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A PEER-REVIEWED SUPPLEMENT TO

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Supplement Editor: Garnette Sutherland

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Controversies in the Management of Intracerebral Hemorrhage

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INTRODUCTION

At the Calgary Brain 03 conference on Cerebral Blood Flow and Metabolism, a satellite symposium entitled Controversies in the Management of Intracerebral Hemorrhage was held June 10, 2004 at the Telus Convention Centre, Calgary, Alberta. The symposium reflected known controversies in the management of patients with intracerebral hemorrhage, as well as emerging therapeutic strategies. Controlling and minimizing clot size and reformation in patients who suffer intracerebral hemorrhage is of considerable importance. Over the past several decades, medical and surgical approaches to this problem have evolved. The authors have prepared engaging manuscripts that reflect and expand upon the ideas and opinions arising as a result of the symposium.

Auer and Sutherland review the pathophysiology of intracerebral hemorrhage. They reflect upon the relationship of pulse pressure to both hypertensive and β-amyloid angiopathies. Based on pathological observations, they account for the mechanism of clot expansion following the initial hemorrhage. The report includes a resolution of the ongoing debate as to the existence of Charcôt-Bouchard aneurysm, concluding that the changes observed by Charcôt-Bouchard represented segmental disease, not a cul-de-sac. The text is well illustrated, clearly showing the spectrum of pathological changes associated with hypertension and β-amyloid accumulation.

Subramaniam and Hill review controversies in the medical management of intracerebral hemorrhage. This manuscript begins with a review of its epidemiology, including racial variances, anatomical distribution, risk factors and prognostic variables. They critically evaluate present treatment approaches, recommending further investigation into several therapeutic strategies including intracranial pressure monitoring, blood pressure control, hypothermia, seizure prophylaxis and manipulation of blood sugar levels. Outcome following intracerebral hemorrhage remains poor with only a small percentage of patients returning to their former activities. The manuscript includes reference to the reversal of anticoagulation and also discusses coupling medical with surgical intervention.

Marchuk and Kaufmann review randomized clinical trials, experimental evidence and management options related to the surgical treatment of intracerebral hemorrhage. This review indicates that clinical trials conducted to date, including the iSTICH trial, remain controversial as to the role or value of surgery. In contrast, the experimental literature suggests that early evacuation of intracerebral clot improves functional outcome. Also included in this paper is the evolution of surgical techniques which may be employed for clot extraction. They suggest that hemostatic therapy rFVIIa may decrease the rate of post operative hemorrhage.

Dr. Mayer reviews the scientific basis for the potential clinical benefit of rFVIIa in intracerebral hemorrhage. The manuscript demonstrates the safety profile for rFVIIa and includes the design and results of the recently conducted phase IIv clinical trial, examining the efficacy of rFVIIa in reducing clot size following intracerebral hemorrhage. Secondary outcome measures include mortality, Barthel index, modified Rankin score and NIH stroke score at 90 days. The article is important as it shows, for the first time, a potential effective therapy for intracerebral hemorrhage. A large phase III trial is now underway.

This supplement is important as it demonstrates contemporary approaches to the medical and surgical management of intracerebral hemorrhage. The authors have based their conclusions on best evidence and have coupled them with the known pathophysiology of this condition. This creates an atmosphere in respect to intracerebral hemorrhage, not unlike a decade ago when tissue plasminogen activator (tPA) was first introduced for ischemic stroke.

Primary Intracerebral Hemorrhage: Pathophysiology

Roland N. Auer, Garnette R. Sutherland

ABSTRACT: We here review the pathophysiology of primary intracerebral hemorrhage to compare and contrast bleeds due to hypertension and congophilic angiopathy. Hypertension is characterized by early proliferation of arteriolar smooth muscle, followed later by apoptotic smooth muscle cell death and collagen deposition. Eventually excess or deficient collagen deposition can lead respectively to arteriolar occlusion, ectasia or both. Collagen has no contractile capability and is brittle, unable to withstand breakage due to pulse pressure. Arterioles physiologically bring down both blood pressure and pulse pressure, but excessive dilatation results in Charcôt-Bouchard aneurysms, which are fusiform, not saccular structures. The distribution of hypertensive hemorrhage reflects the high pulse pressure of arterioles immediately downstream from major end arteries with minimal intervening branching. Cerebrovascular amyloidosis is a stagnant ß-fibrillosis of arterioles, arising from failure of brain egress of ß-amyloid, after amyloid precursor protein cleavage within brain parenchyma. The lobar distribution of changes reflect an impairment of amyloid removal from brain interstitial fluid and Virchow-Robin spaces. Both diseases cause similar brittle arterioles with poor contractile capability, likely accounting for early growth of hematomas when they rupture. Fibrin globes form in concentric spheres and attempt to seal off the site of bleeding. The size of the final sphere of blood at cessation of bleeding determines the clinical spectrum, from asymptomatic to fatal. Since arteriolar bleeding is slower than arterial bleeding, several hours exist where intervention may be useful with recombinant factor VIIa or other therapies. We speculate on the importance of pulse pressure in the etiology of hemorrhage and resolve the debate over the existence of Charcôt-Bouchard aneurysms. The high pulse pressure and brisk interstitial fluid pumping in Virchow-Robin spaces deep within the brain selectively protects against amyloidosis, while leaving these basal arterioles vulnerable to hypertensive damage. Hypertensive hemorrhages occur deep within the centrencephalon, while amyloid hemorrhages occur in a lobar distribution, where pulse pressure and bulk flow are less, away from the major feeding vessels of the brain. The brain distributions of hypertensive and of amyloid hemorrhages are thus different and complementary.

RÉSUMÉ: Physiopathologie de l'hémorragie cérébrale primitive. Nous revoyons ici la physiopathologie de l'hémorragie cérébrale primitive et nous comparons les saignements dus à l'hypertension et à ceux dus à l'angiopathie amyloïde. L'hypertension se caractérise par une prolifération précoce du muscle lisse des artérioles suivie par l'apoptose des cellules musculaires lisses et la formation de dépôts de collagène. Éventuellement, l'excès ou la perte de collagène peut provoquer respectivement l'occlusion ou l'ectasie artériolaire, ou les deux. Le collagène n'est pas contractile et il est friable et incapable de résister à une rupture due à la tension différentielle. Physiologiquement, les artérioles diminuent la tension artérielle et la tension différentielle, mais une dilatation excessive donne lieu à des anévrismes de Charcôt-Bouchard. Ces anévrismes sont fusiformes et non pas sacculaires. La distribution de l'hémorragie hypertensive reflète la tension différentielle élevée des artérioles immédiatement en aval des artères terminales majeures qui ont peu de ramifications. L'amyloïdose cérébrale est une fibrillose-β des artérioles résultant d'un défaut d'évacuation de la b-amyloïde cérébrale après cleavage de la protéine précurseur de l'amyloïde dans le parenchyme cérébral La distribution lobaire des changements reflète un défaut dans l'évacuation de l'amyloïde du liquite interstitiel cérébral et des espaces de Virchow-Robin. Ces deux maladies rendent les artérioles friables et peu contractiles, ce qui pourrait expliquer la formation précoce d'hématomes lors de ruptures artériolaires. Des sphères concentriques composées d'amas de fibrine se forment pour tenter de sceller le point de saignement. La taille finale de la sphère au moment où l'hémorragie cesse détermine l'issue clinique allant de l'absence de symptômes au décès. Comme le saignement artériolaire est plus lent que le saignement artériel, il existe une fenêtre de plusieurs heures pendant laquelle le facteur VIIa recombinant ou tout autre traitement pourrait être bénéfique. Nous discutons de l'importance de la tension différentielle dans l'étiologie de l'hémorragie et nous tranchons le débat sur l'existence des anévrismes de Charcôt-Bouchard. La tension différentielle élevée et le pompage vigoureux du liquide interstitiel des espaces de Virchow-Robin situés profondément dans le cerveau protègent sélectivement contre l'amyloïdose tout en laissant ces artérioles basales vulnérables aux dommages dus à l'hypertension. Les hémorragies hypertensives surviennent profondément dans le centrencephalon alors que les hémorragies dues à l'amyloïde ont une distribution lobaire où la tension différentielle et le débit sont moindres, loin des vaisseaux majeures du cerveau. La distribution cérébrale des hémorragies hypertensives et amyloïdes est donc différente et complémentaire.

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Primary intracerebral hemorrhage is at the dawn of becoming a more treatable entity,[1] and will soon undergo a similar transformation as ischemic stroke did a decade ago. It is well known that stroke patients have a better outcome when managed in a dedicated critical care environment.[2] Other than the recent trial showing that rVIIa, when administered within four hours after symptom onset, limits the growth of the hematoma, reduces mortality, and improves functional outcome, medical and surgical trials have to a large extent been negative.[3-5] Surgery might worsen outcome by virtue of (1) the fragility of the patient population taken to the operating room, (2) the known trauma of the surgery itself and (3) a high post-operative hemorrhage rate.[6] Substantiating these ideas, the recent surgical trial in intracerebral hemorrhage (STICH) trial of 1033 patients showed no overall benefit of surgery for supratentorial intracerebral hemorrhage. But there may exist patients with hemorrhage within 1 cm of the cortical surface, constituting a surgically treatable subset.[5] Bleeding from a vessel with pathology in the arteriolar wall will preclude the normal contraction of that vessel. But the rate of bleeding from small vessels slow enough to allow time for hemostatic intervention to be beneficial. This review discusses the etiology and pathophysiology of primary intracerebral hemorrhage due to two major diseases of arterioles: hypertension and amyloid angiopathy.

Epidemiology

Non-traumatic intracerebral hemorrhage can be classified as primary or secondary. Hypertensive arteriolosclerosis and amyloid angiopathy account for 78-88% of primary hemorrhages.[7] Association with entities such as arteriovenous malformation, aneurysm, neoplasia, cavernous angioma or coagulopathy is termed secondary intracerebral hemorrhage.

Roughly 15% of strokes are due to primary and secondary intracerebral hemorrhage.[8,9] Differences between racial/ethnic groups exist: African-Americans have a higher estimated incidence of 50 per 100,000 compared to 28 per 100,000 among Caucasians.[10] Among Japanese, the incidence increases to 55 per 100,000. The age-specific incidence of stroke increases from roughly 11 in the <55 year age group rising to approximately 200 at ages 55-64, 700 at ages 65-74, 1400 at ages 75-84, and 2500 at age 85+.[11,12] Hypertension is the most common contributing factor to primary intracerebral hemorrhage. Even borderline isolated systolic hypertension carries an increased risk of intracerebral hemorrhage.[10] The risk is increased by a factor of 3-4 among smokers, varying by the number of cigarettes smoked.[13] Alcohol, diabetes, male sex and low serum cholesterol increase the risk further.[14-16]

Clinical Features

The clinical manifestations of intracerebral hemorrhage range from asymptomatic (with the hemorrhage being discovered incidentally at autopsy) to minimally symptomatic[17] to fatal (Figure 1). Damage results from two physical mechanisms: (1) dissection of brain by blood (effectively severing white matter tracts) and (2) the mass effect of blood.[18] The latter may in turn lead to compressive ischemia in nearby tissue, increased intracranial pressure and the various forms of cerebral herniation (trans-tentorial, subfalcine, tonsillar). Most patients tend to make

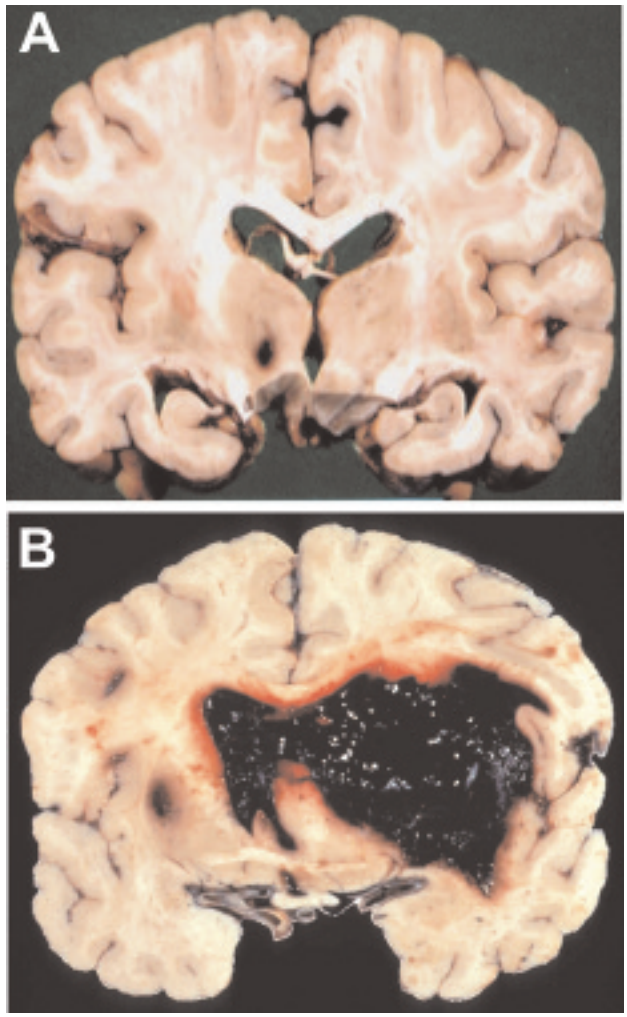

Figure 1: *Clinical spectrum of hypertensive hemorrhage. (A) Asymptomatic intracerebral hemorrhage localized to the left thalamus, not involving the internal capsule. (B) Fatal putamenal hemorrhage with intraventricular extension. The satellite hemorrhage (see text) in the fatal hemorrhage resembles the asymptomatic hemorrhage.*

a very good recovery if clots are <10 ml. But clots over 60 ml in volume, and coma (Glasgow Coma Score of <9) are associated with >90% mortality.[19] The time scale of clinical deterioration is on the scale of hours,[20] not seconds or minutes, due to the source of bleeding being arteriolar, not arterial. Prospective and retrospective studies have shown that clot expansion occurs mostly within the first six hours following symptom onset.[21-24] Clot expansion rates of up to 38%[21] and 36%[24] in the first three hours define the therapeutic window.

