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ABSTRACT

Background

Mild traumatic brain injury (mTBI), defined as blunt trauma to the head resulting in witnessed loss of consciousness, definite amnesia or witnessed disorientation with Glasgow Coma Scale (GCS) score of 14 or 15 is a common occurrence at the Emergency Department. In mTBI, oral anticoagulation is known to be an important risk factor for hemorrhage. Clinical guidelines recommend baseline CT scan and observation for 24 hours plus a CT scan before discharge.

Methods

We have compared the non-anticoagulated and anticoagulated patients presenting at our Emergency Department with mTBI and no neurological signs (GCS=15). Every non-anticoagulated patient underwent only a baseline CT scan whereas the anticoagulated group underwent also a second CT scan as after a 24-hour observation period.

Results

Between April 2012 and April 2013 we observed 908 adult patients presenting with mTBI and GCS 15: 74 (8.1%) were on oral anticoagulants drugs as long term therapy whereas the
remaining 834 (91.9%) were not. In the non-anticoagulation group, 38 patients (4.6%) were positive for hemorrhage. Two patients underwent neurosurgical intervention. In the anticoagulation group, 5 patients (6.8%) were positive for hemorrhage. No patient underwent neurosurgical intervention. None of them died. The differences between the two groups were not statistically significant.

Conclusions
GCS 15 patients on long-lasting anticoagulation therapy who present with mTBI have a risk of cranial hemorrhage which is likely to be similar to that of non-anticoagulated patients. It may be reasonable to envision a protocol including only one CT scan and an appropriate observation period.

HIGHLIGHTS
- No statistically significant differences were detected by comparing anticoagulated and non-anticoagulated patients with mild traumatic brain injury in terms of hemorrhage, neurosurgical interventions and deaths.
- A protocol consisting of a unique CT scan for anticoagulated patients after an adequate observation period seems to be the most suitable solution.
KEYWORDS

mild traumatic brain injury, anticoagulants, GCS 15, minor head trauma, head CT scan

INTRODUCTION

Mild traumatic brain injury (mTBI), defined as blunt trauma to the head resulting in witnessed loss of consciousness, definite amnesia or witnessed disorientation with Glasgow Coma Scale (GCS) score of 14 or 15 (1) is a common occurrence at the Emergency Departments worldwide. There are various clinical guidelines in literature (Canadian head CT rules, New Orleans rules, NICE-National institute for Health and Care Excellence, etc.) attempting to define which patient should undergo head computerized tomography (CT) scan for patients with mTBI (1, 2, 3). Canadian CT head rules are largely the most widely used.

Nowadays the anticoagulation therapy is increasingly being prescribed by Physicians. It has been estimated that about 4 million Americans are on long-term anticoagulation therapy and 7 million people worldwide (4). Canadian CT head rules do not include mTBI—
anticoagulated patients in their criteria. The majority of the studies in literature do not examine these subgroup of patients because there is a general feeling about the high risk of brain hemorrhage in this particular segment of population (5), especially in elderly patients (6). Some national protocols (7, 8) suggest the performance of two subsequent CT scans, a baseline one at the admission and one after an observation period. In everyday clinical practice, the most difficult decisions must be made when handling patients with no neurological sign (GCS of 15). Physicians have to balance the real benefits for the patient against the costs of the exam as well as the potential damage arising out of brain irradiation (9, 10). In this study, we aim to verify the risk for hemorrhage in anticoagulated patients suffering from mTBI with a GCS of 15, i.e. those with absolutely no neurological sign, in an attempt to find out whether these patients really need two consecutive CT scans.

