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Risk of delayed intracranial haemorrhage after an initial negative CT in patients on DOACs with mild traumatic brain injury

Gianni Turcato, MD [a,*], Alessandro Cipriano, MD [b], Arian Zaboli, RN [a], Naria Park, MD [b], Alessandro Riccardi, MD [c], Massimo Santini, MD [b], Roberto Lerza, MD [c], Giorgio Ricci, MD [d], Antonio Bonora, MD, PhD [d], Lorenzo Ghiadoni, MD [e]

[a] Emergency Department, Hospital of Merano (SABES-ASDAA), Merano-Meran, Italy
[b] Emergency Department, Nuovo Santa Chiara Hospital, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy
[c] Emergency Department, Hospital of San Paolo (ASL N°2 Savonese), Savona, Italy
[d] Emergency Department, University of Verona, Verona, Italy
[e] Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

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ABSTRACT

Background: Repeat head CT in patients on direct oral anticoagulant therapy (DOACs) with minor traumatic brain injury (MTBI) after an initial CT scan without injury on arrival in the Emergency Department (ED) is a common clinical practice but is not based on clear evidence.
Aim: To assess the incidence of delayed intracranial haemorrhage (ICH) in patients taking DOACs after an initial negative CT and the association of clinical and risk factors presented on patient arrival in the ED.
Methods: This retrospective multicentre observational study considered patients taking DOACs undergoing repeat CT after a first CT free of injury for the exclusion of delayed ICH after MTBI. Timing between trauma and first CT in the ED and pre- or post-trauma risk factors were analysed to assess a possible association with the risk of delayed ICH.
Results: A total of 1426 patients taking DOACs were evaluated in the ED for an MTBI. Of these, 68.3% (916/1426) underwent a repeat CT after an initial negative CT and 24 h of observation, with a rate of delayed ICH of 1.5% (14/916). Risk factors associated with the presence of a delayed ICH were post-traumatic loss of consciousness, post-traumatic amnesia and the presence of a risk factor when the patient presented to the ED within 8 h of the trauma. None of the patients with delayed ICH at 24-h repeat CT required neurosurgery or died within 30 days.
Conclusions: Delayed ICH is an uncommon event at the 24-h control CT and does not affect patient outcome. Studying the timing and characteristics of the trauma may indicate patients who may benefit from more in-depth management.

1. Introduction

The management of mild traumatic brain injury (MTBI) in patients taking direct oral anticoagulants (DOACs) in the Emergency Department (ED) is still debated [1,2]. Recent evidence suggests that the incidence of post-traumatic intracranial haemorrhage (ICH) in MTBIs is low in patients on DOACs; however, due to the absence of specific indicators, the management of head trauma for patients using Vitamin K antagonists (VKA) has been applied to patients on DOACs [3-5]. The indication to repeat head CT to exclude delayed ICH at discharge of a patient on oral anticoagulant therapy (OAT) is still controversial [6,7]. Studies of patients taking VKAs have reported that the incidence of delayed ICH is low, generally less than 2% and rarely associated with neurosurgery [3,8]. However, the presence of OAT, even in the absence of additional clinical conditions of post-traumatic risk, frequently leads to a repeated CT scan after 24 h of observation for a more safe discharge [9].

The preliminary evidence seems to indicate a limited risk of delayed ICH for patients on DOACs similar to that observed for VKA patients [6,9]. Mourad et al. evaluated 420 patients on DOACs undergoing repeat CT in the absence of ICH at first CT and reported a risk of delayed ICH of 0.5% [10]. For patients taking VKAs, certain characteristics present at the first assessment of the patient, such as the presence of pre- or post-traumatic risk factors or the level of INR, suggest the maintenance of a higher degree of suspicion despite a negative first CT [3,8,10,11]. Currently, such an approach is not available for patients on DOACs, and it

* Corresponding author at: Emergency Department, Hospital of Merano, Via Rossini 5, 39012 Merano, Italy.
E-mail address: gianni.turcato@yahoo.it (G. Turcato).