An adverse outcome following intracerebral hemorrhage is most strongly predicted by level of consciousness, but age and pre-existing heart disease also correlate with a poor outcome.[25] Other, independent predictors of poor outcome relate to the presence of diabetes mellitus and/or admission hyperglycemia. It has been shown that after intracerebral hemorrhage both diabetes

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and hyperglycemia in non-diabetic patients each contribute to higher mortality, measured at 30 days and three months.[26] These findings in intracerebral hemorrhage are analogous to those found 20 years earlier in ischemic stroke.[27] Why are diabetes and hyperglycemia detrimental? Chronic diabetes is associated with vascular physiological changes, including increased myogenic tone and decreased responsiveness to vasodilators.[28] However, there is no evidence, in the absence of hypertension, for a direct structural effect of diabetes on brain arterioles.

Whether or not ischemia accompanies intracerebral hematomas has been controversial.[29,30] It seems logical that ischemia would be an inevitable consequence of intracerebral hemorrhage, since the bleeding artery is effectively severed and stops delivering blood. It follows that hyperglycemia should adversely affect outcome, since ischemia itself is worsened by high blood glucose levels.[27,31,32] Additionally, ischemia might be compressive in etiology,[33] the compression being associated with either the hematoma itself, brain herniation, brain retractor pressure or surgical manipulation. In the presence of ischemia, hyperglycemia would worsen ischemic injury, possibly as a threshold function, with marked exacerbation as blood glucose rises above 12 mM.[34] A likely mechanism is proton production and acidosis.[35,36] Clinical studies have shown that high blood glucose (1) worsens outcome in patients with intracerebral hemorrhage[26,37] and (2) increases the risk of hemorrhage when recombinant tissue plasminogen activator (rtPA) is administered for ischemic stroke.[38] In patients who sustain intracerebral hemorrhage, we recommend normalization of blood glucose levels with insulin.[39]

Location within the Brain

Study of intracerebral hemorrhage reveals that location is a major determinant of etiology. Hemorrhages may be classified as ganglionic (i.e. in the deep gray matter of the thalamus or basal ganglia) and extraganglionic or lobar (i.e. in the gray or white matter of the frontal, temporal, parietal or occipital lobes). Ganglionic hemorrhages are most likely hypertensive in origin, while lobar hemorrhages are frequently due to amyloid angiopathy.[40] The reasons for the inverse distribution of the two types of hemorrhage are given below, after we review the physiology of arterioles.

Hypertension typically leads to centrencephalic hemorrhage in the basal ganglia (35-44%) or thalamus (10-25%), cerebellum (5-10%), pons (5-9%) and neocortex (19-25%).[26] Thalamic hemorrhages may be further subdivided into four locations: anterolateral (21%), medial (15%), posterolateral (55%) and dorsal (9%).[41] In the absence of hypertension, lobar hemorrhages in the elderly should be considered due to amyloid angiopathy, with a predilection for the frontal and parietal lobes.[42] Together, amyloid angiopathy and hypertension account for the vast majority of lobar hemorrhage.[40] Recurrent hemorrhage most likely occurs in the same general location as the first bleed (i.e. if the first hemorrhage was lobar, so is the recurrence, and if the first hemorrhage was ganglionic, so likely is the second bleed).[43]

Hypertensive arteriolar disease

Arteriolar Anatomy and Pulse Pressure

Arterioles, located between the arteries and capillaries, account for half of the resistance in the circulation from aorta to

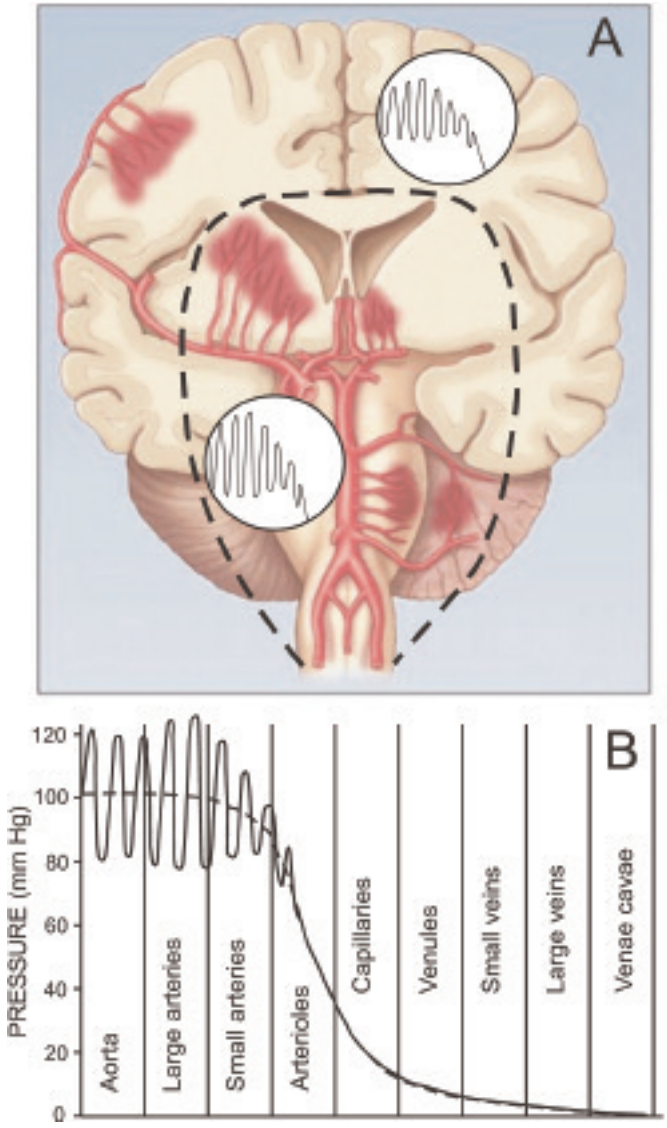

Figure 2: *(A) Locations of the two major types of intracerebral hemorrhage and the proposed relationship between pulse pressures (insets), etiology and location. Centrencephalic hemorrhages (inside dotted line) often associated with hypertension, occur where pulse pressures are high due to proximity to the major arteries. Telencephalic hemorrhages (outside dotted line) occur in regions with lower pulse pressure, and are commonly due to amyloid angiopathy. (B) Pulse pressure and mean pressure in the circulation, showing the marked reduction of pulse pressure in the first arteriolar branch after the small artery, where hemorrhages occur in either disease. The pumping and elimination of ß-amyloid in the Virchow-Robin space is dependent on pulse pressure through a process of bulk flow. This accounts for the characteristic localization of amyloid angiopathy outside the centrencephalon in the telencephalon, where bulk flow is relatively stagnant. Adapted from (A) N. Engl. J. Med. (2001) Qureshi et al 344:1450-1460 and (B) "Textbook of Medical Physiology" (1976) A.C. Guyton, W.B. Saunders Co. Philadelphia, page 238.*

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capillary bed. They contain abundant smooth muscle[44] to regulate blood flow to tissues and organs. But they also bring down both the systemic blood pressure[45] and the pulse pressure (Figure 2). The arterioles do this in a stepwise manner with every branching to take blood pressure from ~85-90 mm Hg at their proximal, arterial end, to ~30-35 mm Hg at their distal, capillary end. In general, there are three branches between terminal arteries and capillaries, from 120 µm arterioles to 70 µm metarterioles to 40 µm precapillary arterioles.[46,47] Data indicate that pulse pressure is markedly reduced in the first branch (Figure 3), the one most prone to rupture, and reaches only 4 mm Hg by the time a 50 µm arteriole is reached.[48] By the time the third branch of the arteriole is reached, there is almost no pulse pressure whatsoever.[46]

As hemorrhage generally occurs in the 50-100 µm range of vessel, we speculate that pulse pressure may be more important than the absolute level of pressure: the pulse pressure causing turbulence, damaging the vessel and resulting in either occlusion if too much collagen is laid down, or rupture if collagen is insufficient in the face of repetitive and progressive cycles of dilatation.

Location along the Vascular Tree

Why are the arteries arising from (1) the A1 and M1 segments, (2) the basilar artery entering the pons, and (3) the arteries supplying the deep cerebellum, so prone to rupture? Above the circle of Willis, in the deep gray matter of the basal ganglia and thalamus, arterioles are closer to the direct pulse pressure of the large supplying arteries. There are no branches prior to the arteriole that allow stepwise reduction in the pulse pressure.

A similar anatomical relationship exists between the basilar artery and the basis pontis, where high arterial mean pressure and pulse pressure account for the vulnerability to pontine hemorrhage.[9]

In the cerebellum, most hemorrhages are not in the long, named, circumferential vessels (the superior cerebellar artery, the anterior inferior cerebellar artery and the posterior inferior cerebellar artery) but rather in the territory of the short and deep vessels supplying the dentate nucleus, accounting for the characteristically deep location of cerebellar hemorrhages.[49-51] Thus, in hypertensive hemorrhage, deep arterioles immediately distal in the vascular tree from major supplying arteries, are an important pathogenetic factor.

Vascular Remodelling

Hypertension is known to be accompanied by a long, clinically silent period where symptoms are absent. During this time, smooth muscle cell proliferation occurs[52] in cerebral arterioles in the form of reactive hyperplasia (Figure 3A), with concomitant accumulation of DNA in the hyperplastic wall.[53] This early, compensatory stage of structural vascular remodelling[54,55] is termed hyperplastic arteriolosclerosis. If increased smooth muscle content can be maintained, the otherwise harmful effects of pressure distal in the arterial tree, hemorrhage or vascular occlusion, will not occur.

In hypertensive arteriosclerosis, smooth muscle cell death (Figures 3B, 4) eventually accompanies smooth muscle cell proliferation, via apoptotic mechanisms,[56-58] rendering the

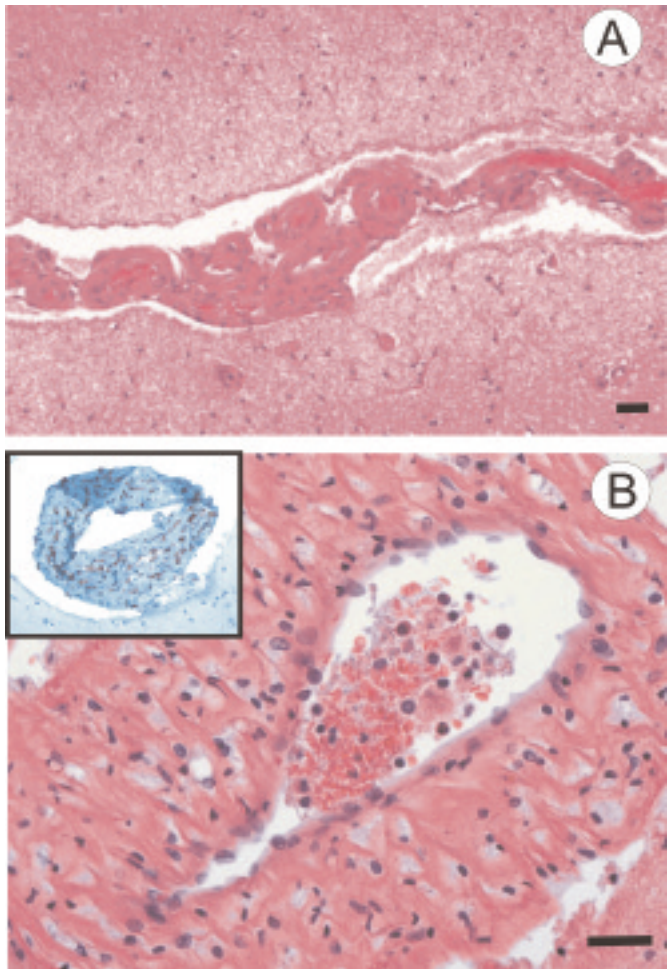

Figure 3: *Smooth muscle cell reactions. Medial hyperplasia (A) due to reactive smooth muscle cell proliferation in early hypertension. This stage represents the compensated phase of arteriolar reaction to sustained high blood pressure. The smooth muscle cells of the tunica media may die en masse even without clinical malignant hypertension, as seen here on H & E stain (B) The presence of macrophages is confirmed by the CD68 immunopositivity (B, inset). Bars = 100 µm.*

arterioles hypocellular or acellular. Such vessels may have no visible smooth muscle cells left in the tunica media whatsoever (Figure 4) and may be accompanied by inflammation and fibrosis.[59] The stage is set for future leakage by a transformation of such vessels essentially into structurally brittle cylinders of collagen.

