REVIEW

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Intracerebral haemorrhage: an often neglected medical emergency

Abstract Intracerebral haemorrhage (ICH) is the deadliest form of stroke, carrying a mortality rate between 30% and 55%, increasing to 67% in patients on oral anticoagulant therapy (OAT). Despite its relevant incidence, the treatment of ICH has been until recently a largely neglected item, addressed by only a few trials. Early treatment of ICH in non-anticoagulated patients with recombinant activated factor VII (rFVII) has been demonstrated to be able to limit the growth of the haematoma, but such a promising result requires further confirmations. In ICH patients receiving OAT a prompt reversal of the anticoagulant effect should be warranted in order to reduce the consequences of this dreadful adverse event. In clinical practice, however, just a small proportion of anticoagulated patients receive this treatment, probably because of the fear of thromboembolic complications. It is now time to check our way of thinking about ICH, regarding and treating it as a compelling medical emergency.

Keywords Intracerebral haemorrhage · Oral anticoagulants · Antiplatelet drugs · Recombinant activated factor VII · Emergency medicine

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Introduction

The gap in medical knowledge between ischaemic and haemorrhagic type of stroke is surprising. Whereas the ischaemic side has been extensively evaluated by an impressive amount of pathophysiological studies as well as of clinical trials, intracerebral haemorrhage (ICH) has been so far a relatively neglected medical issue, addressed by a handful of trials.

Such a difference is even more surprising if we consider some epidemiological features of this disease. ICH is a common disorder, with an estimated overall incidence between 12 and 15 cases per 100 000 people each year [1–5], i.e., 37 000–50 000 cases each year in the USA [2, 3]. The most striking data, however, is its 6-month mortality, ranging between 30% and 55% and increasing up to 67% in patients receiving oral anticoagulant therapy (OAT). Moreover, it is a seriously disabling illness, as 80%–90% of survivors are left with dense neurological deficits [1–5].

In this review we will first examine the pathophysiology of ICH in patients with normal haemostasis and in patients in anticoagulant or antiplatelet treatment, and then we will consider the current therapeutic options for both groups of patients.

Pathophysiology of ICH in patients with normal haemostasis

ICH can be defined as an acute and spontaneous bleeding into the brain parenchyma [5]. In more than two-thirds of cases ICH is classified as primary, as it occurs from spontaneous rupture of small vessels damaged by hypertension (60%–70% of cases) or amyloid angiopathy (15% of cases). In a minority of patients ICH results from trauma, vascular abnormalities (arteriovenous malformations and aneurysm) or other causes listed in Table 1. The incidence

Table 1 Causes of intracerebral haemorrhage

Primary intracerebral haemorrhage (78%–88% of cases)
- Chronic hypertension (60%–70% of cases)
- Cerebral amyloid angiopathy (15% of cases)

Secondary intracerebral haemorrhage
- Trauma
- Arteriovenous malformation
- Intracranial aneurysm
- Cavernous angioma
- Venous angioma
- Dural venous sinus thrombosis
- Intracranial neoplasm
- Coagulation disorders
- Vasculitis
- Cocaine or heavy alcohol use
- Haemorrhagic conversion of ischemic stroke

of ICH increases exponentially with age, is higher in men than in women and is strongly increased by antiplatelet or anticoagulant therapy [6].

ICH has been considered until recently a monophasic event, in which blood clotting and the tampon effect of the surrounding tissues were able to self-limit the extent of the injury. Such a pathophysiological picture has probably conditioned the medical approach to such a disease, usually oriented to a minimalist, if not nihilistic, attitude. The landmark prospective study of Brott et al. [7] was the first to demonstrate that an increase in haematoma volume of more than 33% occurs within 3 h from the ICH onset in more than one third of patients, even in the absence of coagulation defects. This process, known as early haematoma growth, is of paramount clinical relevance, as both mortality and functional outcome have been demonstrated to be strictly related to the haematoma volume [8–10]. On these pathophysiological grounds it is very attractive to hypothesise that an early haemostatic treatment might stop ongoing bleeding and improve outcomes [11].

