16–2.87)

* For cohort negative.

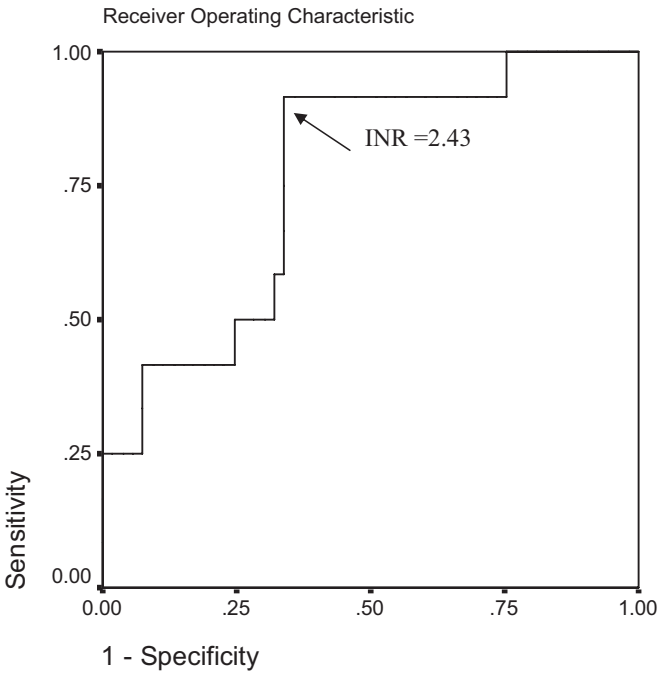

Figure 1. ROC curve of INR in patients with minor traumatic brain injury. Area under curve = 0.76 (95% CI, 0.62–0.91); $p < 0.05$. The *arrow* indicates the sensitivity and specificity (92% and 66%, respectively).

factor at the time of presentation, and that the use of CT scan can safely be limited to patients with these clinical findings (severe headache, vomiting, older than 65 years, drug or alcohol intoxication, deficits in short-term memory, seizure, high-energy trauma, clinical evidence of skull fracture, loss of consciousness, and clotting disorder or current treatment with warfarin).

The results of this study are discordant with these previous findings. Oral anticoagulant therapy and skull fracture seem to be the only risk factors statistically significant to the development of posttraumatic ICH.

Statistical analysis does not point out age as risk factor and a reason for this might be the high average age of study population. About the effect of preinjury anticoagulation (mortality rate and risk of development of ICH) in adult patients with minor head injuries, a relatively large number of studies are available in the literature.

Published reports began appearing in the mid-1990s in an attempt to address this issue. In 1995, Saab et al.[13] reported two cases of patients on warfarin, who developed intracerebral hematoma after an apparent minor head injury. These limited data suggested that all such patients had to be admitted for standard neurologic observation and to have a lower threshold for head CT. The following year, Volans,[14] using three personal cases and reviewing eight cases collected from literature reports, developed a theoretical risk index for ICH in anticoagulated patients with minor head injury. Recommendations were forthcoming to check an INR in this setting and to have a low threshold for CT scanning.

Garra et al.[15] studied 65 anticoagulated patients with minor head injuries, they reported no deaths, and they concluded that this population was not at increased risk. However, only 38 patients of the 65 patients had a documented anticoagulation level.

Li et al.[4] retrospectively reviewed 144 patients who suffered minor head trauma, who had concurrent warfarin use, and who underwent CT of the head. The results showed clinically important injuries in 10 patients (7%). They concluded that head CT have to be performed in all patients on anticoagulants affected by minor head trauma.

The triad of anticoagulation, age >65 years, and minor head injury was considered lethal by Karni et al.[16] on a retrospective review of 278 patients with minor head injuries and CT-documented ICH. Parmar et al.[6] showed that warfarinized patients who were admitted with head injury have a high mortality. Gittleman et al. reported that in a group of 89 patients with cranial injury receiving anticoagulation, who underwent emergency cranial CT, 7 patients with an ICH had a GCS score <15, and the remaining 82 patients with negative CT scan had a GCS score of 14 and did not have neurologic deficits. These findings support the notion that patients receiving anticoagulation who have minor head injury and a normal GCS score may not necessarily require emergency cranial CT.