The normal wall consists of smooth muscle cells, collagen and elastic tissue in the larger arterioles and arteries. It is elastic tissue that is the critical component responsible for the strength of the vascular wall.[60] Vascular tone and caliber is controlled by smooth muscle cells, which, when lost, result in a fragile vessel incapable of contracting. Worse, once vascular walls have been replaced by collagen, further pathology is inevitable over time. When vessels undergo ectasia, occlusion or both, collagen is laid down in a reactive manner; too much or too little are both consequential. Too much results in occlusion (Figure 4B) and too

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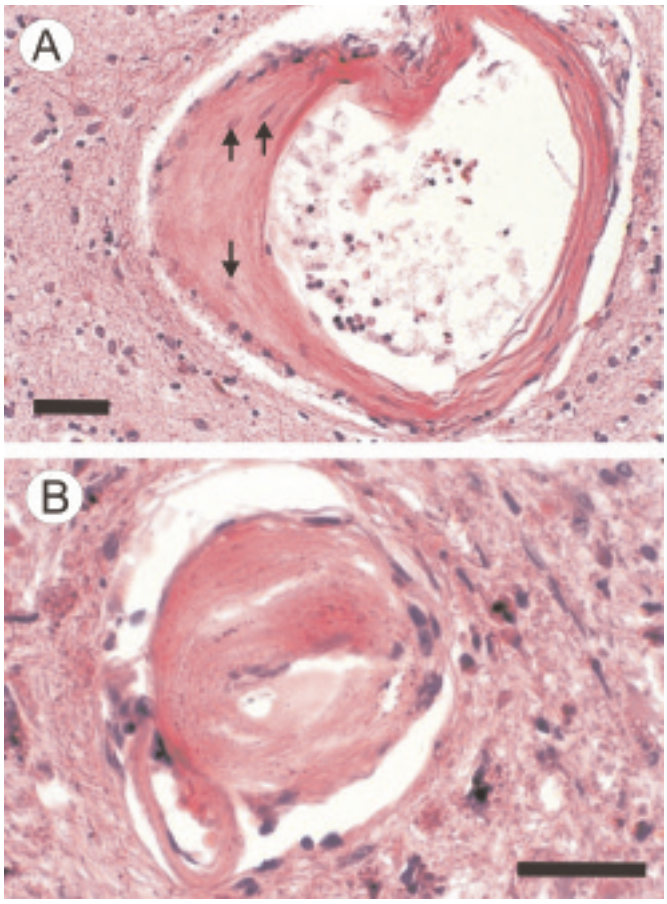

Figure 4: *Collagenization of the tunica media occurs (A) due to smooth muscle cell death. Arrows mark outlines of disappearing myocyte nuclei. Collagenization can result in either ectasia (A) If the collagen deposition is insufficient to prevent progressive dilatation or stenosis (B) If inward deposition of collagen occurs, occluding the lumen. The dilated, collagenized arteriole in A can be considered an early Charcôt-Bouchard aneurysm. Bars = 100 μm.*

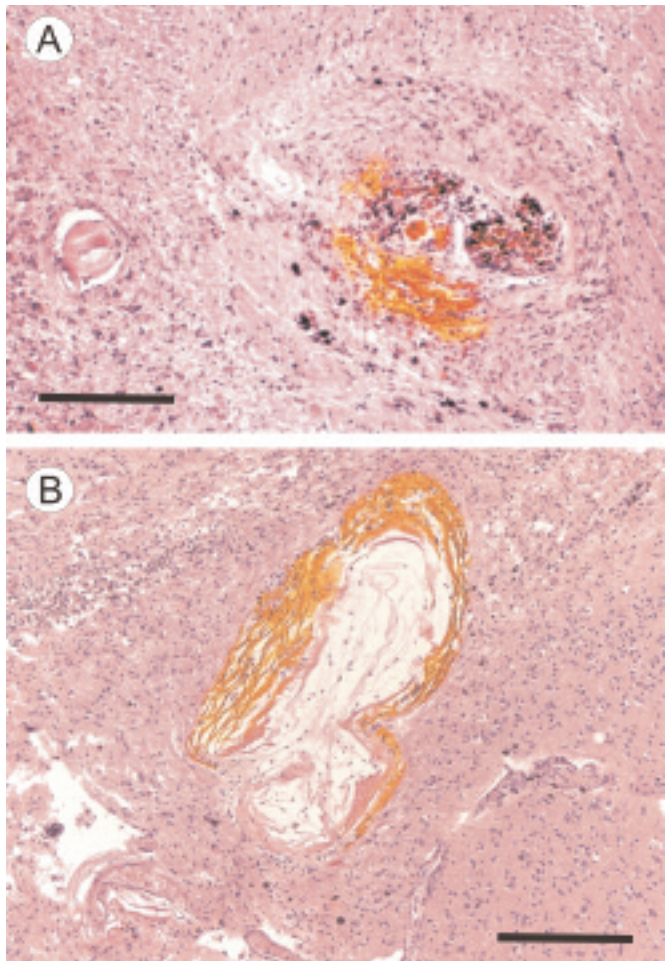

Figure 5: *(A) Occlusion and hemorrhage seen in the same microscopic field. On the left is a small, nearly occluded vessel (seen in higher detail in Figure 4B) and on the right is a 0.5 mm area of hemorrhage, marked by hemosiderin (brown) and hematoidin (bright yellow) indicating previous leakage of Fe from the now obliterated blood vessel. Leakage of hematoidin and hemosiderin is also seen surrounding the vessel in (B), with a diameter of roughly 0.5 mm in this arteriole. The degree of ectasia justifies the term Charcôt-Bouchard aneurysm. Severe stenosis is simultaneously present in the same arteriole, and a lacune is beginning to form at the lower left. Miller Fisher termed these changes "segmental arteriolar disorganization". Bars = 400 μm.*

little, ectasia (Figure 4A), ultimately resulting in hemorrhage (Figure 5). Because of the relationship P=2T/R (P=pressure, T=wall tension, R=vascular radius) wall tension must increase as radius increases, at constant pressure. The increased wall tension stimulates the universal scarring reaction of the body, fibrosis, and further collagen is laid down.

These biophysical considerations imply that, much like a balloon that is being blown up, the vessel will expand more easily once it starts expanding. A runaway process is begun. Positive reinforcement of collagen deposition is stimulated by the ectasia itself. When new collagen is laid down at a rate insufficient to prevent aneursysmal dilation of the arteriole, ectasia results. At some point, the vessel may break. Alternatively, too rapid deposition of collagen results in progressive stenosis, leading to occlusion (Figure 4B). Sometimes collagenosis of the wall in hypertension is unaccompanied by either ectasia or occlusion. The two changes in arterioles, ectasia and stenosis, give rise respectively to the two major kinds of stroke, hemorrhage and infarction.

The degree of vascular pathology, specifically the remaining mural smooth muscle content, will determine the residual contractile capability of the bleeding vessel. The rate of bleeding will be determined by the size of the opening in the leaking vessel and the systemic blood pressure. These variables, together with the factors that determining hemostasis, account for variations in clot size and clot enlargement. The addition of lesion location determines rapidity of clinical presentation and progression.

We emphasize here that the small size of the bleeding vessel contrasts with other causes of intracerebral hemorrhage, for example aneurysmal rupture, where the rent in the vessel wall is often large. Multiple microhemorrhages can occur at the

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arteriolar level, progressively increasing in size. Thus, rather than producing a sudden single fatal intracerebral hemorrhage from hypertension pathologically, less bleeding is seen initially. Early seal of the leak accounts for asymptomatic hemorrhages (Figure 1A). At the tissue level, iron surrounds collagenized arterioles (Figure 5). Over time, arterioles are destroyed completely by the process of hypertensive arteriolosclerosis and are often barely recognizable as arterioles in the center of the microscopic hemorrhages (Figure 5). Sections at other levels along arteries reveal segmental dilatation into the 0.5 mm size range (Figure 5B) normally seen in terminal arteries, not arterioles. The segmental nature of these arteriolar changes was recognized decades ago by Miller Fisher.[61] The above segmental arteriolar pathologic changes determine how a single vascular disease, hypertensive arteriolosclerosis, can give rise to two consequences: infarcts and hemorrhages (Figure 5), by producing vessels that are either blocked or broken.

Charcôt-Bouchard Aneurysm: the Controversy

The thinning vasculopathic arteriolar wall, consisting almost entirely of collagen, is termed a Charcôt-Bouchard aneurysm. It is often forgotten in the search for these structures that this is a segmental outward dilatation of an artery, a fusiform aneurysm, not a saccular aneurysm as seen in subarachnoid hemorrhage due to a berry aneurysm. The English appellation of the noun aneurysm to both is unfortunate. By referring to both fusiform and saccular dilatations as aneurysms, confusion has been created.

In Charcôt's original article,[62] berry aneurysms were drawn with some artistic license,[63] leaving a legacy of searching for a structure that does not exist: a saccular aneurysm at the arteriolar level of the microcirculation. Since that time, people have looked for saccular aneurysms analogous to saccular berry aneurysms, but have failed to find them, leading to ongoing controversy whether Charcôt-Bouchard aneurysms exist at all.[63-67] But these aneurysms are fusiform, not saccular. Morphologically they represent segmental disease, not a cul-de-sac. The use of alkaline phosphatase techniques reveal segmental fusiform dilatation by a factor of two or three, over lengths of 100-200 µm.[63] The debate about the existence of Charcôt-Bouchard aneurysms[64-67] is clarified by recognition of the fundamental vascular changes reviewed here. In the debate, aneurysms are referred to from different perspectives of technique and terminology.[68,69] Dependent on the plane of section through the vessel wall, a fusiform aneurysm may rarely have a berry-like, or saccular appearance. We wish to retain the term Charcôt-Bouchard aneurysm for the fusiform, spindle shaped, fibrotic, segmental ectatic disease, notwithstanding the inaccuracy of the original diagrams.[62,63]

Neuropathologists should also be aware of the occasional presence of Charcôt-Bouchard aneurysms and fibrin globes in neurosurgical material from hypertensive intracerebral hemorrhages. Charcôt-Bouchard aneurysms are seen in neurosurgical material as endothelial lined extensions of a recognizable vessel extending into a fresh hematoma (Figure 6). In neurosurgical evacuations, nature's attempts to stop the hemorrhage can also be seen as fibrin globes that comprise progressive concentric spheroidal fibrin formations in intracerebral hematoma (Figure 7). These represent polymerized fibrin. Their success in stopping further bleeding determines clinical outcome along the spectrum from asymptomatic to death. Pharmacological compounds such as rVIIa may act as a therapeutic agent by increasing fibrin globe polymerization.[1]

Amyloid Angiopathy

Amyloid ß Accumulation

There are three potential origins of vascular amyloid: (1) the blood, (2) the vessel itself and (3) the brain. Several factors

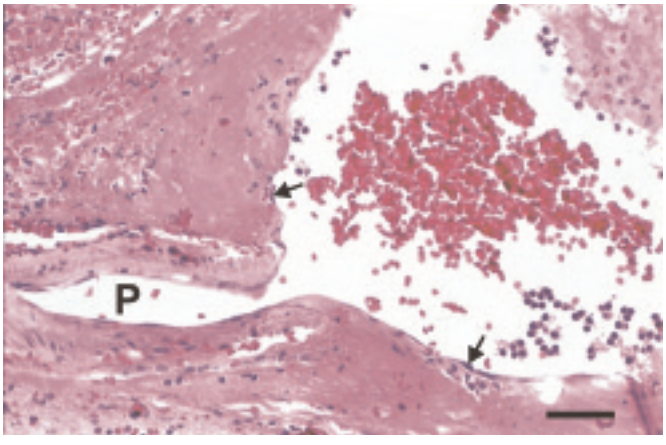

Figure 6: *Charcôt-Bouchard aneurysm as seen in neurosurgical material from evacuation of an intracerebral hematoma. Endothelial cells (arrows) lining the cavity attest to its vascular origin. Parent vessel (P) of Charcôt-Bouchard aneurysm is indicated. Bar = 100 µm.*

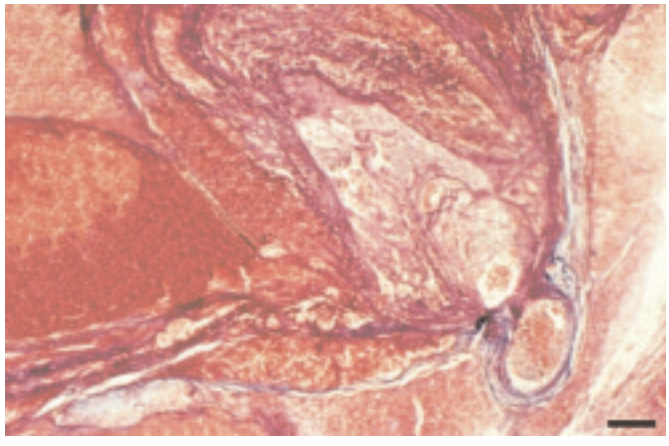

Figure 7: *Fibrin globes, consisting of concentrically contained spheres of fibrin reflect ongoing bleeding (in turn due to inability of the source vessel to contract) and arrest of bleeding (due to hemostatic mechanisms). Here, a collagenized (blue) vessel at the lower right shows a rent from which the fibrin globes arise. Bar = 100 µm.*

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might underlie a blood origin for cerebrovascular amyloid. One is the fact that amyloidosis is not a systemic disease, as it is restricted to the brain. Another factor is the anatomical location of the amyloid within cerebral vessels: amyloid accumulation begins in the outer portions of vessel walls, at the media-adventitia junction.[70,71]

There are reasons why vessels are not the source of cerebrovascular amyloid. Firstly, as smooth muscle cells die and the tunica media of vessels become acellular, mural amyloid continues to accumulate, making a local source from smooth muscle cells unlikely. Secondly, supporting the idea that amyloid is not produced by the smooth muscle cells, is the fact that larger cerebral vessels, rich in smooth muscle, are relatively free of amyloid.