A further mechanism involved in neurological deterioration is the process of perihaematomal brain injury. The development of perihaematoma oedema starts early, in most cases within 3 h from ICH onset, and it progressively increases for at least 72 h [9, 11]. Although apparently paradoxical, the main role in promoting perihaematoma oedema is played by thrombin. Activation of the coagulation cascade with release of thrombin during clotting, indeed, appears to be the triggering event that initiates formation of brain oedema, because thrombin itself is able to activate both inflammation and cytotoxicity and disrupts the blood–brain barrier [12–14].

Pathophysiology of ICH in patients receiving antithrombotic therapies

Any antithrombotic treatment negatively affects both the incidence and the prognosis of ICH. Oral anticoagulant treatment (OAT) significantly increases the risk of ICH in comparison with patients who are not on OAT, leading to an estimated incidence as high as 1.8%/year [15–19]. Risk factors for ICH in OAT patients are listed in Table 2. The relationship between intensity of anticoagulation and the risk of ICH is a relevant point. Although International Normalised Ratio (INR) values exceeding 3.5–4 are associated with a higher risk of ICH, the majority of OAT-related ICH (OAT-ICH) occur when the INR is within the therapeutic range [20–22]. Oral anticoagulation with INR to maintain levels between 2 and 3, even if carefully regulated, increases several times the relative risk of ICH, with an absolute risk ranging from 0.3 to 0.6%/year [17–22].

Thus, OAT not only increases the risk, but also worsens the prognosis of ICH, increasing its severity as well as the likelihood of death [23–25]. Although the dynamics of haematoma expansion in OAT-ICH is not fully established, it is reasonable to assume that the persistent coagulopathy may lead to haematoma growth over a longer period than in non-OAT patients [25]. This finding is of great clinical relevance, as it provides the pathophysiological rationale for the treatment of OAT-ICH, which should be aimed to immediately reverse the anticoagulant effect in order to limit haematoma expansion.

In the general perception antiplatelet drugs are very safe, carrying only a small risk of gastrointestinal adverse effects. This perception is not at all correct, because aspirin (the most widely used antiplatelet drug) carries a significant risk of ICH, ranging between 0.2% and 0.3%/patient/year, slightly higher than the estimated absolute rate in the general population [6], not receiving aspirin. Such a figure is further worsened by the combination of clopidogrel and aspirin, which may increase ICH by a clinically relevant magnitude in patients with cerebrovascular diseases [26, 27]. Moreover, it has been recently demonstrated in a population-based study that regular aspirin use before ICH onset increases 2-fold the risk of death, independently from the severity of bleeding [28]. Similar findings had already been obtained in previous studies [29, 30], although they were not confirmed in a very recent one [31]. A possible explanation for the observed increase in mortality is an early enlargement of haematoma because the impairment of the haemostasis lasts for a few days even after aspirin withdrawal [28, 30].

Finally, the association of warfarin and aspirin should be considered. This is a very common clinical problem, as

Table 2 Risk factors for developing intracerebral haemorrhage during oral anticoagulant therapy

- Age (especially over 75 years)
- Hypertension (especially systolic blood pressure >160 mmHg)
- Previous stroke
- INR levels
- Concomitant use of antiplatelet drug
- Cerebral amyloid angiopathy

it has been estimated that approximately 20% of patients taking warfarin for atrial fibrillation also receive antiplatelet drugs for concomitant coronary heart disease [32]. Data about the risk of ICH during this combination therapy are conflicting, as some studies show an increased risk when anticoagulant and antiplatelet therapy are combined [33, 34], whereas others do not [35, 36]. Although the inconsistency of data precludes any evidence-based firm conclusion, it seems reasonable to assume that the ICH risk is further increased by the association of warfarin and antiplatelet drugs.