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is not yet possible to determine whether the study of clinical and laboratory factors at the time of the first ED evaluation of the patient can help in predicting or excluding the risk of delayed ICH after an initial CT without any injury.

The aim of the study was to assess the incidence of delayed ICH after 24 h from an initial CT free of injury in a large cohort of patients taking DOACs with MTBI from five centres to determine which trauma-related characteristics and clinical risk factors may be associated with the risk of delayed ICH in these patients.

2. Methods

2.1. Setting

This retrospective multicentre observational study was conducted in the EDs of five centres in Northern Italy: the Ospedale Civile Maggiore of Verona (90,000 annual visits), the Policlinico Universitario of Pisa (90,000 annual visits), the General Hospital of Merano (70,000 annual visits), the Policlinico Universitario of Verona (50,000 annual visits) and the General Hospital of San Bonifacio (60,000 annual visits). The study period was from January 1, 2016 to February 1, 2020. In all five study centres, a management protocol for head trauma based on national guidelines has been implemented since 2014 [12]. Patients on OAT with MTBI require a CT scan on arrival in the ED, a 24-h observation in the ED and a possible repeat of the CT scan on discharge at the discretion of the physician [12].

The study was conducted with the approval of the local ethics committees (Ethics Committee for Clinical Trials, Verona, Italy, approval number 889CESC; Ethics Committee for Clinical Trials, Bolzano, Italy, approval number 75–2019; Ethics Committee for Clinical Trials, Pisa, Italy 11924_CIPRIANO) and was conducted according to the ethical principles for medical research involving human subjects in the Declaration of Helsinki.

3. Patients and study protocol

The study included all patients undergoing OAT with DOACs evaluated in the ED and undergoing repeat CT after an initial negative CT for post-traumatic ICH after 24 h of observation in the ED.

MTBI was considered to be any closed trauma of the craniofacial region associated with a Glasgow Coma Scale (GCS) score of 14–15 at presentation regardless of loss of consciousness immediately after the trauma [13,14].

Charts of all patients submitted to CT during the study period were extracted from the respective computer databases using the dedicated management software (FirstSTATA for Verona, Pisa and San Bonifacio, and QlikView for Merano) and manually reviewed by a group of Emergency Physicians for each centre. Only patients with MTBI undergoing therapy with DOACs who received a second CT after a first CT without injury after 24 h of observation were selected.

Patients were excluded for the following reasons: under 18 years of age; a time between trauma and ED presentation of more than 48 h; and the presence of ineffective anticoagulant therapy, defined as the last intake of DOACs more than 24 h before trauma. Patients who did not undergo repeat CT (second CT) within 24 h from an initial negative CT were not considered for the main analysis of the study but, where available, 30-day medical follow-up was conducted to identify any delayed ICH not undergoing repeated CT.

Trauma characteristics (time to first CT in ED, mode of trauma and presence of a major trauma dynamic), pre- and post-traumatic risk factors present at the time of ED assessment (reason for OAT, trauma modality, presence of a transitory loss of consciousness, post-traumatic amnesia, seizure after trauma, GCS in the ED, evidence of trauma above the clavicles, concomitant anti-platelet therapy, presence of other fractures, HAS-BLED score, vomiting, headache or signs of skull base fracture) were recorded.

4. Outcomes

The main outcome of the study was the presence of delayed ICH at the second CT scan performed after 24 h of observation and after a first CT scan without injury performed on arrival in the ED. CT positivity was considered to be the presence of subdural, epidural or parenchymal haematoma, subarachnoid haemorrhage or cerebral contusion [15]. The secondary outcome of the study was the presence of a major outcome, defined as the need for neurosurgery (craniotomy, craniectomy, placement of a burr hole or subdural drain) or death from post-traumatic ICH within 30 days following trauma. Patient follow-up was reconstructed by evaluating the medical records available in the computer databases of the EDs involved in the study, and mortality was confirmed through the registry office.