MATERIALS AND METHODS

After Ethics Board approval from our Institution, we have retrospectively analyzed 3021 consecutive patients presenting at the Emergency Department of Varese, in Northern Italy, with traumatic head injury from April 2012 to April 2013. 834 of them had mTBI, and matched Canadian head CT rules criteria for the performance of CT scan and GCS of 15, whereas 74 matched the same criteria but were on long-term anticoagulation therapy. We have excluded from this analysis the patients under single or double antiplatelet treatment. We have divided our population into two groups: anticoagulated and non-
anticoagulated patients. The former underwent only one CT scan after at least two hours from the arrival to the Hospital. The latter, too, had a baseline CT scan after at least two hours from the arrival, but it also underwent another CT scan after an observation period of 24 hours. Patients were divided at admission as per a national color-code method: white for no-risk patients, green for non-urgent situations, yellow for urgent situations, red for emergency situations. The written records for each group included demographic characteristics, clinical data, Canadian CT head rules matching criteria, the presence or absence of hemorrhage at CT scan (we considered as positive all types of bleeding, even the smallest), neurosurgical interventions, if any, and survival information.

Statistical analysis was performed using the "R" software for Mac OS X Version 3.1.1 (11). Statistical significance was considered achieved for $P<0.05$. Since the variables considered were dichotomous, no normality testing was performed. We have used a binomial Generalized Linear model with logistic regression using a logit link function. In the end the two models were compared using ANOVA (Analysis Of VAriance) with Chi-square test.

RESULTS

A total of 908 adult patients were assessed for mild traumatic brain injury (mTBI) and GCS 15. Mean age at the moment of trauma was of 67.5 years (range 18–98; mean 75 ± 22.5). Four hundred and thirty-eight patients were male (48.3%) and 470 (51.7%) were
female. The vast majority (689, 75.8%) of patients were triaged as green codes, followed by yellow codes (206, 22.6%), white codes (9, 1%) and red codes (4, 0.4%). The causes of trauma were registered by emergency physicians as follows: accidental fall (69%); bicycle accidents (4.4%); car vs pedestrian accident (3.8%); car accident (6.2%); motorcycle accident (4.3%); beating (4%); fall from elevation (2.1%); other causes (5.4%). In particular, 834 (91.8%) patients matched at least one Canadian Head CT rules criterion (1). For 74 (8.1%) patients these rules were not applicable because of anticoagulation therapy. These patients represented the anticoagulation group. We performed CT scans based on Canadian Head CT rules criteria in the non-anticoagulation group, whereas every anticoagulated with mTBI patient underwent 2 consecutive head CT scans, the first at 2 hours from trauma and the second after a 24-hour observation period. Table 1 shows which criteria were matched in both anticoagulation and non-anticoagulation groups. 43 patients out of 908 resulted positive for hemorrhage at CT head scan. We considered as positive every patient who presented an even minimal sign of bleeding (i.e. a single petechia) at CT scan. In the non-anticoagulation group, the number of baseline CT scan which resulted positive for hemorrhage was distributed as follows: 14 patients with petechiae, 15 subdural hematomas, 7 parenchymal contusions, 2 subarachnoid hemorrhages. In the anticoagulation group the number of baseline CT scan which resulted positive for hemorrhage was distributed as follows: 1 patient with petechiae, 2 subdural hematomas, 2 subarachnoid hemorrhages. 4 out of 5 patients with long-term
anticoagulation therapy positive for hemorrhage, were taking warfarin and 1 acenocoumarol. It has been possible to compare the severity of the hemorrhage of the two groups by taking into consideration the number of surgical interventions, the days of hospital admission as well as the, head CT scan findings. Patients with negative baseline CT head scan (one scan for the non-anticoagulation group and two consecutive for the anticoagulated) were discharged home, in the absence of other clinical problems. Relevantly, in the anticoagulation group no patient with a negative CT scan showed a delayed hemorrhage at the control scan. Patients with positive baseline CT head scan were admitted to hospital. Average hospital admission time was of 5 days (range 2–27) for non-anticoagulation group, and of 6.2 days for anticoagulation group (range 2–12). Two patients in the non-anticoagulation group (5% of hemorrhagic patients) underwent neurosurgical interventions for delayed neurological decline (subdural hematoma evacuation), whereas no hemorrhagic patient in the anticoagulation group met any criteria for intervention throughout their clinical course. Moreover, in case of initial hemorrhage in the patients included in the anticoagulant group, even if some minimal progression was evident at control assessments, none of them was deemed clinically relevant.

