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Review

Resuming anticoagulant therapy after intracerebral bleeding

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ABSTRACT

The clinical benefit of resuming anticoagulant treatment after an anticoagulants-associated intracranial hemorrhage (ICH) is debated. No randomized trial has been conducted on this particular clinical issue. The risk of ICH recurrence from resuming anticoagulant therapy is expected to be higher after index lobar than deep ICH and in patients with not amendable risk factors for ICH. Retrospective studies have recently shown improved survival with resumption of treatment after index anticoagulants-associated ICH. Based on these evidences and on the risk for thromboembolic events without anticoagulant treatment, resumption of anticoagulation should be considered in all patients with mechanical heart valve prosthesis and in those with amendable risk factors for anticoagulants-associated ICH. Resumption with direct oral anticoagulants appears a reasonable option for non-valvular atrial fibrillation (NVAF) patients at moderate to high thromboembolic risk after deep ICH and for selected NVAF patients at high thromboembolic risk after lobar ICH. For VTE patients at high risk for recurrence, resumption of anticoagulation or insertion of vena cava filter should be tailored on the estimated risk for ICH recurrence.

Contents

1. Introduction

The age-standardized incidence of intracerebral hemorrhage (ICH) varies between 14.5 and 159.8 per 100•000 person-years worldwide [1]. In a systematic review of population-based studies involving over 9 million patients from 21 countries, ICH was reported to have an estimated incidence of 24.6 per 100•000 person-years (95% confidence interval [CI] 19.7–30.7), with no substantial decrease over time between 1980 and 2008 [2]. In the same review, the median case fatality was about 40% at 1 month (range 13.1–61.0) and about 55% at 1 year (range 46.0–63.6), with no significant decrease over time; the 12-month independency rate, as assessed by modified Rankin Scale (mRS) or Glasgow Outcome Scale, was low and varied from 12 to 26% [2].

The incidence of ICH in patients on anticoagulant treatment varies between 0.6 and 1.0% annually [3]. In an analysis including 52•993 patients with ICH admitted to US hospital, in-hospital mortality ranges between 42 and 40% in warfarin-associated ICH and between 29 and 25% in non-warfarin-associated ICH (adjusted Hazard Ratio [HR] 1.35, 95% CI 1.24–1.47) [4]; while in-hospital mortality remained substantially unchanged over time for warfarin-associated ICH, it exhibited a trend to decline each year for non-warfarin-associated ICH [4]. At the time of

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discharge, about 60% of patients with an anticoagulant-associated ICH have a major functional disability [5].

The clinical benefit of resuming anticoagulant treatment after anticoagulants-associated ICH is debated and no randomized clinical trial has evaluated the clinical benefit of resuming anticoagulant treatment after ICH. Both the risk of a subsequent ICH if anticoagulation is resumed and the risk of thromboembolic events if anticoagulation is withheld need to be carefully evaluated, with a decision based upon risk factors and patient condition.

2. Risk of recurrent ICH if anticoagulation is resumed

The risk of recurrence from resuming anticoagulant therapy can be estimated by considering the type of index ICH, patient risk factors as well as specific findings from Magnetic Resonance Imaging (MRI).

2.1. Index ICH and risk of recurrence

Based on the site of bleeding, ICH is classified as intraparenchymal hemorrhage, subarachnoidal hemorrhage and epidural or subdural hematoma. These events can occur isolated or co-exist in a single patient.

Based on the presumed etiology, ICH can be classified as either spontaneous or secondary. Secondary ICH (15 to 20% of overall ICHs) is clearly associated with trauma, arterio-venous malformations, neoplasms, drugs, and coagulopathy (inherited, or acquired). The risk of recurrence after secondary ICH can be reduced by amending underlying modifiable risk factors or predisposing conditions, as currently recommended in the specific setting of non-valvular atrial fibrillation (NVAF) [6]. Spontaneous ICH (80 to 85% of overall ICHs) is mainly associated with small vessel disease, which is the results of systemic disorders also affecting the brain; principally systemic hypertension and amyloid angiopathy [7]. At neuroimaging, spontaneous parenchymal hemorrhage can be distinguished as two types: deep and lobar (Fig. 1).

ICH is defined as 'deep' when it has basal ganglia, thalamus, internal capsule, cerebellum or brain stem involvement; its distribution originates from the lipohyalinosis of arterial perforators deep in the brain [8] that is strongly associated with systemic hypertension [9–10].