In our study, we confirm the negative impact of preinjury warfarin treatment on the development of ICH for patients with minor head injuries, especially the strong relationship between INR values and the probability of a positive CT scan. Previous studies have shown the link between an increased risk of ICH and abnormally prolonged PTs. Hylek and Singer[17] suggested that the rate of intracranial hematoma in the population is equal to an inherent baseline risk multiplied by the intensity of anticoagulation, finding a doubling of risk with each 0.5 increase in PTs. Franko et al.[7] observed how INR values >3.5 to 5.0 (intense anticoagulation) are strongly associated with ICH. Cohen et al.[18] suggested to admit for neurologic observation all patients with minor head injury who are supratherapeutically anticoagulated because of the known increased bleeding risk with increasing levels of anticoagulation.

Knowing the diagnostic importance of INR values in patients with minor head injuries, we searched for an INR value that represents a cutoff level related with the probability to develop ICH in patients with minor head injuries. The high NPV (97%) of the identified cutoff level could be used to exclude ICH in warfarinized patients without other risk factors, with INR value at admission <2.43. The above statement and the cutoff limit are indicative and represent a very preliminary finding that needs further prospective studies with a larger sample size. Currently, the only useful diagnostic tools are clinical findings and CT scan. The use of INR as risk index needs further investigations. Once the results of this study are confirmed, the INR could represent a useful tool for the risk stratification and management of minor cranial trauma patients being treated with oral anticoagulants in the emergency department.

REFERENCES

1. Gittleman AM, Ortiz AO, Keating DP, Katz DS. Indications for ct in patients receiving anticoagulation after head trauma. *AJNR Am J Neuroradiol.* 2005;26:603–606.
2. Guidelines for minor head injured patients' management in adult age. The Study Group on Head Injury of the Italian Society for Neurosurgery. *J Neurosurg Sci.* 1996;40:11–15.
3. Haydel MJ, Preston CA, Mills TJ, Luber S, Blaudeau E, DeBlieux PM. Indications for computed tomography in patients with Minor Head Injury. *N Engl J Med.* 2000;343:100–105.
4. Li J, Brown J, Levine M. Mild head injury, anticoagulants, and the risk of intracranial injury. *Lancet.* 2001;357:771–772.
5. Reynolds F, Dietz PA, Higgins D, Whitaker TS. Time to deterioration of the elderly, anticoagulated, minor head injury patient who presents without evidence of neurologic abnormality. *J Trauma.* 2003;54:492–496.
6. Parmar KA, Rao S, Abu-Zidan FM. Head injuries in warfarinised patients. *Singapore Med J.* 2006;47:676.
7. Franko J, Kish KJ, O-Connel BG, Subramanian S, Yuschak JV. Advanced age and preinjury warfarin anticoagulation increase the risk of mortality after head trauma. *J Trauma.* 2006;61:107–110.
8. Pieracci FM, Eachempati SR, Shou J, Hydo LJ, Barie PS. Degree of anticoagulation, but not warfarin use itself, predicts adverse outcomes after traumatic brain injury in elderly trauma patients. *J Trauma.* 2007;63:525–530.
9. Wojcik R, Cipolle MD, Seislove E, Wasser TE, Pasquale MD. Preinjury warfarin does not impact outcome in trauma patients. *J Trauma.* 2001;51:1147–1151.
10. Kennedy DM, Cipolle MD, Pasquale MD, Wasser T. Impact of preinjury warfarin use in elderly trauma patients. *J Trauma.* 2000;48:451–453.
11. Mina AA, Knipfer JF, Park DY, Bair HA, Howells GA, Bendick PJ. Intracranial complications of preinjury anticoagulation in trauma patients with head injury. *J Trauma.* 2002;53:668–672.
12. Lavoie A, Ratte S, Clas D, et al. Preinjury warfarin use among elderly patients with closed head injuries in a trauma center. *J Trauma.* 2004;56:802–807.
13. Saab M, Gray A, Hodgkinson D, Irfan M. Warfarin and the apparent minor injury. *J Accid Emerg Med.* 1996;13:208–209.
14. Volans AP. The risks of minor head injury in the warfarinised patient. *J Accid Emerg Med.* 1998;15:159–161.
15. Garra G, Nached AH, Capobianco L. Minor head trauma in anticoagulated patients. *Acad Emerg Med.* 1999;6:121–124.
16. Karni A, Holtzman R, Bass T, et al. Traumatic head injury in the anticoagulated elderly patient: a lethal combination. *Am Surg.* 2001;67:1098–1100.
17. Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in outpatients taking warfarin. *Ann Intern Med.* 1994;120:897–902.
18. Cohen DB, Rinker C, Wilberger JE. Traumatic brain injury in anticoagulated patients. *J Trauma.* 2006;60:553–557.