The brain thus remains as the likely source of cerebrovascular amyloid. It is known that amyloid accumulates progressively over each decade of life. Amyloid results from the proteolytic cleavage of the trans-membrane amyloid precursor protein by beta- and gamma-secretases, to produce A-ß protein. Human data indicates a brain origin of A-ß, travelling via drainage from central nervous system interstitial fluid.[72]

Distribution of ß-amyloid

The distribution of vascular amyloid within the brain is the inverse of the distribution of hypertensive intracerebral hemorrhage (Figure 2A). Hypertensive hemorrhages are deep within the hemisphere, while amyloid hemorrhages are lobar. The near-complete absence of amyloid angiopathy from centrencephalic brain and the mesial temporal lobe is accounted for by the normal removal process of amyloid from the cerebrum.

Amyloid ß-protein is normally eliminated from the brain, together with the extracellular fluid, by bulk flow along the perivascular pathways.[73] Interstitial fluid is produced by the brain as an ultrafiltrate from blood at the arteriolar end of the microcirculation. There is resorption at the venular end of the microcirculation. However, a small amount of fluid is not resorbed. Driven by pulse pressure, pumping of interstitial fluid occurs[74,75] from the extracellular space into the directly continuous perivascular space. The extracellular fluid is continuously pumped by arterial pulsations, moving it along the Virchow-Robin space into the contiguous subarachnoid space. Theoretically, away from the centrencephalon, where pulse pressure would be less, the egress of A-ß via Virchow-Robin spaces would be stagnant, compared to deep telencephalic regions supplied by arteries such as the lenticulostriate and thalamo-perforating end arteries. Furthermore, in brain regions where bulk flow is known to be rapid, i.e. white matter, and flow of interstitial fluid is known to be brisk,[75] vascular amyloidosis does not generally occur.[76] Thus, the interstitial fluid drainage pathways[77] of the brain are where amyloid is seen to accumulate.[71] Amyloidosis spares the vessels of the hippocampus,[76] probably due to proximity to the posterior cerebral artery and circle of Willis.

Familial amyloid angiopathy underscores the risk of hemorrhage in amyloid angiopathy, showing structurally identical amyloid microangiopathy to the sporadic form, with a more widespread distribution.[78]

Pathophysiology

Cerebral amyloid angiopathy is an important cause of lobar hemorrhage in the elderly. Distinct from the primary and secondary generalized amyloidosis, cerebral amyloid angiopathy results from the deposition of insoluble amyloid protein in the tunica media and adventitia of the leptomeningeal and cortical arteries and arterioles[73] in vessels of restricted size distribution: 50 to 500 µm. This leads to reduced compliance and a tendency to rupture in response to minor trauma or sudden changes in blood pressure.[79]

Cerebral amyloid angiopathy increases exponentially with age and is found in about 5-8% of population in the seventh decade versus 58% of those over 90.[73,76] Cerebral amyloid angiopathy predominantly occurs in the lobar regions of the brain (Figure 8A). While hypertensive hemorrhage may have small bleeds before a major, fatal bleed, the bleeding in amyloid angiopathy is distinguished by its recurrent (Figure 8A) and multi-focal nature. Patients with lobar intracerebral hemorrhage (ICH) have a 3.8 fold increased risk of recurrent hemorrhage, the lobar location being an important predictor of recurrence.[78] Cortical microbleeds, seen on T2*-weighted MR imaging, may be a marker of amyloid angiopathy.

The pathophysiology in the vessel wall that is the source of the bleeding may explain these clinical differences from hypertensive hemorrhage. Amyloid deposition is a passive process resulting from lack of removal, while hypertensive change is an active process related to the activity of the heart. Thus, ectasia is rarely seen in amyloid angiopathy and fusiform aneurysms do not seem to occur as in hypertensive micro-angiopathy. Vessels rupture without prior ectasia or dilatation in amyloid angiopathy. No cycles of collagen replacement and destruction occur as in hypertension, only relentless and steady amyloid accumulation which cannot sustain dilatation. In spite of deposition in vessels ranging from 50 to 500 µm, amyloid tends to rupture small arterioles in the size range of 50 µm (Figure 8B). Because such small vessels are the source of bleeding, the possibility of survival and recurrence of bleeding in another vessel exists more commonly than in hypertension.

Replacement of arteriolar smooth muscle by amyloid causes a pressure-passive cerebral circulation, due to impairment of regional cerebral blood flow control. In the case of vascular amyloid deposition, smooth muscle degeneration occurs in the walls of vessels,[79] leaving vessels unable to constrict or dilate, affecting their dilation and constriction.

Satellite hemorrhages

Both hypertensive and amyloid angiopathy induce widespread changes in the brain, not limited to a single vessel. This in turn impairs global autoregulation. Coincident with intracerebral hemorrhage is the release of catecholamines, resulting in marked blood pressure increase as a normal bodily response that might be otherwise innocuous in the absence of brain vascular disease. Hemorrhage-induced pain gives rise to a further hypertensive stimulus. Hypertension in the presence of impaired autoregulation and bleeding vessels is obviously detrimental, and a systolic blood pressure threshold of 150-160 mm Hg has been found critical for hematoma enlargement.[80] Therefore, the presence of acute hypertension worsens clinical outcome[81] in the presence of disseminated disease of arterioles,

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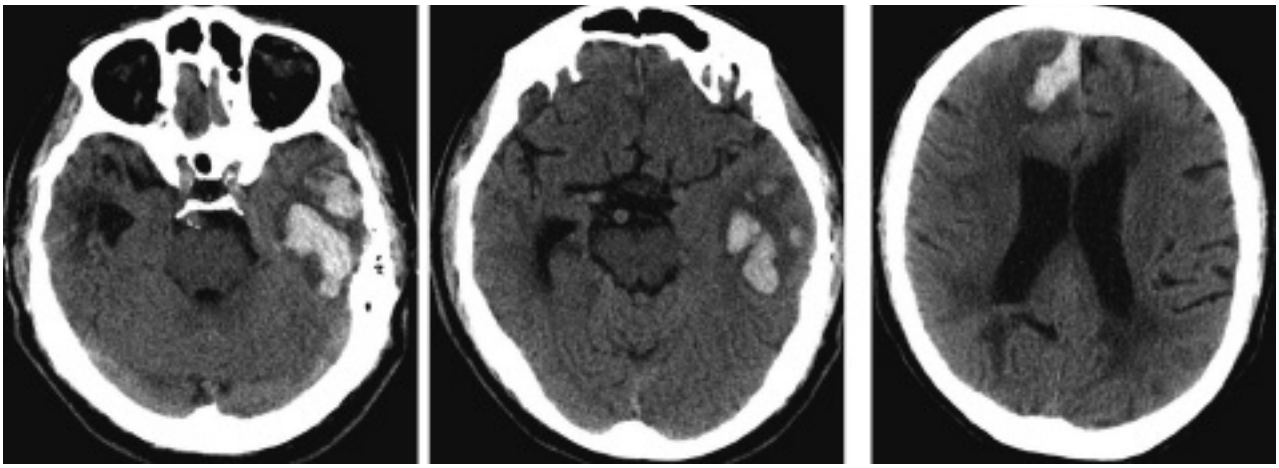

Figure 8A: *Computed tomogram (CT) images from a man with amyloid angiopathy. At age 76, left temporal hemorrhages (left, middle) were discovered after he presented with confusion. Note sparing of the mesial temporal lobe, including the hippocampus (middle). The left image also shows encephalomalacia associated with remote, right-sided hemorrhage. At age 77, he presented again, with increased confusion, CT imaging (right) revealed right frontal hemorrhage in the cingulate/parasagittal region.*

by causing two undesirable effects. First it enlarges the initial primary hemorrhage that led to the patient's presentation. Secondly, new rupture of other, diseased arterioles may occur, giving rise to multiple, satellite hemorrhages. The body's response to hemorrhage may cause both enlargement of the initial bleed, as well as additional satellite hemorrhages in other, diseased brain vessels.

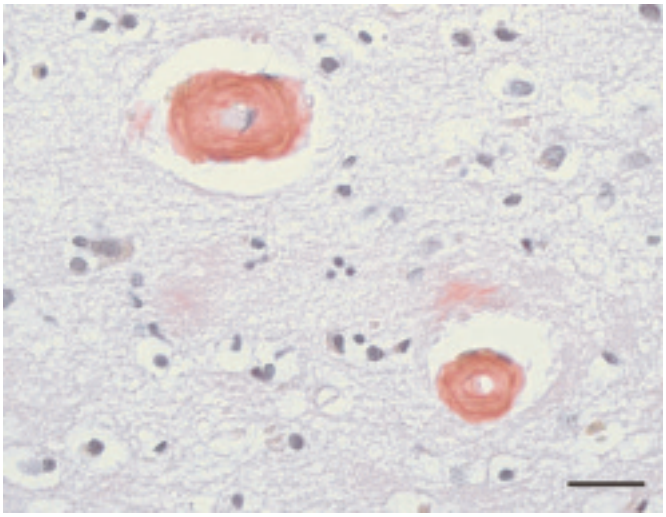

Figure 8B: *Microscopy of amyloid angiopathy reveals two cortical arterioles that are acellular due to amyloid deposition. Also seen is parenchymal amyloid and amyloid in the perivascular (Virchow-Robin) space surrounding the vessel, in keeping with current theories of amyloid being produced by the brain and coursing through the Virchow-Robin space. Bar (B) = 50 μm.*

We here present the current state of knowledge on primary intracerebral hemorrhage, comparing and contrasting hypertensive and amyloid-generated bleeds. We have proposed a novel explanation for the mirror image, inverse distribution of the two etiologies: high pulse pressure accounts for hypertensive hemorrhage while low pulse pressure accounts for the distribution of ß-amyloid accumulation in vessels. We have accounted for the ongoing debate as to whether or not Charcôt-Bouchard aneurysms exist. Understanding vascular physiology is important in explaining the pathology pathophysiology, which in turn explain the mechanism of action of therapies such as rVIIa.

Conflicts of Interest

GRS has received honouraria from NovoNordisk Canada and has participated as a member of a NovoNordisk Canadian advisory board.

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Controversies in Medical Management of Intracerebral Hemorrhage

Suresh Subramaniam, Michael D. Hill

ABSTRACT: Intracerebral hemorrhage (ICH) is a devastating form of stroke that is associated with a very high mortality rate. Both medical therapies to control blood pressure, blood sugar, temperature, and surgical therapies to remove or contain clot remain controversial. The decision when to offer medical versus surgical treatment is very challenging and uncertain. Novel therapies are currently being developed and may be successful in containing the neurological injury associated with ICH. This review will highlight the controversies underlying medical management of ICH and the current ongoing research in the field.

RÉSUMÉ: Controverses entourant la prise en charge médicale de l'hémorragie cérébrale. L'hémorragie cérébrale (HC) est un type d'accident vasculaire cérébral dévastateur qui comporte un taux de mortalité très élevé. Les traitements médicaux pour contrôler la tension artérielle, la glycémie, la température et les traitements chirurgicaux pour extraire ou contenir le caillot demeurent controversés. La détermination du moment où on doit offrir un traitement médical ou chirurgical reste un défi et comporte beaucoup d'incertitude. De nouveaux traitements sont actuellement en développement et pourraient limiter les dommages neurologiques suite à une HC. Cette revue résume les points saillant des controverses concernant le traitement médical de l'HC et les recherches actuelles dans ce domaine.

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Intracerebral hemorrhage (ICH) is characterized by non-traumatic abrupt onset of severe headache, altered level of consciousness and focal neurological deficits secondary to focal collection of blood within the brain parenchyma. Intracerebral hemorrhage accounts for approximately 7-15% of all strokes and is the most devastating stroke type; it carries a high early mortality rate of 34-51% with half of the fatalities occurring within the first two days of the ictus.[1] There is no acute treatment proven to alter mortality or morbidity.