4.1. Statistical analysis

Continuous variables were described as means and standard deviations (SD) or as median and interquartile range (IQR) depending on their distribution. Categorical variables were expressed as percentage and number of events out of the total. The univariate analysis of continuous variables was conducted using the Mann–Whitney test. Fisher's exact test was used to compare dichotomous variables with the study outcome, while the chi-square test was used for the univariate analysis between categorical variables and the study outcome. An alpha value of $p < 0.05$ was used to determine statistical significance. All analyses were conducted with the statistical software STATA 16.1 (StataCorp, College Station, TX, USA).

5. Results

A total of 1426 patients receiving DOACs were evaluated for an MTBI in one of the five EDs included in the study. The baseline characteristics of the patients are shown in Table 1.

Patients were older and predominantly female (54.8%). Most patients were on direct factor Xa inhibitor therapy (67.3%), with Apixaban and Rivaroxaban being the most commonly used DOACs. The main indication for OAT was atrial fibrillation and the most frequent mechanism of injury was an accidental fall. All patients underwent head CT on ED admission. Post-traumatic ICH at the first CT performed in the ED (immediate ICH) was found in 6% of patients (85/1426).

Table 1
Baseline characteristics of patients receiving DOACs evaluated in the ED for MTBI.

Variable	Global
Patients, n (%)	1426 (100)
Gender, n (%)	
Male	644 (45.2)
Female	782 (54.8)
Age in years, median (IQR)	83 (78–88)
Type of DOACs, n (%)	
Direct thrombin inhibitor	323 (22.7)
Dabigatran	323 (22.7)
Direct factor Xa inhibitor	1103 (67.3)
Apixaban	503 (35.3)
Rivaroxaban	464 (32.5)
Edoxaban	136 (9.5)
Reason for therapy with DOACs, n (%)	
Atrial fibrillation	1288 (90.3)
Pulmonary embolism	90 (6.3)
Others	48 (3.3)
Modality of trauma, n (%)	
Accidental fall or precipitation	1069 (74.9)
Road incident	79 (5.5)
Transitory loss of consciousness	252 (17.6)
Direct trauma	26 (1.8)
Presence of immediate ICH on CT performed on ED arrival, n (%)	85 (6)

Of the patients with a first negative head CT ($n = 1341$), 68.3% (916/1341) underwent a second CT after 24 h of observation in the ED. The characteristics of patients who underwent a repeat CT scan are reported in Table 2. (See Table 3.)

Patients who underwent a repeat head CT presented with a shorter time between trauma and ED admission (median 2 h vs 7 h, $p < 0.001$) and were more often treated with a direct factor Xa inhibitor (79.1 vs 72.2, $p = 0.005$). Of the clinical risk factors, only the presence of evidence of trauma above the clavicles was associated with a repeat CT scan. However, the presence of at least one clinical risk factor in patients who presented to the ED within 3 h or within 8 h from trauma was found to be a factor associated with a repeated CT. The presence of any associated body fracture was also a factor in favour of a repeat CT (42.1% vs 27.3%, $p < 0.001$). In a subgroup of patients whose HAS-BLED was available, the presence of a constitutional risk of haemorrhage was not found to influence the decision to repeat the CT scan.

Delayed ICH was found in 1.5% (14/916) of patients who underwent a repeat CT. No patient with delayed ICH resulted with a serious outcome such as the need for neurosurgery or death due to ICH.

Consideration of the time between trauma and ED assessment appeared to be important in evaluating the risk of delayed ICH, as no patients with delayed ICH were evaluated after 8 h. Post-traumatic transitory loss of consciousness (TLOC) (21.4% vs 2.4%, $p = 0.005$) and post-traumatic amnesia (35.7% vs 9.1%, $p = 0.007$) were found to be associated with the presence of delayed ICH. In addition to being assessed within 8 h of trauma, all patients with delayed ICH had at least one clinical risk factor at the time of the first evaluation ($p = 0.001$). Finally, among patients who did not repeat CT at 24 h after an initial CT without injury ($n = 424$), only one patient presented with a delayed ICH at eight days after injury, which resulted in the patient's death.

