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Haemorrhagic progression of contusions after traumatic brain injury in orally anticoagulated patient. The Rule of (6I's)

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ABSTRACT

Traumatic brain injury carries a high risk of neurological disability and fatality[1-8]. The extent of the injury to the neuronal tissue following a head impact defines the primary injury. The acceleration energy delivered at the time of impact provokes this injury. There are numerous secondary responses to the injury that mostly intensify the primary injury. When a head impact causes a contusion, the hemorrhagic injury frequently progresses over the first few hours after impact, either growing or developing new, non-contiguous hemorrhagic lesions, a condition known as the hemorrhagic progression of a contusion[1,2,4,7,9-14].

ILLUSTRATED CASE

An 88-year-old woman was admitted with a severe headache, multiple emetic episodes, and a brief loss of consciousness after falling while doing housework. Her past medical history included anticoagulation with warfarin for atrial fibrillation (international normalized ratio (INR): 3.75). She had normal vital signs and a grossly intact neurological examination on admission. A cranial computed tomography (CT) scan was performed 45 minutes after arrival to the emergency department, which revealed small bifrontal contusions (Fig 1). It was decided to transfer her to the intermediate care unit with non-invasive hemodynamic monitoring, analgesia, continuous neurological evaluation, and neurosurgical evaluation. At 18 hours, she started

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having emetic episodes and drowsiness. An emergent follow-up cranial CT scan showed extensive bifrontal and bitemporal contusions with intraventricular bleeding (Fig 2). Due to rapid deterioration of the respiratory pattern, the airway was protected with a sequence of rapid intubation, sedation, protective mechanical ventilation, osmotherapy, fresh frozen plasma, and prothrombin complex concentrate. The patient progressed to coma and expired 36 hours after her presentation.

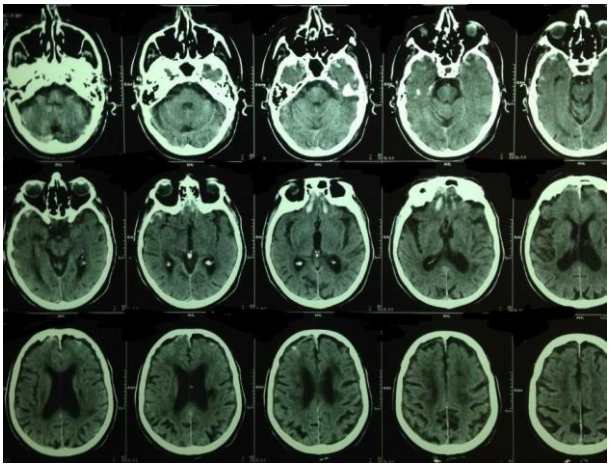

Figure 1. CT scan head on admission

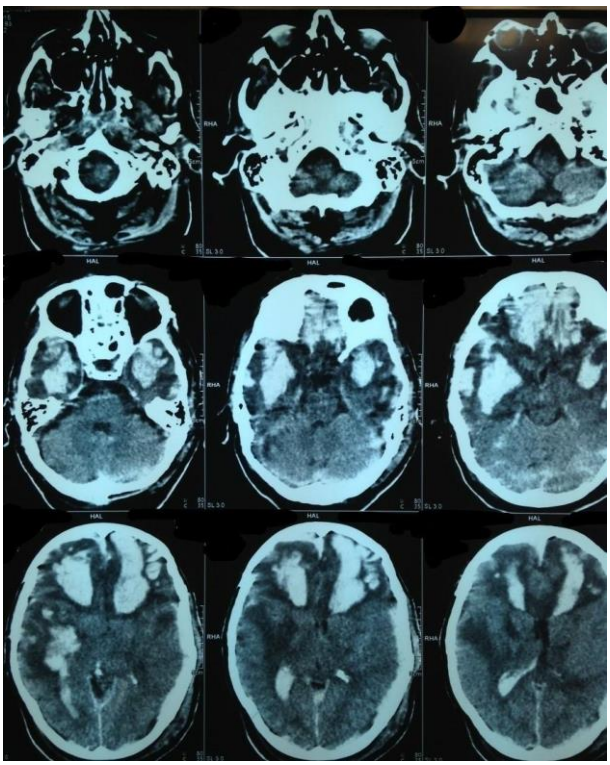

Figure 2. Follow-up CT scan showing marked changes with extensive intracerebral bleeding

Anticoagulant-associated ICH

Anticoagulated patients represent a major neurocritical care burden, as anticoagulation is one of the leading risk factors for intracranial hemorrhage (ICH) after a head impact.[15] The risk of developing ICH after a head injury is 42.2 times higher in patients on oral anticoagulants than in control patients.[16] Aggravating factors associated with anticoagulant-induced bleeding complications include older age, alcohol abuse, renal and hepatic insufficiency, uncontrolled anticoagulant, the targeted intensity of anticoagulant, prior stroke, concomitant anti-platelet therapy, and hypertension.[6,8,9-13] As a result, prompt screening strategies, and interventions that promote better neurological outcomes in the anticoagulated population after head impact are critical.