Emergency treatment of ICH

Recent insights into the pathophysiology of ICH are expected to profoundly modify the treatment of this disease. The key message strongly emerging from the current literature is that "time is brain" [37], and therefore ICH should be regarded and treated as a compelling medical emergency. It is therefore time to leave the minimalist, if not nihilistic, approach to the therapy of ICH that has been the predominant attitude in the past.

Emergency management of ICH patients includes airway management, control of intracranial pressure and treatment of hypertension [38]. The latter point is of great relevance, as extreme hypertension is a common finding within the first hours from ICH onset, and raised blood pressure negatively affects ICH outcome [39, 40], although a recently published study fails to find such an association [41]. Treatment of hypertension can be performed in an emergency setting by intravenous boluses of labetalol (10–80 mg bolus every 10 min, up to 300 mg), whereas in intensive care units blood pressure can be controlled by continuous infusion of labetalol, esmolol or nicardipine [3]. Sodium nitroprusside should be avoided in this setting because of its tendency to raise intracranial pressure through cerebral vasodilatation [42]. As far as intracranial pressure control is concerned, emergency measures to lower it are required for comatose patients as well as for those with signs of cerebral herniation [38]. However, no anti-oedema treatment (steroids, osmotic diuretics, haemodilution) has been demonstrated to reduce mortality and disability in these patients [43–45].

Alongside these supportive therapies should stand aetiological treatments aimed to reduce haematoma size, for instance by surgical removal. The effectiveness of surgical removal of haematoma is still a controversial issue, namely if localised in the basal ganglia, the most common site of ICH. Current treatment strategies usually reserve surgical treatment for those patients with subcortical or cerebellar haematoma of more than 3 cm in diameter and impaired consciousness. However, most patients cannot be included in this category, and the benefit of surgical evacuation is not clearly assessed for these cases. The recently published STICH trial included 1033 ICH patients for whom the attending neurosurgeon was uncertain about the choice between surgical or conservative treatment [46]. The STICH trial showed no benefit in outcome from surgery performed within 24 h from randomisation after supratentorial ICH [46]. This result does not mean that surgery is always useless in ICH, as patients who were considered to have benefited from early haematoma evacuation were excluded from the study. However, data from the STICH trial are challenging the views that early neurosurgery can be an effective treatment for every form of ICH.

Despite this disappointing finding of the STICH trial, there are new hopes for an effective medical treatment of this dreadful type of stroke.

Since its approval by the Food and Drug Administration in March 1999 for the treatment of bleeding in haemophilia patients with inhibitors to factor VIII and IX and in patients with acquired haemophilia, recombinant activated factor VII (rFVIIa) has been regarded with great interest by physicians as a potential "pan-haemostatic" agent able to control bleeding in patients with both inherited and acquired coagulation disorders [47]. Administration of a high dose of rFVIIa results in a huge increase of VIIa level, compared to the physiological state, causing faster and higher thrombin generation by binding of TF exposed at the site of endothelial injury. In addition, at pharmacological doses (26–50 nM), rFVIIa can bind to the surface of activated platelets and directly activate FX in the absence of TF. rFVIIa has been also shown to be an effective promoter of haemostasis in bleeding patients with an otherwise normal coagulation system [47]. Many biochemical features of rFVIIa make it very attractive for an early haemostatic therapy of ICH: the very rapid action mainly localised to the site of vascular injury, the short half-life of 2.5 h, and a good safety profile, at least in haemophilia patients [48].

Hence, a recent randomised, placebo-controlled, dose-ranging study was conducted to assess the use of rFVIIa in non-coagulopathic patients with ICH [49]. In this trial 399 patients with primary ICH diagnosed by CT within three hours after the onset of symptoms were randomly assigned to receive placebo or a single intravenous dose of 40, 80 or 160 µg/kg of rFVIIa within one hour after the baseline CT scan. Patients on OAT were excluded from the study. The primary end-point was the percent increase of the volume of ICH at 24 h; secondary end-points were clinical outcomes (survival, disability evaluated according to Modified Rankin, Extended Glasgow Outcome and National Institutes of Health Stroke scale and Barthel Index as well as percent of serious thromboembolic events) at 90 days. Results are extremely encouraging, as patients treated with rFVIIa show a significantly lower increase in the haematoma volume compared to placebo-treated patients (relative, 14% *vs.* 29%, *p*=0.01; absolute, 4.2 *vs.* 8.7 ml,