Traditionally, ICH has been managed surgically as a space occupying lesion. However, much controversy exists over surgical management. A paucity of large randomized prospective clinical trials have led to an evidence gap. The recently completed International Surgical Trial in Intracerebral Hemorrhage (ISTICH) trial concludes that acute surgical management has no place in the treatment of ICH, leaving ICH as a medical disease.[2] Evidence-based management at present advocates primary supportive and early rehabilitative care, ideally on a stroke unit.

However, the situation is not bleak. Alternative novel therapeutic approaches, based upon better understanding of pathophysiology, have been proposed and are being tested. In the near future, ICH will be treated as a hyperacute emergency in a stroke unit/stroke intensive care unit (ICU) equipped with multidisciplinary specialists team, intensive monitoring of neurologic status, efficient management of seizures, brain edema and blood pressure. Surgery may be offered to selected patients with adjuvant medical therapy to prevent rebleeding. This paper will present a review of the recent literature concerning the presentation and medical management of non-traumatic ICH, highlighting controversies and areas where developments are occurring rapidly.

Epidemiology and Etiology

Intracerebral hemorrhage is more common in men than women, older than 55 years of age.[3] The worldwide incidence of ICH in the post-CT era ranges from 10-20 cases per 100,000 population.[4] Incidence figures for ICH prior to the advent of computerized tomography (CT) scanning were less reliable, with estimates ranging from as low as nine cases per 100,000 in

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Rochester, Minnesota to 80 cases per 100,000 in China.[5,6] Differences between racial/ethnic groups exist: African-Americans have a higher estimated incidence of 50 per 100,000 compared to 28 per 100,000 among Caucasians.[7] It has been hypothesized that hypertension, limited access to health care and educational differences result in the higher incidence of ICH within the African-American community. The higher incidence of ICH in the Japanese population (55 per 100,000) may be related to the higher incidence of hypertension, alcohol consumption and possibly low cholesterol levels.[8]

The mechanism of ICH can be classified as either primary or secondary. Primary ICH, accounting for 78-88% of cases, originates from spontaneous rupture of small vessels without an obvious underlying cause. Intracerebral hemorrhage due to hypertension or amyloid angiopathy are included in this category. Secondary ICH accounts for a minority of cases (20%) and occurs in association with vascular malformations including aneurysms, trauma, sympathomimetic drug use, tumors and coagulopathies.[4] The risk factors for primary ICH include hypertension, cerebral amyloid angiopathy, low serum cholesterol, alcohol, cigarette smoking and iatrogenic causes.[9-17]

Hypertension typically leads to hemorrhage in the basal ganglia (35-44%), thalamus (10-25%), cerebellum (5-10%), lobar (19-25%), pons (5-9%) and medulla (rare).[18] The classic pathology underlying hypertensive ICH is small vessel lipohyalinosis, characterized by degeneration of tunica media and hyalinization of intima of 100 to 600 micron arterioles.[19] However, it is probably not true that Charcot-Bouchard aneurysms are a significant source of small vessel ICH.[20]

In contrast, cerebral amyloid angiopathy (CAA) is an important cause of lobar hemorrhage in the elderly. Distinct from the primary and secondary generalized amyloidosis, CAA results from the deposition of insoluble amyloid protein in the tunica media and adventia of the leptomeningeal and cortical arteries, arterioles and capillaries,[21] leading to reduced compliance and a tendency to rupture in response to minor trauma or sudden changes in blood pressure.[22] Cerebral amyloid angiopathy increases exponentially with age and is found in about 5-8% of population in the seventh decade versus 58% of those over the age of 90.[21,23] Cerebral amyloid angiopathy predominantly occurs in the lobar regions of the brain and the recurrent and multi-focal nature of CAA is a distinguishing feature compared with hypertensive hemorrhage.[24] Patients with lobar ICH have a 3.8 fold increased risk of recurrent ICH and the lobar location is an important predictor of recurrent hemorrhage.[25] Cortical microbleeds, seen on T2*-weighted magnetic resonance (MR) imaging, may be a marker of amyloid angiopathy.

Low serum cholesterol is a controversial risk factor of ICH. It has been found to be associated with an increased risk for ICH in the Japanese, Korean and Hawaiian population.[26-28] None of the large randomized cholesterol lowering clinical trials have shown an increased incidence of ICH in patients treated with statins.[29-31] However, these large trials, by actively including patients with ischemic vascular disease may have excluded patients with low serum cholesterol, meaning that these results are not generalizable to the entire population.

Excessive consumption of alcohol is associated with an increased risk of ICH,[32] independent of the associated increase in blood pressure. Consumption of three or more alcohol equivalents is associated with a relative risk of 1.38 for ICH.[33] Unlike SAH and ischemic stroke, tobacco smoking does not appear to increase the risk of ICH.[34,35]

Anti-platelet drugs, heparins, coumarins and thrombolytic agents can all be associated with intracerebral hemorrhage[36-40] (Figure 1). Concurrent causes may need to be present before ICH occurs. For example, the risk of coumadin-related ICH has a higher incidence among patients with leukoencephalopathy, ApoE4 genotype, and higher intensity anticoagulation.[41] Anticoagulation may be associated with a larger volume of hemorrhage rather than an increased propensity to hemorrhage.

Case control studies have demonstrated that phenyl-propanolamine, a sympathomimetic drug commonly found in appetite suppressants and as a decongestant in cough or cold remedies, is linked to ICH, often occurring after the first use of these products and most commonly in women.[42] The mechanism of phenylpropanolamine related ICHs might be due to acute hypertension, vasospasm or possibly drug-induced angitis. Other sympathomimetic drugs in over-the-counter cold remedies (pseudoephedrine, phenylephrine and oxymetazoline) have also been implicated in both ICH and ischemic stroke.[43] Drugs such as cocaine hydrochloride, crack cocaine, amphetamines, heroin, methylphenidate have all been associated with ICH.[44-46]

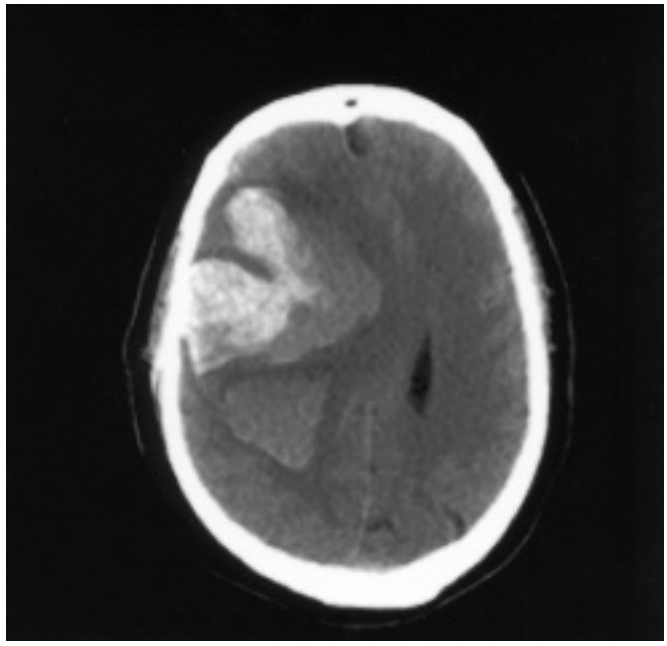

Figure 1: *Massive coagulopathic ICH.*

Prognosis

The most important predictors of outcome following ICH are the volume of ICH, level of consciousness of the patient (as measured by the Glasgow Coma Scale (GCS) score), and

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presence of intraventricular blood.[47-51] Combined together, volume of ICH with the GCS score can alone predict an overall 30-day mortality rate with 96% sensitivity and 98% specificity.

An ICH with volume greater than 60 ml and a GCS score of less than or equal to eight carries a mortality rate of 91% at 30 days, as compared to 19% for those with a volume of less than 30 ml and a GCS score greater than or equal to nine.[52] Intraventricular extension of ICH carries a mortality of 45 to 75% in general, irrespective of the ICH location, in part due to the occurrence of obstructive hydrocephalus from impaired cerebrospinal fluid circulation.[53,54] Hematoma volume assessment can be made accurately with CT scan data using the ABC/2 rule to estimate the volume of an ellipsoid.[55]

A - the largest diameter of the hemorrhage on the CT slice with the larger area of ICH (units = cm).
B - the largest perpendicular diameter on the same slice as A (units = cm)
C - the number of 1 cm slices containing hemorrhage
VOLUME = (A x B X C) / 2 cm^3

Note: all units are in cm.

Box 1: ABC/2 Rule for Volume Estimation

This volume can then be used in the ICH score[56] to predict prognosis. The ICH score is a validated model using four factors to predict outcome after supratentorial ICH. The factors are: age, ICH volume, Glasgow Coma Scale, intraventricular extension of hemorrhage and hemorrhage location. Alternate scoring by the scale developed by Tuhrim et al provides similar prognostic value but incorporates pulse pressure into the equation.[57] Other factors such as anatomic location of ICH, increasing patient age, midline shift, and intubation are correlated with poor outcome.[58-61]

Box 2: ICH Score

		Points	Total Score	30-day Mortality
GCS	3-4	2	0	0%
	5-12	1	1	13%
	13-15	0	2	26%
ICH volume (cm3)	>=30	1	3	72%
	<30	0	4	97%
IVH	Yes	1	5	100%
	No	0		
Infratentorial	Yes	1		
	No	0		
Age > 80 years	Yes	1		
	No	0		

Adapted from: Hemphill JC 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. Stroke. 2001;32:891-897

Hematoma growth in the first few hours after onset is associated with early neurological deterioration and a significant mortality. Earlier assumptions that considered bleeding into the ICH as self-limiting and neurological decline due to secondary mass effect and cerebral edema have proven incorrect.[62] It is estimated that early hematoma growth occurs in 18% to 38% of ICH patients scanned within three hours of onset.[63-65] After three hours, only 11% of patients show hematoma enlargement implying that this is a hyper-acute phenomenon. The mechanism of this growth may be due to mechanical rupture of surrounding veins.[66] Potential predictors of this effect include thalamic location of hemorrhage, larger initial hemorrhage, systolic blood pressure greater than 160 mmHg, and diabetes.[66,67] The dynamic nature of ICH enlargement during the first several hours poses a challenge and an opportunity for intervention; hyperacute ICH enlargement could be used as a surrogate outcome in clinical trials (Figure 2).

Perihematoma edema, defined as a low density rim surrounding ICH on CT scan commonly occurs in the acute and subacute stages of ICH and may contribute to morbidity and mortality after ICH (Figure 3). It typically develops over the first three to 96 hours.[68-71] In humans, serial CT and MRI scans indicate that perihematoma edema develops within three hours of symptom onset in most patients, increases rapidly in the first 24 hours and reaches its peak between ten and 20 days post-ictus.[72-73] Acutely both vasogenic and cytotoxic edema occur. Interstitial edema caused by early clot retraction and osmotic edema from liquefaction of the hematoma occurs several days following ICH.[74,75] Red cell breakdown products and thrombin may promote edema formation. Experimental infusion of whole blood into the cerebral hemisphere of pigs leads to perihematoma edema formation within one hour after infusion but this is delayed when plasma-free blood is infused or when heparinized blood is used.[76] Thrombolysis-related ICHs have less visible perihematoma edema on CT scan with lower amounts of absolute and relative edema volumes.[77] Thrombin, a serine protease generated by the cleavage of prothrombin and present in the brain in large amounts after ICH, may mediate perihematoma edema following ICH.[78,79] Paradoxically, thrombin in low concentrations induces neuroprotection via preconditioning.[80,81] Thrombin pretreatment significantly attenuates brain edema and is blocked by the thrombin inhibitor hirudin.[82]

Clinically, edema contributes to the mass effect of the hematoma, increasing intracranial pressure and intracranial brain shifts. Paradoxically, high relative edema volume is associated with better functional outcome,[73] which makes it highly uncertain whether edema is a target for new treatments or merely a prognostic variable.