Table 2
Baseline, clinical and anamnestic characteristics of the patients enrolled in the study, divided between those who received a second head CT after 24 h of observation in the ED and those who did not receive a second CT.

Variable	No second CT performed	Second CT performed	*p*-value
Patients, n (%)	424 (29.7)	916 (68.3)	
Age in years, median (IQR)	82 (77–87)	83 (78–88)	0.056
Time between trauma and ED evaluation			
Continuous, hours, median (IQR)	7 (2–15)	2 (1–7)	<0.001
Categorial, n (%)			<0.001
Within 3 h	134 (31.5)	542 (59.2)	
Between 3 and 8 h	99 (23.3)	167 (18.2)	
More than 8 h	192 (45.2)	207 (22.6)	
Type of DOACs, n (%)			0.005
Direct factor Xa inhibitor	307 (72.2)	725 (79.1)	
Direct thrombin inhibitor	118 (27.8)	191 (20.9)	
Risk factors, n (%)			
Major dynamic	18 (4.2)	27 (2.9)	0.254
Post-traumatic TLOC	17 (4.0)	25 (2.7)	0.239
Post-traumatic amnesia	28 (6.6)	87 (9.5)	0.093
Post-traumatic seizure	0 (0.0)	4 (0.4)	0.314
GCS < 15	25 (5.9)	102 (11.1)	0.002
Alcohol or drug intoxication	4 (0.2)	18 (2.0)	0.247
Evidence of trauma above the clavicles	256 (60.2)	624 (68.1)	0.005
Concomitant anti-platelet therapy	59 (13.9)	46 (5.0)	<0.001
Vomiting	10 (2.4)	16 (1.7)	0.523
Headache	19 (4.5)	27 (2.9)	0.196
Signs of skull base fracture	0 (0.0)	4 (0.4)	0.314
At least one risk factor, n (%)	322 (75.8)	730 (79.7)	0.116
At least one risk factor with ED arrival within 3 h after the trauma, n (%)	101 (23.8)	439 (47.9)	<0.001
At least one risk factor with ED arrival within 8 h after the trauma, n (%)	179 (42.1)	564 (61.6)	<0.001
Presence of other fractures, n (%)	116 (27.3)	386 (42.1)	<0.001
HAS-BLED ($n = 1081$)			
Continuous, median (IQR)	2 (2–3)	2 (2–3)	0.325
Categorial, n (%)			
> 3	67 (31.2)	303 (35)	0.298

Note: TLOC = transitory loss of consciousness.

6. Discussion

The management of MTBI in patients on DOACs is still debated [3,8,10,16]. The presence of an alteration in the coagulative state caused by DOACs therapy, despite the known pharmacokinetic differences compared to VKAs, has led to the use of the same indications previously proposed for VKA patients in the management of traumatic brain injury in DOACs patients [8,12,14]. Repeat CT after an initial CT without injury during the evaluation of an MTBI is a common practice in OAT patients but poorly supported by evidence. Studies conducted in VKA patients have shown that the risk of delayed ICH is uncommon (<2%) and rarely has serious neurosurgical implications [3, 8,17]. In addition, the risk of delayed ICH in VKA patients seems to be related to the presence of predictive factors such as excessive prothrombin time (PT), prolongation on arrival (PT >3) or trauma-related characteristics (mechanism of injury, trauma dynamic) [17]. This evidence suggests that a repeat CT after a previous CT without post-traumatic ICH should not be routinely performed on VKA patients, despite the ongoing OAT, and that the study of patient characteristics may indicate a risk profile where it may be useful to consider the exclusion of a delayed ICH [17,18].

Currently, limited information is available for patients on DOACs on the incidence of delayed ICH or any clinical and laboratory risk characteristics associated with the possible prediction of delayed ICH. This study, which examined a large cohort of patients undergoing DOACs therapy and included five Italian centres, presents some novel findings that can be used in the clinical practice of MTBI management of patients taking DOACs.