ICH is defined as 'lobar' when it involves cortical and cortico-subcortical structures located in the frontal, parietal, temporal or occipital lobes. Lobar hematomas are generally associated with sporadic or familial cerebral amyloid angiopathy (CAA); this condition is characterized by amyloid fibrils deposition in small to medium-sized cortical and leptomeningeal arteries [11]. The prevalence of CAA has been shown to increase with age, from 2.3% in subjects 65 to 74 years old to over 12% in those over 85 years, but even consistently greater in subjects with Alzheimer disease [12].

Deep and lobar hemorrhages have different risks of death and recurrence [13–16]. In a prospective study, lobar ICH had more severe presentation, larger volume and more common subarachnoid or subdural extension than nonlobar ICH at admission [13]; recurrent ICH only occurred after a first lobar ICH (annual risk of recurrence 11.8%; 95% CI, 4.6–28.5%) [13]. In a cohort of 207 patients surviving a first intracerebral bleeding, recurrent intracerebral hemorrhage was more common after lobar than deep localization (cumulative 2-year rate 22% vs 4%, $p = 0.007$) [15]. The higher risk for recurrence after lobar ICH has been confirmed in a systematic review of 9 studies [14]. Similarly, according to prediction models, the rate of recurrence at 1 year was estimated to be 15% after lobar ICH and about 2% after deep ICH [16]. Oral anticoagulant treatment was associated with lobar hemorrhage when compared with no antithrombotic treatment (OR 1.70, 95% CI 1.03–2.81) [17]. Furthermore, the case fatality at 30 days has reported to be higher after lobar ICH [18].

In order to include these physiopathology hints, the etiology-based SMASH-U classification, distinguishes ICH associated with Structural vascular lesions, Medications, Amyloid angiopathy, Systemic disease, Hypertension, or Undetermined etiology [19]. Amyloid and hypertensive angiopathies account for 20% and 35%, respectively, anticoagulant treatment for 14%, structural vascular lesions and systemic diseases (liver cirrhosis, thrombocytopenia, and other rare conditions) for 5% each [19]; in 21% the etiology of ICH remains undetermined. Patients with structural lesions had the smallest hematomas and the best prognosis (3-month mortality near 4%), whereas patients with anticoagulation-related ICHs had the largest ICHs and the poorest prognosis (3-month mortality about 54%) [19].

2.2. Patient risk factors and risk of recurrent ICH

Limited data are currently available on risk factors for recurrent ICH after resuming anticoagulant treatment. No significant predictor for recurrence was found in 91 patients reinitiating warfarin after a first ICH while on vitamin K antagonists (VKAs) [20]. Trends toward incresed risks of recurrence were observed for male sex, hypertension, prosthetic valves, previous ischemic stroke, renal failure, cancer, and spontaneous events [21]. Few data are available on uncontrolled hypertension and the risk for ICH and recurrent ICH [21–23]. However, all studies to date have been statistically underpowered to provide definitive conclusions on risk factors for recurrent anticoagulation-related ICHs; indeed, in addition to the low incidence of intracranial bleedings,

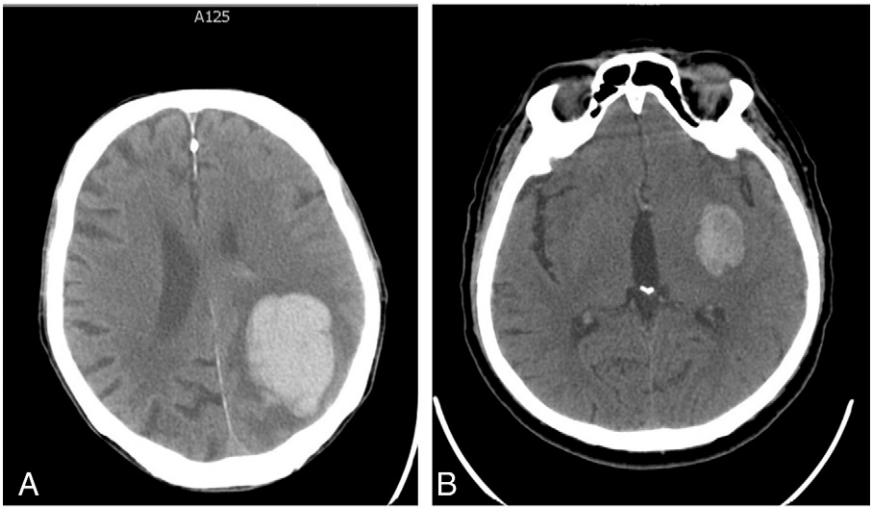

Fig. 1. Parenchymal hemorrhage can be distinguished at neuroimaging as lobar ICH (A) and deep ICH (B).