Clinical Management

The management of ICH is controversial because of a lack of proven medical or surgical therapies. Randomized, non-randomized controlled studies and meta-analyses have yielded conflicting results with no proven benefit from either acute medical or surgical management. While there have been several hundred randomized clinical trials in the area of ischemic stroke, only a handful of small randomized medical and surgical trials

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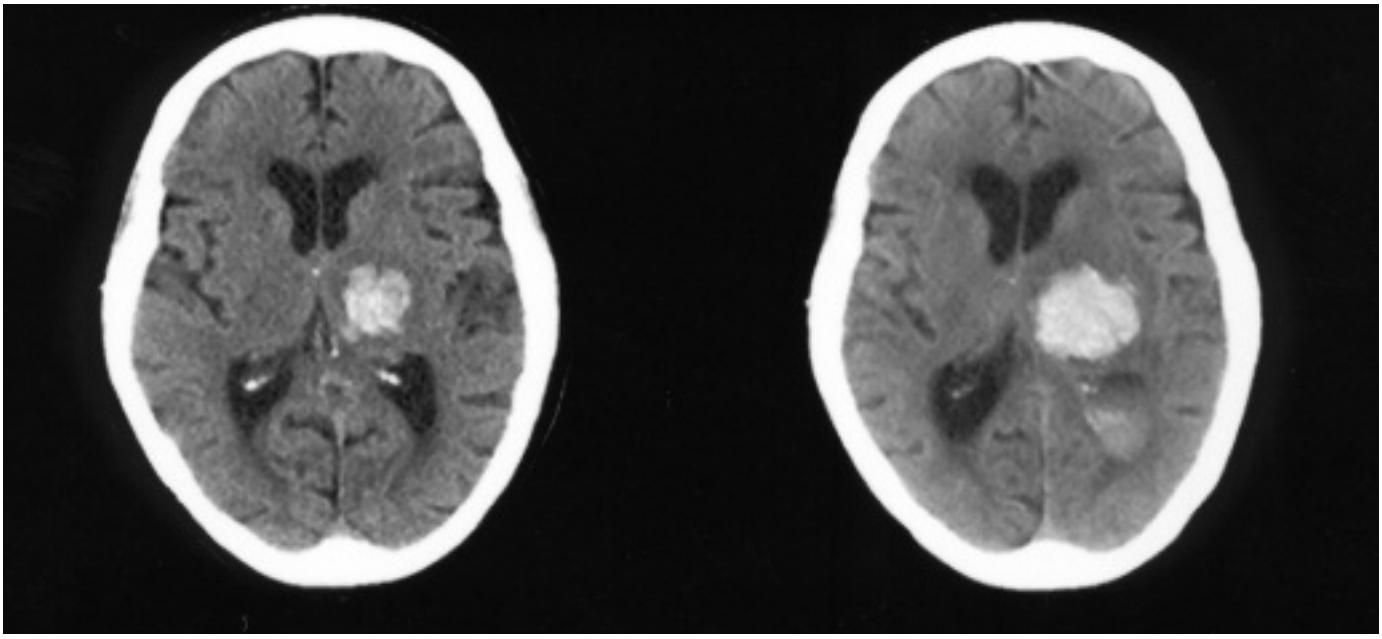

Figure 2: *Enlargement of a left thalamic hemorrhage. (Left) 90 minutes from onset; (Right) three days after stroke onset.*

have been published on ICH. The guidelines for the management of ICH published by a special writing group of the Stroke Council, American Heart Association serves as a benchmark tool.[83]

Intracerebral hemorrhage is a medical emergency. Intracerebral hemorrhage patients should be ideally admitted to neuro-intensive care or stroke units. Recent reports suggest improved outcome in stroke patients cared for by stroke teams and in stroke units.[84] Admission to a neuro-intensive care unit is associated with reduced mortality rate after intracerebral hemorrhage.[85]

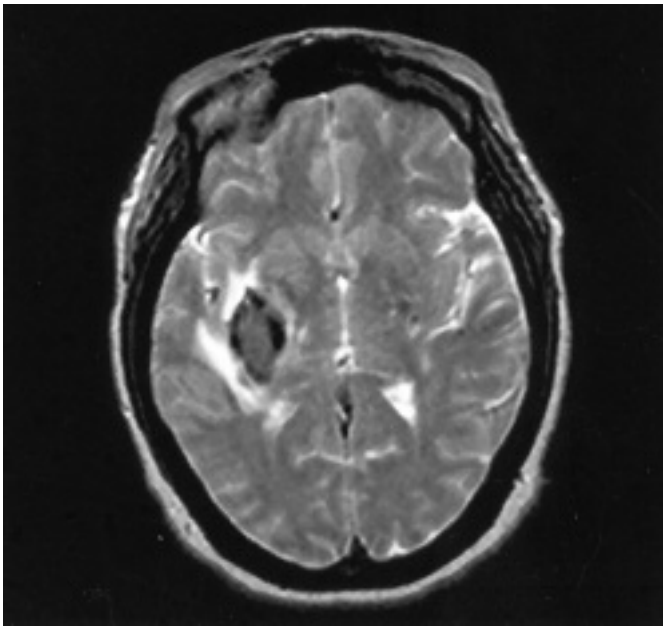

Figure 3: *Subacute T2-weighted axial MR image of a spontaneous right putamenal hemorrhage showing peri-hematomal edema.*

Blood Pressure Management

Controversy still exists over initial blood pressure management in ICH patients. There are no randomized trials on optimal therapy of acute blood pressure elevation following ICH. Two clinical and theoretical issues preside. The first is hematoma expansion; in the hyper-acute phase, elevated blood pressure may be a factor in the promotion of hematoma growth. Second, perihematomal penumbral tissue may exist due to elevated tissue pressure reducing regional perfusion pressure. Perilesional penumbra has been extensively researched. While SPECT studies have suggested the presence of reduced perfusion, PET and MRI-perfusion studies have shown that perilesional tissue is hypometabolic ("stunned") rather than ischemic.[86-91] On this basis, it is at least safe to lower blood pressure acutely without fear of inducing concomitant ischemia.

A mean arterial pressure of greater than 125 mm Hg is associated with a high mortality rate of 43% compared with 21% in those with a mean arterial pressure less than 125 mm Hg up to six hours following ICH.[4,14] The American Heart Association guidelines recommend that blood pressure levels be maintained below a mean arterial pressure of 130 mm Hg.[83] In patients with elevated intracranial pressure, the cerebral perfusion pressure (mean arterial pressure less the intracranial pressure) should be maintained greater than 70 mm Hg. The goal in the normotensive patient is less clearly defined but it has been suggested that the target mean arterial pressure should be

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110 mm Hg.[83] It remains controversial whether aggressive hypertension treatment should be undertaken in the acute phase of ICH and this area of management warrants a randomized clinical trial evaluating 30-day mortality as the primary outcome.

Seizure Management and Prophylaxis

Compared to ischemic stroke, seizures occur frequently in ICH. The incidence of seizures complicating ICH is approximately 25%.[92] Most seizures occur early, which is defined as the first two weeks post ictus, and about 57% are seen in the first 24 hours.[93] Lobar ICHs independently predict seizures particularly those in the temporal and parietal lobes.[94,95] Electrographic seizures, most often subclinical, are quite common after ICH and clinical or electrographic seizures are associated with clinical worsening and poorer outcome.[96] Patients presenting with clinical seizures at the onset of ICH should receive intravenous anticonvulsants. After 30 days, anticonvulsant therapy should be discontinued if there are no further seizures. Long term anticonvulsant therapy is indicated in the presence of further seizures more than two weeks after the onset of ICH. The high frequency of electrographic seizures with associated poor clinical outcome makes seizure prophylaxis a question for a randomized trial.

Blood Sugar Management

Hyperglycemia produces profound brain edema and perihematomal cell death in experimental ICH.[97] Hyperglycemia in nondiabetics and diabetics at the time of admission is a predictor of poor outcome in ICH, perhaps due to a higher incidence of cerebral and infectious complications in diabetics and hyperglycemic nondiabetic patients.[98] Concomitant high blood pressures (SBP > 200 mm Hg) and hyperglycemia favours hematoma enlargement. Hyperglycemia is an important predictor of symptomatic ICH following thrombolysis for ischemic stroke.[99] A large clinical trial outlining the beneficial effects of acute blood sugar lowering in ICH is needed. In the absence of this evidence, our practice is to start subcutaneous or intravenous regular insulin on sliding scale dosing for hyperglycemic patients with ICH. The management goal is to maintain normoglycemia (4 to 8 mmol/L).

Management of Body Temperature

Growing evidence suggests that hypothermia is a robust therapy for human global ischemia.[100,101] While animal data are strong, it remains to be proven as a treatment for human focal ischemic stroke. In contrast, very few experimental animal data indicate that hypothermia improves outcomes following ICH by reducing brain edema.[102,103] There are no human data showing the effect of hypothermia on ICH patients. Delayed rather than early hypothermia is beneficial after ICH in animal models, perhaps because hypothermia does induce a mild coagulopathy and more randomized clinical trials are needed to evaluate its neuroprotective efficacy. Fever is associated with a poor outcome following ICH.[104] Normothermia should be maintained in these fever patients by administering antipyretics or cooling blankets.

Intracranial Pressure Management

Increased intracranial pressure related to mass effect and perihematomal edema is an important predictor of mortality. Increased intracranial pressure is defined as intracranial pressure greater than 20 mm Hg for more than five minutes. The usual management goal is to lower the intracranial pressure to less than 20 mm Hg and try to maintain the cerebral perfusion pressure at or greater than 70 mm Hg.[83] Headache, vomiting, visual abnormalities, pupillary dysfunction, seizures and papilledema all herald the onset of increased intracranial pressure and warrant urgent assessment. Intracranial pressure monitoring using external ventricular drains are generally offered to patients with a GCS score less than nine and in all deteriorating patients due to elevated intracranial pressure.

The initial control of increased intracranial pressure must recognize that monitoring of intracranial pressure provides a global assessment, while the pathophysiology is focal. Hyperventilation and osmotherapy are short-term measures, usually to buy time to proceed with operative intervention. They should generally not be used prophylactically. However, aggressive use of hyperventilation and mannitol in controlling increased intracranial pressure reduces transtentorial herniation and has been associated with favourable outcome.[105] Corticosteroids should be avoided, because randomized trials have failed to show any benefit in ICH. Neuromuscular paralysis in combination with adequate sedation reduces intracranial pressure by preventing increase in intrathoracic and venous pressures associated with coughing, straining, and suctioning. Non-depolarizing neuromuscular blockers are usually the preferred choice. Barbiturate induced coma has been considered as a last resort in the treatment of refractory intracranial pressure.[83] Many of the aspects of the acute management of intracranial pressure in focal brain injury are under investigation and require proper trials to determine the way forward.

Hemostatic Therapy for ICH

The fact that hematoma enlargement occurs for several hours after onset of ICH presents an opportunity for therapeutic intervention. Procoagulant drugs may reduce the rate of rebleeding and prevent neurological deterioration in ICH patients, if offered ultra-early. Factor VIIa (rFVIIa), a hemostatic agent, is a promising drug therapy for ICH. FVIIa is in use clinically for hemophiliac patients with acquired FVIII or FIX antibodies. It initiates local hemostasis by formation of a complex between tissue factor and FVIIa following injury and bypasses the early components of the intrinsic coagulation pathway. rFVIIa has been tested in a large phase II dose-finding muti-centre randomized clinical trial within a time window of four hours from the onset of ICH.[106] In this study, a benefit to rFVIIa treatment emerged on the primary outcome of hematoma growth reduction measured on the 24-hour CT scan as well as on clinical outcomes. These positive results will lead to a definitive phase III trial where the primary outcomes are clinical to begin in the current year. Antifibrinolytic compounds such as aminocaproic acid have been successfully used to reduce the incidence of ICH among infants requiring extracorporeal membrane oxygenation, but have not been tested in spontaneous ICH.[107] In one study by Wilson et al,[108] patients who received

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aminocaproic acid prior to extracorporeal membrane oxygenation had significantly less bleeding and received fewer blood transfusions. None of the patients on aminocaproic acid developed new ICH or extension of previous ICH.

Thrombolytic therapy for ICH - an Oxymoron?

Thrombolytic therapy for ICH and intraventricular hemorrhage promotes chemical reduction in hematoma volume. Instillation of t-PA into the hematoma cavity stereotactically and aspirating it once the clot is dissolved is a promising approach to ICH treatment.[109] Daily administration of t-PA into the hematoma cavity beginning 12 to 24 hours after a stereotactic placement of a catheter reduces the volume of hematoma by 70 to 85% in two to four days.[110,111] Adverse effects of this approach include intracranial bleeding and rebleeding. Randomized clinical trials are required to show that the risk-benefit ratio is favourable.

Intraventricular hemorrhage complicates ICH in about 40% of cases and carries a very high mortality rate.[112] Ventricular blood produces obstructive hydrocephalus or a direct mass effect of the ventricular blood on periventricular structures and is associated with global hypoperfusion of the overlying cortex.[113] Traditional treatment of intraventricular hemorrhage consists of external ventricular drain placement for the drainage of blood and cerebrospinal fluid from the ventricular system and normalization of intracranial pressure. However, this approach alone is not effective and complicated by external ventricular drain clotting.

Instillation of thrombolytic drugs, rt-PA or urokinase, have been used in early trials to reduce intraventricular hematoma volume.[114-117] Complications of thrombolytic therapy for intraventricular hemorrhage include rebleeding, hemorrhage along the catheter track, meningitis and ventriculitis.[118-120] A pilot study of urokinase injection via an external ventricular drain catheter in 20 patients with intraventricular hemorrhage every 12 hours until external drainage of cerebrospinal fluid was no longer required, reduced the expected mortality rate from a predicted 58% to an actual 25% at one month.[115] A phase II randomized clinical trial of intraventricular thrombolysis using t-PA is currently underway.

Iatrogenic ICH Management

Anticoagulation-associated ICH is treated with rapid reversal of the anticoagulation. This is accomplished with 1mg vitamin K for those on coumarins with international normalized ratios values between 4.5 and 10.[121] However, treatment with vitamin K requires eight to 24 hours to correct an elevated prothrombin time. Additional fresh frozen plasma immediately replenishes the diminished clotting factors and should be given at a dose of 20 mL/kg. Factor VIIa may be a logical rapid treatment for anticoagulation associated ICH but it remains to be tested in a formal clinical trial.