Warfarin versus direct oral anticoagulants (DOACs)

Recent randomized trials on orally anticoagulated participants for atrial fibrillation have demonstrated a 50% reduction in the incidence of ICH with DOACs compared to warfarin.[17-20] Nevertheless, given the high prescription rates of DOACs and unavailability of the specific reversal agents, ICH development with DOACs has become an important issue and can result in permanent disability and fatality, as with warfarin.[18-21] In a randomized clinical trial by Hankey et al[22] (2014), the fatality rate from anticoagulant-associated ICH was 49% (85/172), and among 85 participants who experienced fatality due to anticoagulant-associated ICH, 50% (54/85) were assigned with warfarin and 48% were assigned with rivaroxaban (31/85). Given the fact that there is an insignificant difference in fatality rate between DOAC and warfarin, the natural history of DOAC-associated ICH should be broadly investigated, and prospective studies on hematoma expansion in this specific group are warranted.

European Federation of Neurological Societies (EFNS) guidelines

In 2002, EFNS set guidelines targeting all anticoagulated participants with normal initial CT scans after sustaining a minor head impact.[4-6] The EFNS guidelines entailed one-day admission for close neurological observation, and a second head CT scan before discharge to rule out delayed ICH.[4-6] However, the growing body of research showed heterogenicity

to support EFNS recommendations for anticoagulated patients after minor head impacts.

A recently published meta-analysis by Puzio et al[7] (2021) estimated 2.43% (95% CI, 1.31-3.88%) and 2.31% (95% CI, 1.26-3.66%) for delayed ICH on DOACs and warfarin, respectively. Only a minority of 0.6% (2/1263) and 0.48%(8/1788) of those on DOACs and warfarin, respectively, reported fatalities, while the majority 86% (59/69) had no clinical complications. The authors concluded that screening for delayed ICH for those on oral anticoagulants is not warranted based on their estimated overall crude risk of fatality 0.36% (11/3051).[7]

In contrast, in a published study by Menditto et al[1] (2012) on the delayed ICH in orally anticoagulated participants, it was found that 6% (5/87) of participants with normal initial scans, developed delayed ICH, which was evident in a CT scan performed 24 hours after the trauma. The estimated relative risk of delayed ICH with an initial INR greater than 3.0 was 14 (95% CI, 4-49).[1] In a meta-analysis by Betchelor et al[14] (2012) the estimated higher odd ratio of fatalities in patients on warfarin with the head impact was 2.0008 (95% CI, 1.634-2.467). Accordingly, the authors supported the advisability of a second head CT scan as advocated by EFNS guidelines.

Confounding Factors of Haemorrhagic Progression

The challenges in defining the confounding factors of hemorrhagic progression in specific patients on oral anticoagulants include a paucity of relevant clinical data. However, various predictors have been reported in the literature concerning post-traumatic hematomas associated with trauma in general participants.

I. Increased age

In a published study by Melamed et al[23] (1980) and Purkayastha et al[24] (2014), increased age has been associated with contusion progression through several mechanisms. Increased age induces structural weakness in the cerebral microvasculature, endothelium loss, and reduced resting cerebral blood flow, which can consequently contribute to contusion progression.[23,24]

II. Intractable headache and emesis

The most common symptoms of a cerebral contusion are headache, emesis, concentration problems, and memory loss.[25] Patients struggling with continued symptoms despite proper medical management should warrant a second screening with a CT scan as the progression of contusion is highly expected.

III. Increased systemic blood pressure (BP) at admission

In a retrospective study by Wan et al[8] (2017), hypertensive participants had 4.5 times the incidence of ICH progression compared to normotensive participants, which can be ascribed to increased baseline blood-brain barrier permeability.

IV. Inclined Glasgow coma score (GCS) at admission

The initial GCS has been a predictor for contusion progression. The contusion progression was reported with GCS <14 by White et al[9] (2009), GCS ≤5 by Qureshi et al[10] (2015), and GCS <8 by Carnevale et al[11] (2018).

V. INR level >1.2, Platelet count <100 × 10^9 /L

Regarding laboratory parameters, White et al[9] (2009) and Wan et al[8] (2017) demonstrated contusion progression three times in participants whose initial INR was>1.2 compared to participants whose initial INR was ≤1.2. It has been shown by Sharma et al[12] (2016) that contusion progression increases seven times for each unit increase in INR. Additionally, Juratli et al[13] (2014) showed a strong association between contusion progression and platelet count <100 × 10^9/L, about six times the increased risk.

VI. Intoxication by alcohol

Several studies have shown a higher frequency of contusion progression with alcohol intoxication.[11,13,26,27] Alcohol intoxication contributes to coagulopathy through several mechanisms, including impairment of platelet function and reduction of vascular tone; both counteract each other on contusion progression.[27] Although the association has been reported, the causality remains unknown.

6I's Rule

1.	Increased age
2.	Intractable Headache and emesis
3.	Increased systemic BP at admission
4.	Inclined GCS at admission
5.	INR Level >1.2, PLT < 100 × 109 /L
6.	Intoxication by alcohol

As a goal to prevent deaths in patients with head impact and oral anticoagulants, we proposed the 6 Is rule (Table 1). The presence of any of the (i) in context with the history of current oral anticoagulant use indicates admission and performance of serial CT scans after 24 hours or according to neurosurgeon criteria. Applying and spreading the rule of the (6Is) will facilitate the identification of high-risk individuals and thus early recognition of possible delayed ICH or contusion progression. This can be a potentially useful, and reliable objective screening tool for emergency physicians, nurses, and nursing assistants.

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