p=0.01). A dose response is evident, as the difference is significant for higher doses (160 µg/kg), but not for intermediate and lower doses (80 and 40 µg/kg). More interestingly, the reduction in the haematoma growth is accompanied by improved survival and better clinical outcomes in the treated group. Such a beneficial effect is impressive: 90 days mortality is reduced in the rFVIIa group from 29% to 18%, with an odds ratio for survival of 1.8 and a number needed to treat of approximately 9. Equally striking is the effect on severe disability, with a 13% absolute reduction on unfavourable outcomes measured according to the Modified Rankin Scale (odds ratio for improvement 2.2, p=0.0004) and a more than double score on Barthel Index (60.0 *vs*. 25.0, p=0.006) for the treatment group. On the other hand, fears about the thrombogenic potential of such a powerful haemostatic drug are at least partially borne out. Arterial thromboembolic serious adverse events occur significantly more frequently in the rFVIIa-treated than in placebo-treated patients (5% *vs*. 0%), primarily as myocardial ischaemic events and ischaemic stroke, half of them occurring in the largest dose group. However, most patients recovered from these complications, and the overall frequency of fatal or seriously disabling ischaemic events does not differ between rFVIIa and placebo.

How can we transfer the results of this innovative trial into everyday clinical practice? Should we modify our guidelines in order to assure every ICH patient has early rFVIIa treatment? If the question is so radically asked, the answer is certainly not, as stated by a recent systematic review from the Cochrane Library [50]. Many issues suggest caution before recommending rFVIIa as the standard of treatment for ICH. First, in this trial there was no adjustment for blood pressure, a factor known to affect the outcome of ICH [38–40], although the trend of this parameter did not differ among the treatment groups. In future trials, great attention should be paid to this issue in order to identify possible interactions of rFVIIa with blood pressure that could modify the magnitude of benefit of this drug in ICH patients. Second, treatment with rFVIIa is effective only in patients treated within 3 h of symptoms onset, whereas in patients treated later no difference in the haematoma growth is found compared to the controls [51]. This suggests that the time window for this intervention is very narrow, and only a subset of ICH patients could benefit from such a treatment. Indeed, a recently published population-based cohort study estimates that only 13%–18% of ICH patients would have qualified for treatment with rFVIIa by Meyer's trial criteria [52], 2–3 times the rtPA eligibility rate of ischaemic stroke patients [53]. Although the absolute number of treated patients would likely be less than those with ischaemic stroke, it can be postulated that in the USA between 5000 and 9000 ICH patients could be eligible for rFVIIa treatment each year. Such an impressive figure is expected to raise both organisational and financial problems for health care services, but more than 1200 lives may be saved annually [52].

Finally, some concerns have been raised about a possible increase of perihaematoma oedema because of rFVIIa-mediated enhanced thrombin generation, as thrombin has been implicated in the pathogenesis of oedema formation in acute ICH [13, 14]. However in this trial [51] the mean volume of ICH, perihaematomal oedema and intraventricular haemorrhage at 72 h were significantly lower in the rFVII than in the placebo group (mean difference from placebo –11 ml, p=0.003), arguing against an oedema-enhancing effect of the haemostatic treatment.

In conclusion, rFVIIa must be viewed as a promising new therapeutic approach to ICH. Hopefully the ongoing phase III rFVIIa in Acute Hemorrhagic Stroke Treatment (FAST) trial will clarify some of these relevant issues, such as the most effective and safe dose and the potential interactions of rFVIIa with blood pressure control.