Heparin associated ICH should be treated by discontinuing the drug and administering intravenous 1% protamine sulphate over ten to 20 minutes. One milligram of protamine neutralizes approximately 100 USP heparin units. Protamine sulphate is given 1 mg intravenously for the amount of heparin infused in the previous two hours and the dose should not exceed 10 mg over a ten minute period.[122]

Thrombolytic-associated ICH may be treated empirically by administration of 10 units of cryoprecipitate, 2 units fresh frozen plasma every six hours for 24 hours along with 4-6 units platelet concentrate until fibrinogen levels are > 11.1 mmol/L. Fibrinogen levels must be checked every four to six hours and cryoprecipitate must be transfused as needed. In practice, it is very unclear if this therapy results in a useful improvement in outcome; most thrombolysis associated symptomatic hemorrhages are ultimately fatal.

Surgical ICH Management

Surgical management of ICH, while traditionally offered, remains controversial. The surgical procedures available for evacuation of ICH include craniotomy, burr hole aspiration, endoscopic aspiration and thrombolytic instillation/aspiration. A major issue with early hematoma evacuation is a high rate of rebleeding in the post-operative period.[123] Adjuvant medical therapy to prevent early rebleeding has the potential to rejuvenate surgery for ICH by allowing ultra-early intervention. The recently published STICH trial[124] compared early surgery versus conservative medical management. Of the 468 patients randomized to early surgery, 122 (26%) had a favorable outcome compared with 118 (24%) of 496 randomized to initial conservative treatment (odds ratio 0.89 [95% CI 0.66-1.19], p=0.414); absolute benefit 2.3% (-3.2 to 7.7), relative benefit 10% (-13 to 33). The STICH trial showed no overall benefit from early surgery compared to medical management. The only significant result from this trial was that patients with hematomas 1 cm or less from cortical surface were more likely to have a favorable outcome with craniotomy compared to deep hematomas. The optimal surgical therapy for the ICH patient is unknown. A parallel article in this supplement discusses surgical therapy.

Box 3: Targets for future randomized trials in ICH

1. Hypertension treatment
2. Hyperglycemia treatment
3. Temperature reduction/Antibiotic use
4. Seizure prophylaxis
5. Hemostatic therapy (FVIIa) to prevent hematoma growth
6. Clot evacuation/reduction (surgery, thrombolysis)

Future Directions

Intracerebral hemorrhage is a devastating condition that is associated with a very high early mortality and morbidity if left untreated. It has received very little attention from the medical community. Conservative medical management still continues to be the standard of care although several novel treatment approaches have been recently advanced. As in ischemic stroke, hyperacute and combination therapy are likely the best approach. Areas for continued and future research include procoagulant therapy, procoagulant therapy plus surgery, thrombin inhibitors, inhibitors of matrix metalloproteinases, blood pressure management, blood sugar management, and anti-seizure treatment. Collectively, controversies underlying medical and

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surgical management of ICH are a fertile research area for well designed clinical trials.

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Conflicts of Interest

MDH has received honouraria from NovoNordisk Canada and has participated as a member of a NovoNordisk Canadian advisory board.

Statement of Authorship

A draft outline was developed by both authors. SS wrote the first draft which MDH edited. Both authors reviewed and edited the final version.

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Spontaneous Supratentorial Intracerebral Hemorrhage: The Role of Surgical Management

Graeme Marchuk, Anthony M. Kaufmann

ABSTRACT: Spontaneous supratentorial intracerebral hemorrhage is a vexing clinical problem. Without established guidelines, clinicians are often forced to make case-by-case decisions, based on their own interpretation of relevant studies and experience. A number of randomized studies and several meta-analyses have been unable to provide a clear indication for surgery for this condition. Data from both experimental and clinical studies suggest that early surgical evacuation in some circumstances may be beneficial. This may include a subset of patients with moderate sized hemorrhages and associated moderate neurological deficits; specifically those patients that are likely to survive the primary bleed but with significant permanent neurological deficits. Minimal access surgical techniques may offer advantages over standard large craniotomies, although a role for stereotactic aspirations has not yet been established. The timing of any surgery may also be important with theoretical advantages associated with early and thorough clot evacuation. Future surgical advances will require techniques or adjuvant medical treatment to reduce the occurrence of clot expansion and rebleeding, that have been identified as a source of early deteration and post-operative condition. We review the randomized clinical trials, experimental evidence and management options related to surgical treatment of spontaneous supratentorial intracerebral hemorrhage.

RÉSUMÉ: Rôle de la chirurgie dans le traitement de l'hémorragie sus-tentorielle spontanée. L'hémorragie cérébrale sus-tentorielle spontanée est un problème clinique vexant. Comme il n'existe pas de lignes directrices, les cliniciens sont souvent contraints de prendre des décisions au cas par cas, selon leur interprétation des études et leur expérience. Jusqu'à maintenant, les études randomisées et plusieurs méta-analyses n'ont pu établir d'indication claire pour le recours à la chirurgie dans le traitement de cette pathologie. Selon des données provenant d'études expérimentales et d'études cliniques, un recours précoce à l'évacuation chirurgicale dans certaines circonstances pourrait être bénéfique, particulièrement chez des patients qui ont une hémorragie de taille restreinte avec des déficits neurologiques modérés et qui sont susceptibles de survivre à l'hémorragie initiale mais dont les déficits neurologiques permanents seront importants. Les techniques chirurgicales utilisant un accès minimal pourraient être plus avantageuses que la craniotomie standard. On ne sait cependant pas si l'aspiration stéréotaxique serait bénéfique. Le moment de la chirurgie pourrait également être important et une évacuation précoce et minutieuse du caillot présente des avantages théoriques importants. Les progrès dans le domaine de la chirurgie nécessiteront des techniques ou des thérapies médicales d'appoint pour diminuer le risque d'expansion du caillot et d'un nouvel épisode de saignement qui sont des facteurs importants de détérioration et qui conditionnent l'état postopératoire du patient. Nous revoyons les essais cliniques randomisés, les données expérimentales et les options thérapeutiques du traitement chirurgical de l'hémorragie cérébrale sus-tentorielle spontanée.

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Primary intracerebral hemorrhage (ICH), defined as hemorrhage into brain parenchyma in the absence of trauma, vascular malformation, aneurysm or tumor, is a devastating form of stroke. Compared to ischemic stroke and subarachnoid hemorrhage it is associated with the highest mortality rate; 50% of affected individuals are dead at six months, and only 20% are living and working independently at six months.[1,2] There is considerable controversy over the best management, although it is the least well studied form of stroke in terms of overall clinical outcomes. Only a few randomized medical[3-6] and surgical[7-15] studies have been published to date, compared to a more abundant literature on ischemic stroke and subarachnoid hemorrhage. As suggested in a recent review by Broderick,[16] this relative disinterest may reflect a pervasive pessimistic attitude towards treatment of ICH.

A fundamental question is whether a policy of early evacuation of ICH will improve outcomes. There is general

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agreement that such surgery may be indicated for patients with large intracerebellar hemorrhages or some with aneurysmal ICH. A non-surgical approach is advocated for brainstem or thalamic hemorrhages, as well as massive or small supertentorial hemorrhages (Figure 1). The controversy is centered around management decisions for patients with moderate sized hemorrhages, most commonly hypertensive putaminal hemorrhages. These patients are likely to survive the primary bleed, but with significant permanent neurological deficits. While there is some clinical and experimental support for a surgical approach, attitudes regarding optical management vary widely (Figure 2). This paper reviews issues related to the surgical treatment of spontaneous supratentorial intracerebral hemorrhage (sSICH), excluding cases related to vascular malformations, aneurysms, or tumor. What follows is a summary of the published randomized evidence that evaluates surgery as a management option for sSICH, and the inherent limitations of these studies. Experimental studies on the pathophysiological events surrounding an ICH are examined, and the potential rational for surgical treatment of sSICH presented.

Randomized Clinical Trials

To date, there have been nine randomized controlled trials evaluating surgery as a primary option for managing sSICH published in English-language journals.[7-15] Surgical modalities studied include craniotomy and corticectomy for hematoma evacuation, stereotactic aspiration with or without the instillation of local thrombolytics, and endoscopically-mediated hematoma evacuation. These studies are listed in Table 1, stratified according to year of publication, number of patients randomized, symptom-to-surgery time, and patient outcomes.

The era of randomized studies aimed at investigating the surgical management of sSICH began in 1961, when McKissock et al[10] published a study comparing surgery with what was deemed best medical management. Surgery consisted of open craniotomy, and the primary outcome measurement was functional status (including death) at six months. There was no difference between open craniotomy and medical management versus medical management alone, with similar numbers of patients dead or disabled at six months. The treatment groups were well matched with respect to age, neurological examination on admission, and hematoma location. However, McKissock's study failed to provide applicable information for several reasons. Firstly, patients in the "surgical" group who were found to have basal ganglia or thalamic hematomas (24 out of 89 patients) did not undergo open craniotomy, but were still classified in the surgical group for outcome assessment. Secondly, no patient received an operation until at least a day after the initial ictus, 24 hours being the point at which the patient's level of consciousness was determined for study purposes. Finally, surgeons operated on patients without the benefit of CT, the operating microscope or advanced neuroanesthesiology and neurocritical care available today. The conclusions of McKissock's study are therefore inapplicable to the modern surgical management of spontaneous ICH today.

The next study in which the surgical management of sSICH was analyzed in a randomized fashion was that of Juvela et al,[9] published almost thirty years after McKissock's initial trial.

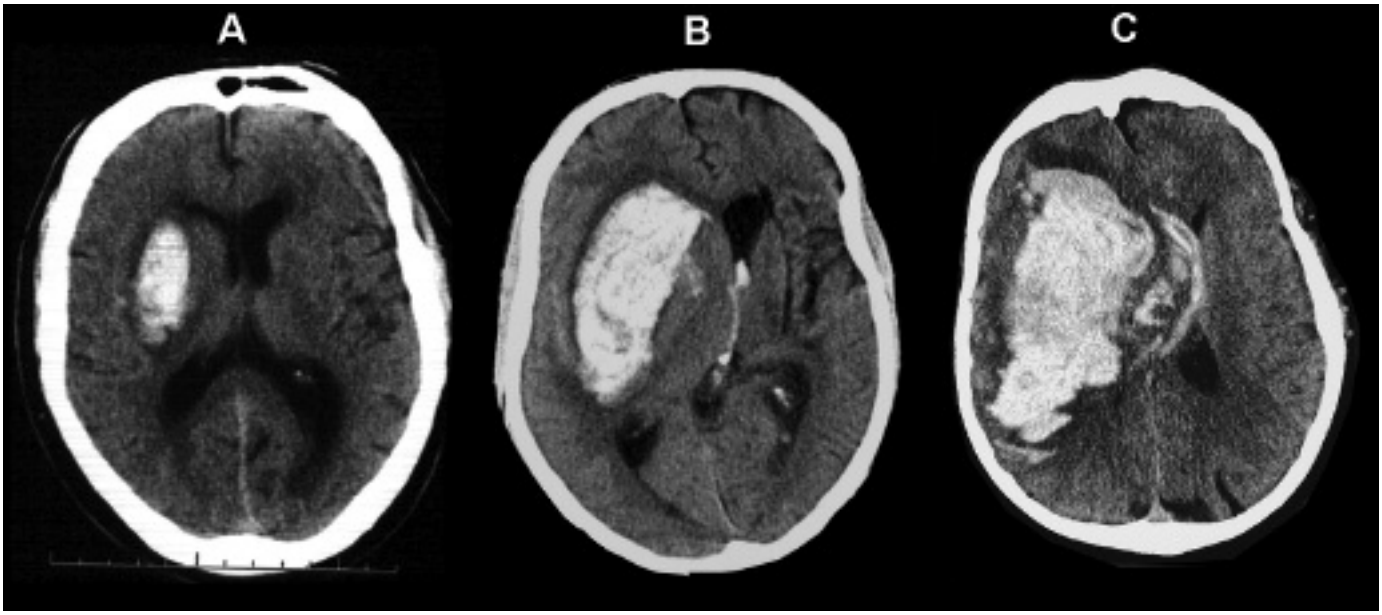

Figure 1: *Hypertensive Putaminal Hemorrhage. Three examples of this most common form of spontaneous supratentorial intracerebral hemorrhage. Medical management is typically advised for cases such as A and C, where the anticipated outcomes would be excellent and poor, respectively. Conversely, there is a wide range of attitudes regarding surgical evacuation in Case B.*

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Table 1: Surgical Trials for sSICH

Author and year of publication	Number randomized	Mean Presenting GCS (medical vs. surgical)	Mean Hematoma Volume (cc) (medical vs. surgical)	Symptom to surgery time (mean)	Surgery performed	Independent Outcome (surgical vs. medical)	Conclusions
McKissock[10] (1961)	180	Not stated	Not stated	> 24 h	Craniotomy	11% vs. 12%	Surgery not advantageous
Juvela[9] (1989)	52	12 vs. 9	56 vs. 67	(14.5 h)	Craniotomy	7% vs. 31%	Surgery not advantageous
Auer[7] (1989)	100	Not stated	Not stated	< 48 h	Endoscopic drainage	40% vs. 25%	Surgery advantageous in selected patients
Batjer[8] (1990)	17	Not stated	Not stated	< 24 h	Craniotomy	22% vs. 25%	Neither medicine nor surgery advantageous
Morgenstern[12] (1998)	34	11 vs. 10	44 vs. 49	(5.1 h)	Craniotomy	Not stated	Early surgery feasible
Zuccarello[15] (1999)	20	11 vs. 13	30 vs. 35	(8.6 h)	Craniotomy or stereotaxy	56% vs. 36%	Early surgery feasible and promising
Morgenstern[13] (2001)	11	15 in survivors 10 in deaths	55 in survivors 37 in deaths	(3.2 h)	Craniotomy	Not stated	Ultra-early surgery complicated by rebleeding
Teernstra[14] (2003)	71	10 vs. 9.5	52 vs. 66	< 72 h	Stereotaxy	Not stated	Stereotaxy moderately reduces hematoma volume

Similar to McKissock's work but much smaller in scale, Juvela randomized 52 patients to undergo craniotomy within 48 hours of symptom onset followed by best medical management, or best medical management alone. The major difference in study design was the availability of CT scanning, which minimized but did not completely eliminate the diagnostic error rate (one patient had a brain tumor discovered at autopsy). Although randomization had to occur within 24 hours of symptom onset, the delay to surgical intervention could be up to 48 hours. Using these methods, Juvela and colleagues found no difference in the six-month morbidity or mortality between the surgical and conservative treatment groups, and concluded that surgery offered no benefit over conservative management. However, there were significant differences between the treatment groups. The surgical group had a significantly lower admission GCS and a significantly higher percentage of intraventricular hemorrhage, both of which are known to correlate with poor outcome, and the delay from onset to surgery was quite prolonged.