Study results confirmed a low incidence of delayed ICH in patients on DOACs; even if delayed ICH was present, there was a low incidence of neurosurgery or death. In a review of the previously available data on the incidence of ICH in patients on OAT (VKA and DOACs), Puzio et al. estimated, using a random-effects model, that the risk of delayed ICH for patients on DOACs was 2.43% (95% CI 1.31–3.88%), which was identical to the risk for patients on VKA [19]. The mortality rate following delayed ICH was lower in patients on DOACs than on VKAs (0.16% vs 0.45%), indicating that although the risk of ICH in patients taking DOACs is higher than in non-anticoagulated patients (0.4%), the impact on patient outcome appears to be very limited [17,19,20]. More recently, three studies assessed the risk of delayed ICH in cohorts of patients on DOACs only. Mourad et al., using the current largest patient cohort, reported that only 2 of 420 patients undergoing repeat CT after 12 h from the first negative CT presented with delayed ICH [10]. Similarly, Barmparas et al. found only 3 patients (1.2%) with delayed ICH at a second CT performed within 4–6 h out of a total cohort of 203 patients who repeated CTs [21]. In a study involving 314 patients repeating a CT scan within 72 h of a previous negative CT scan, Soleimani et al. identified only 3 patients with delayed ICH, none of whom underwent neurosurgery [6]. All three studies considered patients with traumatic brain injury and did not focus only on MTBI. While the rates of delayed ICH are similar to those reported in the present study, there appears to be heterogeneity in the ED management of these patients and in the timing of re-evaluation.

In contrast to the studies previously mentioned, the present study attempted for the first time to define a risk profile for delayed ICH by assessing the clinical characteristics presented on arrival in the ED, taking into account the timing and dynamics of the trauma [10,19,21]. The analysis of the risk factors may have been partly limited by the small number of delayed ICHs. Interestingly, none of the patients assessed later than 8 h after trauma presented an ICH. In the study performed by Mourad et al., patients presenting after 12 h following trauma and after an initial

Table 3
Baseline, clinical and anamnestic characteristics of patients divided between those who were found to have a delayed ICH and those who did not report a delayed ICH.

Variable	Global	No delayed ICH	Delayed ICH	*p*-value
Patients, n (%)	916 (100)	902 (98.5)	14 (1.5)	
Type of DOACs, n (%)				0.088
Direct factor Xa inhibitor	725 (79.1)	717 (79.5)	8 (57.1)	
Direct thrombin inhibitor	191 (20.9)	185 (20.5)	6 (42.9)	
Time between trauma and ED evaluation, n (%)				0.033
Within 3 h	542 (59.2)	533 (59.1)	9 (64.3)	
Between 3 and 8 h	167 (18.2) 207	162 (18)	5 (35.7)	
More than 8 h	(22.6)	207 (22.9)	0 (0)	
Risk factors, n (%)				
Major dynamic	27 (2.9)	25 (2.8)	2 (14.3)	0.061
Post-traumatic TLOC	25 (2.7)	22 (2.4)	3 (21.4)	0.005
Post-traumatic amnesia	87 (9.5)	82 (9.1)	5 (35.7)	0.007
Post-traumatic seizure	4 (0.4)	4 (0.4)	0 (0)	1.000
GCS < 15	102 (11.1)	98 (10.9)	4 (28.6)	0.060
Alcohol or drug intoxication	18 (2.0)	18 (2.0)	0 (0)	1.000
Evidence of trauma above the clavicles	624 (68.1)	613 (68.0)	11 (78.6)	0.566
Concomitant anti-platelet therapy	46 (5.0)	46 (5.1)	0 (0)	1.000
Vomiting	16 (1.7)	15 (1.7)	1 (7.1)	0.220
Headache	27 (2.9)	27 (3.0)	0 (0)	1.000
Signs of skull base fracture	4 (0.4)	4 (0.4)	0 (0)	1.000
Presence of other fractures, n (%)	386 (42.1)	381 (42.2)	5 (35.7)	0.787
At least one risk factor, n (%)	730 (79.7)	716 (79.4)	14 (100.0)	0.086
At least one risk factor with ED arrival within 3 h after the trauma, n (%)	439 (47.9)	430 (47.7)	9 (64.3)	0.283
At least one risk factor with ED arrival within 8 h after the trauma, n (%)	564 (61.6)	550 (61)	14 (100.0)	0.001