A statistical analysis was performed, at first, by examining the correlation between hemorrhage and anticoagulation therapy. This was implemented using the standard Chi-square test that scored non-significant (X-squared = 0.3233, degrees of freedom = 1, p-value = 0.5697), thus suggesting no influence of long-term anticoagulant therapy on
bleeding for GCS 15 mTBI patients. In order to understand the effect of the anticoagulation variable on hemorrhage, we subsequently analyzed a nested Generalized Linear Model trying to determine the impact of the anticoagulation predictor on the probability of hemorrhage. Since all parameters involved (input factors and outcome) were dichotomous, we used a binomial logistic model using a logit link function. We fitted a function of the conditional mean response assuming that the response variable followed a binomial distribution; and we estimated parameters using maximum likelihood. We evaluated all the patients by considering all Canadian CT Head Rules criteria plus other variables such as pharmacological therapy, history of disease, presence or absence of limb fractures, presence or absence of vertebral fractures. We then extracted all significant variables and included them in a logistic model along with anticoagulation therapy as a single variable. The results of the logistic regression analysis are shown in Table 2. As was reported, anticoagulation therapy was not statistically significant as a variable influencing likelihood of hemorrhage.

**DISCUSSION**

In clinical practice many patients who suffer from mTBI undergo head CT scan (about 30% of subjects with GCS of 14–15). This is true even when physicians scrupulously comply with clinical guidelines (12). Head CT scan is undoubtedly very sensitive in discerning cerebral hemorrhage after blunt trauma to the head, however very often it turns out to be
negative in patients suffering from mTBI (13). In literature there is more and more evidence of the potentially harmful effects of ionizing radiations; it is widely known that high doses of these radiations can cause cancer. These data are even more worrying if we consider that CT scan rates have substantially risen in the last 30 years. Thus, practitioners will increasingly need to weigh the benefits of CT scans in clinical practice against the potential risks to justify each CT scan decision (14). Efforts by international Authors have been made to optimize the use of this diagnostic technique, with the intent of both preventing patients from being exposed to high ionizing radiation doses and rationalizing economic charges to national health systems as well as the time spent by healthcare workers. Still, the number of head CT scans remains very high in comparison to the number of positive exams (15). The most widely spread guideline seems to be the Canadian head CT rules, but it is not fit for anticoagulated patients (16). On the contrary, oral long-term anticoagulation therapy is a specific criterion for the exclusion from the guidelines. Besides international guidelines, hospitals have developed worldwide their own institutional protocols regarding this particular subset of patients. For example, a recent article from Docimo et al. maintains that the protocol requiring a second CT scan for all patients on oral anticoagulant therapy after a negative first CT scan should be questioned (17). NICE guidelines are very clear about this topic: while they claim the need for a head CT scan 8 hours after the admission at the emergency department, they also mention the fact that there is no consensus in literature and that further studies are needed in the
Many other guidelines, among which the ones from the Italian Society of Neurosurgery (7, 8), demand the performance of a **baseline** head CT scan 2 hours after the arrival at the Emergency Department and a pre-discharge head CT scan after a 24-hour observation period if the first CT scan is negative for hemorrhage. On these bases we wanted to evaluate whether a second CT scan is really needed for the specific subgroup of neurologically intact anticoagulated patients with mTBI. In our study, we have found 38 head CT scans positive for hemorrhage in the non-anticoagulation group, whereas only 5 in the anticoagulation group. Relevantly, no anticoagulated patients deteriorated neurologically in the subsequent 24 hours in which they stayed in hospital for the observation period before undergoing a second CT scan and no head CT scan turned out to be positive at second exam while being negative at first exam. The comparison between the 2 groups did not show statistically significant differences in terms of likelihood of hemorrhage, necessity of surgical intervention or hospital stay. No patient died in either group. Apparently, in this subset of patients, anticoagulation therapy is not such a significant factor as to exclude the patients from the Canadian head CT rules criteria. Since the performance of one single head CT scan at 2 hours from trauma is universally accepted for non-anticoagulated adult patients, we could infer from the outcome that one single head CT scan is enough also for adult patients with mTBI and GCS of 15 on long-term anticoagulation therapy. A potential drawback of this study is the fact that, for now, our numbers are too small and new studies are necessary to confirm this impression. In
addition, in this study there was the absence of patients in long-term anticoagulation therapy with new anticoagulating drugs that are becoming more and more used all over the world (i.e. rivaroxaban or dabigatran). There is, in fact, initial evidence that at least rivaroxaban may exacerbate intracranial hemorrhage in patients with mTBI (19). Moreover, in this study we have not evaluated patients with antiplatelet therapy, since even on this therapy there is no consensus yet in literature (20). Finally, this is a retrospective and not a prospective study. Our data are however encouraging and urge us to plan on carrying out further studies on the subject.