Treatment of ICH in anticoagulated patients

ICH is the most fearful and potentially fatal complication of OAT. Although the incidence, time course and rate of haematoma expansion of OAT-ICH are not well defined, it seems reasonable to expect that a rapid restoration of the haemostatic ability will help to stop ongoing bleeding, thus preventing haematoma growth. Against this sensible approach stands the fear of thromboembolic complications because of discontinuation of antithrombotic therapy. The resultant of such opposite forces is often a null vector. In most cases the therapeutic approach is therefore restricted to simply waiting for the disappearance of the anticoagulant effect, even though this can last for several days.

Such a nihilistic approach is particularly astonishing as many guidelines suggest (although with weak strength of recommendations because of the lack of solid evidence) that patients with diagnosed warfarin-associated ICH should receive emergent reversal of anticoagulation [54–58]. However, lack of well designed trial of good methodological quality makes it very difficult to formulate strong recommendations, leaving the optimal treatment of OAT-ICH an already open issue. Treatment options include the use of vitamin K, fresh frozen plasma (FFP), prothrombin complex concentrates (PCC) and rFVIIa [38].

There is a general consensus on vitamin K administration as the first step of warfarin reversal, but as it takes several hours to achieve its full therapeutic effect, concomitant administration of coagulation factors is required in order to immediately reverse the anticoagulant effect. FFP contains all coagulation factors, and it is generally assumed that 1 ml/kg body weight of FFP increases the levels of coagulation factors by 1–2 IU [59]. It is a common experience that the FFP volume required to ensure anticoagulation reversal may vary between 800 and 3500 ml [19]. The latter large volumes may cause a circulatory overload, namely in patients with

impaired cardiac function, which represent a substantial proportion of warfarin-treated patients. FFP carries other drawbacks, such as the need for compatibility testing, the time required for thawing and a small, but definite, risk of adverse reactions, including transfusion-associated lung injury, blood-borne infections and allergic reactions [59].

Many of these problems can be overcome by PCC use. PCC contain coagulation factors II, IX, X and VII (the latter not in preparations licensed in Italy) in a concentrated form and in well standardised amounts. These products are virally inactivated, and therefore are safer than plasma with respect to the risk of transmission of the human immunodeficiency, hepatitis B or hepatitis C virus. A thrombogenic effect has occasionally been reported, but reports dealt with patients at very high thromboembolic risk [60]. Moreover, only a very small volume of product is required in order to ensure complete reversal of anticoagulation: a standard dose of 30–50 IU/kg of PCC consisted of 50–150 ml of reconstituted product, which can be administered within a few minutes.

Studies on small numbers of patients suggest that PCC correct a prolonged INR more rapidly and completely than FFP [61, 62] and reduce the risk for haematoma growth [61], although they does not appear to improve long-term outcome [63, 64].

The already reported biochemical features of rFVIIa make it a promising candidate also for OAT-ICH treatment, but so far the data on this subject are very limited [65, 66]. The very short half-life of rFVIIa can be a serious drawback for the treatment of bleeding in anticoagulated patients. Indeed, rFVIIa action is expected to stop long before the vitamin-K-dependent factors are restored, thus exposing patients to a potentially dangerous time window of persistent anticoagulation.

Patients with OAT-ICH urgently need a definitive improvement in the treatment of their severe complication. Very recently published data show that in Italy, only about a third of patients admitted to emergency departments with warfarin-related ICH undergo procoagulant medical treatment [67]. Moreover, a recently published retrospective review of a single-centre experience on the management of OAT-ICH found a strikingly long delay in time to intervention, as a median period of 210 min is required from computed tomography to FFP administration for patients referred from other hospitals [68]. The Authors found that every 30-min delay in FFP administration is independently associated with a 20% decrease in the probability of successful INR reversal within 24 h [68]. Once again, "Time is brain" [37], and each hospital should have protocols for the treatment of ICH, as they do for ischaemic stroke. Table 3 reports a protocol recently proposed by FCSA (Italian Federation of Anticoagulation Clinics) for the emergency management of ICH in anticoagulated patients.