Note: TLOC = transitory loss of consciousness.

negative CT scan were excluded from a second CT scan, suggesting that the presumed risk of delayed ICH may be zero after this time [10]. The time frame in which the risk of delayed ICH should be ruled out with confidence is not universal, and some authors previously suggested considering repeat CT even beyond 24 h after trauma for patients taking VKAs [14,22,23]. Unfortunately, both the current study and the study by Mourad et al. do not consider the time interval between trauma and the last intake of DOACs, limiting the possibility of correlating this information with the risk of delayed ICH [10]. Within 8 h of trauma, the absence of clinical risk factors appears to significantly reduce the risk of delayed ICH. Earlier studies had suggested that normal neurological status on arrival or the absence of clinical risk factors most commonly reported in the literature reduce the risk of general ICH and delayed ICH [8,16,24]. In the study by Mourad et al., one of the two patients with delayed ICH presented with an altered GCS on arrival and the Injury Severity Score (ISS) value on admission seemed to suggest an increased risk of bleeding after a negative first CT [10]. However, the ISS value used in major trauma appears to be more complicated in the assessment of minor trauma as it requires an extensive and not immediate diagnostic assessment [25]. Concussion, in the present study was found to be associated with the presence of delayed ICH, is widely reported to be a risk condition for the traumatic brain injury patient. Uccella et al. suggested that the absence of concussion, even in the anticoagulated patient, limits the risk of ICH, while Easter et al. had previously suggested that in the absence of concussion the presence of ICH resulted in a low risk of neurosurgical outcome [26,27]. Therefore, even for patients on DOACs, it seems that careful assessment of the clinical condition at admission may be predictive of general and delayed ICH [16,24].

The study presents some limitations. Firstly, the retrospective nature of the study exposes it to possible biases typical of this study design. However, the large number of patients, the different centres involved and the presence of a protocol that standardises the clinical assessment and considers a large number of variables should have limited these biases. Secondly, the repeat CT was not performed on all patients with a first negative CT. Rather, the decision to perform a repeat CT was left to the physicians managing the patient. Finally, the categorisation of the time interval between trauma and CT was performed arbitrarily, using eight hours as described in NICE guidelines [14].

7. Conclusions

The current study used the largest multicentre cohort exclusively of patients taking DOACs with MTBI who underwent a repeat CT after an initial CT free of ICH. Study results confirmed earlier evidence on the reduced incidence of delayed ICH in this patient group and its low impact on patient outcome. None of the patients evaluated 8 h after trauma with a first negative CT presented with delayed ICH, and among patients who had their first CT within 8 h of trauma, assessment of risk factors may indicate a risk profile of delayed ICH even in patients taking DOACs. Although further confirmation of the presented results is needed, repeated CT appears to be unnecessary and the assessment of trauma and patient characteristics may help to exclude the risk of delayed ICH.

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Gianni Turcato: Writing – original draft, Data curation. **Alessandro Cipriano:** Writing – original draft, Methodology, Conceptualization, Data curation. **Arian Zaboli:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft. **Park Naria:** Writing – original draft, Data curation. **Alessandro Riccardi:** Conceptualization, Data curation. **Massimo Santini:** Data curation. **Roberto Lerza:** Data curation. **Giorgio Ricci:** Data curation. **Antonio Bonora:** Data curation, Methodology, Writing – original draft. **Lorenzo Ghiadoni:** Writing – original draft, Supervision, Data curation, Conceptualization.

Declaration of Competing Interest

All authors have no conflicts of interest.

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