CONCLUSIONS

In GCS 15 patients receiving long-term anticoagulation therapy presenting at the Emergency Department with mTBI, the risk of hemorrhage is comparable to non-anticoagulated patients. It is therefore potentially useful to limit both the radiological and clinical assessments to a single CT scan followed by an appropriate observation period.

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3. NICE—National institute for Health and Care Excellence guidelines: https://www.nice.org.uk/guidance/cg176


11. The R project for statistical computing. https://www.r-project.org/


Table 1: Canadian Head CT Rules Criteria matched by anticoagulation and non anticoagulation group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Non anticoagulation group</th>
<th>Anticoagulation group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected open or depressed skull</td>
<td>11 (1.7%)</td>
<td>2 (2.7%)</td>
</tr>
<tr>
<td>fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any sign of basilar skull fracture</td>
<td>14 (1.2%)</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 2 episodes of vomiting</td>
<td>64 (8.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Age ≥ 60 yr</td>
<td>510 (8.2%)</td>
<td>67 (10.5%)</td>
</tr>
<tr>
<td>Retrograde amnesia in event ≥ 60 mm</td>
<td>1 (8.2%)</td>
<td>1 (9.2%)</td>
</tr>
<tr>
<td>Cerebral Edema</td>
<td>23 (5.7%)</td>
<td>39 (5.7%)</td>
</tr>
<tr>
<td></td>
<td>Estimate</td>
<td>Std. Error</td>
</tr>
<tr>
<td>---------------------</td>
<td>----------</td>
<td>------------</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>0.6053</td>
<td>0.5224</td>
</tr>
<tr>
<td>Skull fracture signs</td>
<td>1.1575</td>
<td>0.5022</td>
</tr>
<tr>
<td>Limb fractures</td>
<td>-1.1941</td>
<td>0.5926</td>
</tr>
<tr>
<td>Amnesia</td>
<td>0.9790</td>
<td>0.4175</td>
</tr>
<tr>
<td>Neurological signs</td>
<td>1.4370</td>
<td>0.4104</td>
</tr>
<tr>
<td>Critical dynamic</td>
<td>1.7610</td>
<td>0.6057</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.0813</td>
<td>0.3520</td>
</tr>
</tbody>
</table>

Significance codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Null deviance: 346.23 on 907 degrees of freedom
Residual deviance: 304.58 on 900 degrees of freedom

Table 2 - Results of logistic regression analysis about predictors of hemorrhage in mTBI
Abbreviation List

**mTBI:** mild traumatic brain injury  
**GCS:** Glasgow Coma Scale  
**ANOVA:** Analysis Of Variance