Many issues remain to be clarified in OAT-ICH, and probably the most compelling is if and when to restart anticoagulation following the development of such a serious adverse effect of warfarin therapy. There is no strong scientific evidence that can help the physician in this difficult decision, which should be made on an individual patient basis, carefully balancing haemorrhagic and thromboembolic risks. As a rule, the risk of recurrence is considerably greater in lobar than in deep hemispheric ICH [69], reflecting a different underlying pathophysiology: hypertension in the former, and cerebral amyloid angiopathy in the latter [70]. The latter disorder is characterised by the deposition of

Table 3 Protocol for the emergency management of intracerebral haemorrhage in anticoagulated patients

In anticoagulated patients with suspected/possible ICH:
    a. Provide a venous access of adequate size
    b. Provide a blood sampling for routine test, including:
        i. Blood count including platelet count
        ii. Prothrombin time – International Normalised Ratio (PT-INR)
        iii. Activated partial thromboplastin time (APTT)
        iv. Serum creatinine
    c. Perform a cerebral computed tomography (CT) in every symptomatic case or following head trauma. The CT should be repeated after a few days if negative or in case of persisting/arising symptoms.
    d. If the CT is positive for intracranial haemorrhage it is MANDATORY to immediately restore normal haemostasis. Then:
        i. Withhold warfarin therapy
        ii. Give vitamin K1 (10 mg by slow IV infusion)
        iii. Give prothrombin complex concentrates at the following doses:
            1. 20 IU/kg if INR<2.0
            2. 30 IU/kg if INR 2.0–4.0
            3. 50 IU/kg if INR >4.0
        iv. If PCC are unavailable, give fresh frozen plasma 15–20 ml/kg. In this case, consider the concomitant administration of diuretics in order to prevent circulatory overload.
        v. Control PT-INR at the end of the infusion and repeat PCC (or FFP) if PT-INR>1.5
        vi. Provide prophylaxis of venous thromboembolism by mechanical methods (graduated compression stockings or intermittent pneumatic compression)
The decision of if, and when, to restart anticoagulation should be made on an individual patient basis, carefully balancing thromboembolic and bleeding risk. As a rule, prophylactic doses of low molecular weight heparins can be safely administered after 3 days and following a normal CT scan.

amyloid peptide in small- and medium-sized blood vessels of the brain, thus resulting in vascular fragility. The clinical syndrome is typified by spontaneous lobar haemorrhage in elderly patients, usually less severe than hypertensive ICH. However, the recurrence rate is considerably higher in patients with lobar ICH and probable amyloid angiopathy (5%–15% patients/year) than in those with hypertensive ICH (2%/year when blood pressure is well controlled).

On these grounds it would seem reasonable to advise against restarting OAT following a lobar ICH. However, this does not mean that for the vast majority of patients with deep hemispheric haemorrhage anticoagulation therapy can be recommended, with a possible exception for patients at very high risk of ischaemic stroke [71].

Further clarification of risk factors for developing OAT-ICH may help to clarify the risk-benefit analysis of warfarin administration in individual patients. Genetic risk factors may have a role in this effort, as the possession of apolipoprotein E (apoE) ε2 or ε4 allele appears to be associated with increased risk of lobar ICH and recurrent ICH resulting from cerebral amyloid angiopathy [72]. In addition, genetic polymorphisms have been identified that predispose to decreased dose requirements for warfarin and may predispose to increased risk for high INR [73, 74]. Finally, remember the profound influence of blood pressure control upon the prevention of ICH. In a recently published randomised trial involving patients on either antiplatelet or anticoagulant therapy, haemorrhagic stroke rate is halved by a mean 9 mmHg reduction in systolic blood pressure [75]. This very simple and inexpensive intervention is the first proven preventive therapy for patients with a history of haemorrhagic events, and should therefore be extended to every patient receiving antithrombotic drugs.

Conclusions

Many issues regarding the appropriate treatment of ICH need to be clarified by properly designed trials. Nevertheless, there is a growing body of literature providing new insights into this serious disease and giving new realistic hopes to ICH patients. The goal of substantially improving the outcome of this dreadful disease is certainly demanding, but is now more feasible than a few years ago.

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