Also in 1989, Auer et al[7] published the results of 100 patients randomized to undergo surgery or best medical management. The surgical modality chosen was endoscopic hematoma evacuation and drain placement, guided by intraoperative ultrasound guidance. Patients were randomized if they had hematoma volumes of 10 cc or more, were between 30 and 70 years of age, and had "neurological impairment or depressed level of consciousness (LOC)". The median time from symptom onset to surgery was not mentioned, but all patients underwent surgery within 48 hours. The results have generated much discussion in the evidence-based literature regarding the surgical management of ICH.[17,18] Auer et al found a significant survival benefit in patients undergoing endoscopic surgery for subcortical hematomas (70% versus 30% in the medical group). Patients with smaller hematomas (i.e. < 50 cc) who underwent surgery had a better functional outcome but no mortality benefit. Those with larger hematomas (> 50 cc) had improved mortality rates, but those who survived had no better postoperative function. What is more, good results were limited to those patients whose preoperative level of consciousness was alert or somnolent (as opposed to stupor or comatose), and to those less than 60 years of age. This again underscored the importance of preoperative

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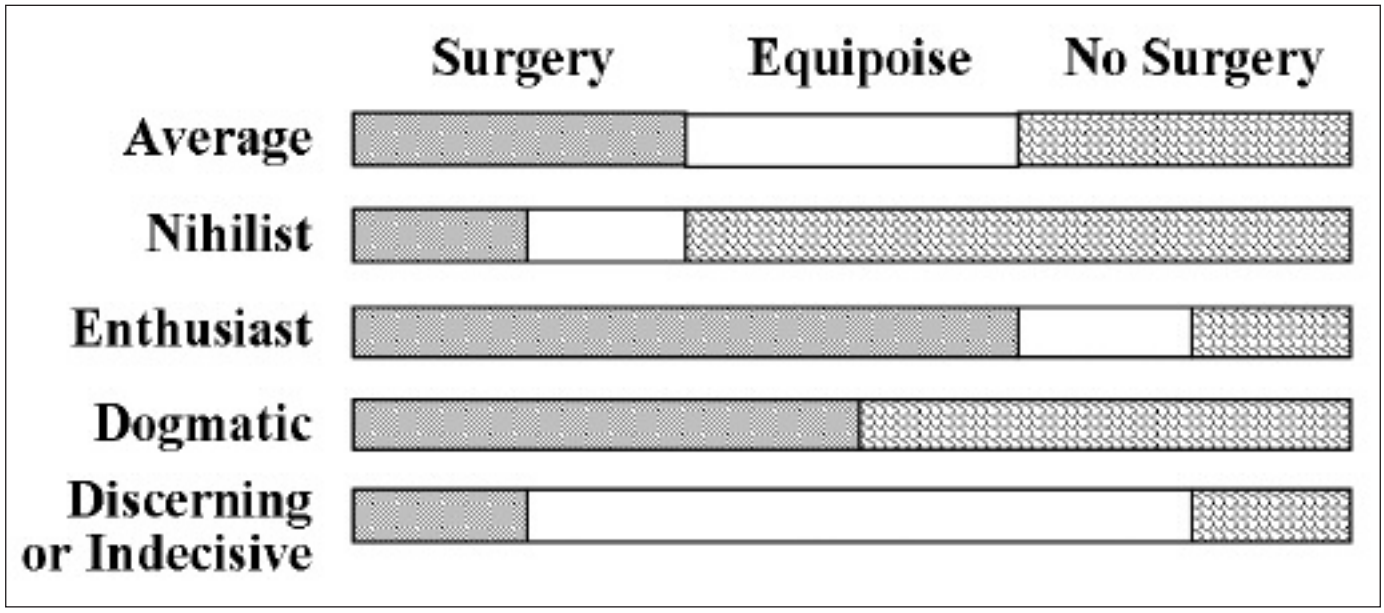

Figure 2: *Attitudes regarding surgical treatment of sSICH.*

neurological status as a powerful predictor of outcome, as only 10% of Auer's stuporous or comatose patients had an eventual good result.

One year later, Batjer and colleagues published a small study detailing the results of 17 patients with large hypertensive putaminal hemorrhage randomized to surgery (which consisted of open craniotomy) and best medical management, or best medical management alone (with or without intracranial pressure monitoring).[8] Patients had to have a documented history of hypertension, and randomization had to occur within 24 hours of symptom onset. The results were strongly discouraging, as over 70% of the 17 patients were dead or dependent at six months (Table 1). Batjer concluded that current medical and surgical management had little to offer patients with hypertensive putaminal hemorrhage and emphasized the need for more effective preventative and acute measures for treating this disease. The patient subgroup studied, however, tended to have large hematoma volumes and severe deficits at presentation.

One decade later, thinking began to shift about the timing of surgery for sSICH, perhaps stimulated by basic science research and the emerging concept of "brain attack". Zuccarrello and colleagues[15] presented their results of patients randomized to "early" surgery (in this case defined as surgery within 24 hours of symptom onset) versus best medical management alone. Patients were randomized to undergo open craniotomy, stereotactic catheter placement with instillation of urokinase at regular intervals, or medical therapy. There was a much shorter symptom-to-surgery time compared to previous studies (8.6 hours) but still only a non-significant trend towards improved outcome with early surgery in the small study group. Interestingly, the patients who underwent stereotactic catheter placement were all independent at three months, although these patients had lower initial hematoma volumes and better admission Glascow Coma Scale (GCS) scores (three out of four suffered from putaminal hemorrhage). They concluded that an expanded randomized trial for early surgery in sSICH was indeed feasible.

In the same time period, Morgenstern and colleagues[12,13] presented their results of a single center investigation of early craniotomy in sSICH. Patients were randomized to undergo surgery within 12 hours of symptom onset in the first study (which was achieved for most patients),[12] and within four hours in the second study.[13] The median symptom-to-surgery time was 5.1 hours in the first study and 3.2 hours in the second study. Patients were generally well matched in the first study, the only significant difference being a higher proportion of putaminal hemorrhages in the surgical group of patients (such differences were not mentioned in the second study). A six-month mortality or morbidity benefit could not be demonstrated. In fact, the second trial was stopped because the mortality was higher than that of the medical group in the first trial (40% compared to 24%). Postoperative rebleeding was identified as the principal contributor to mortality in the latter trial. Morgenstern concluded, similarly to Zuccarrello, that it was indeed feasible to perform early surgery for sSICH, even within the four-hour window. An outcome benefit, however, would require a means to minimize the risk of early and postoperative hematoma expansion.

In another trial investigating the surgical management of sSICH, Teernstra and colleagues[14] investigated the effect of stereotactic catheter placement and urokinase infusion at regular intervals compared to best medical management. The time to treatment from symptom onset was within 72 hours (and therefore was not early), and patients in the surgical group had

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Table 2: Meta-Analyses of Surgical Trials

Meta-Analysis	Studies Analyzed	Odds of death or dependency with surgery	Conclusions
Hankey and Hon	McKissock, Juvela, Auer, Batjer	1.23 (0.77 – 1.98)	Insufficient evidence
Prasad et al.	McKissock, Juvela, Auer, Batjer	1.99 (0.92-4.31)	Insufficient evidence
Saver et al.	Juvela, Auer, Batjer	0.72 (0.38 – 1.44)	Trend towards improved outcome
Fernandes et al.	McKissock, Juvela, Auer, Batjer, Chen, Morgenstern, Zuccarello	1.20 (0.83 – 1.74)	Trend towards improved outcome in modern studies

worse admission Glascow Coma Scale (GCS) scores than the medical group. The trial was stopped because of poor patient accrual. They failed to demonstrate a mortality or morbidity benefit, and indeed had a higher mortality rate than other recent studies (57% overall). They concluded that a modest reduction in hematoma volume could be achieved with this method, but that it did not contribute to improved outcome.

Four meta-analyses on various combinations of the aforementioned studies have been carried out,[18-21] and none has provided convincing evidence of a clear benefit or disadvantage of surgery in the setting of sSICH (Table 2). In the analysis by Saver et al,[21,22] the elimination of McKissock's study did allow for a demonstrated significant benefit from surgery. However, this was limited to a reduction in mortality only, and no analyzed combination of studies has shown a significant benefit in terms of the degree of functional dependency.[19] Examination of the randomized clinical trials does show a trend to better outcomes with surgery for younger non-comatose patients with smaller hematoma volumes.[7,12,15] Each author emphasized the need for further, well-designed and larger trials to provide more information on the role of surgery in the management of sSICH.

The international surgical trial in intracerebral hemorrhage was undertaken with hopes of defining the role of early surgery for patients with sSICH.[11] A total of 1,033 patients were recruited from 83 centers in 27 countries over an eight-year period. Although the number of patients randomized exceeded the total number of patients in all preceding randomized controlled trials, the authors acknowledge the results still leave much uncertainty. There was no significant difference in survival or functional outcome between patients in the surgical and initial conservative management groups, based upon intention-to-treat analysis. Analysis among United Kingdom patients suggested early surgery may reduce hospital stay, expense, and recovery time without compromise of outcome, although differences were not statistically significant.

Several aspects of this unique study deserve further discussion. Firstly, the patients with CT evidence of sSICH were eligible for inclusion "if the responsible neurosurgeon was uncertain about benefit of either treatment (the uncertainty principle)". Between countries, however, the assignments of equipoise between treatment options varied wildly, between 2% and 74%,[23] indicating the subjective nature of the inclusion criteria. Secondly, among patients assigned to initial conservative treatment, 59% deteriorated by three or more GCS points, and 26% ultimately underwent surgical evacuation of the ICH. Thirdly, subgroup analysis indicated that surgery may be more likely to provide benefit when hematomas came to within 1 cm of the cortical surface while patients with GCS of eight or below nearly all had unfavorable outcome. Again, all these results must be interpreted with respect to the "uncertainty principle" inclusion criteria. Another important shortcoming of the surgical trial in intracerebral hemorrhage was the broad definition of "early" surgery, including patients within 72 hours of ictus, with only one half being randomized within 20 hours. As outlined in the next section, the potentially reversible deleterious effects of ICH may be more effectively minimized with earlier hematoma evacuation, provided this can be accomplished safely.

Experimental Studies

Despite the relative inattention ICH has received in the clinical literature,[16] substantial experimental work has been focused on the pathophysiology that surrounds an intracerebral hematoma,[24-27] as well as on the possible therapeutic benefits of early hematoma evacuation.[28-31] In the study by Nehls et al,[28] experimental ICH was mimicked by inflating a microballoon within the right caudate nucleus of rats either temporarily (i.e. for ten minutes) or permanently (i.e. for the duration of the study). The two groups of rats were then contrasted at 24 hours in terms of alterations in cerebral blood flow, changes in brain specific gravity (a measure of cerebral edema), and neurological outcome. The investigators found that those rats in the "permanent" injury group suffered significant alterations in global and regional cerebral blood flow, had a higher percentage of cerebral tissue perfused within an "ischemic range" of cerebral blood flow, and were neurologically worse at 24 hours than those whose balloon was deflated immediately. From this work, Nehls and colleagues concluded that early removal of a

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spontaneous intracranial mass lesion could improve blood flow, reduce ischaemia, and improve neurological outcome.

Further to this, Wagner and colleagues[29,30] at the University of Cincinnati developed a lobar intracerebral hemorrhage model using autologous blood deposited into the right centrum semiovale of pigs. In their initial study, they documented that the generation of an ICH was associated with a marked and immediate (i.e. within one hour) increase in brain water content around the hematoma by a factor of 10 to 15 percent.[29] Because this perihematomal edema increased in the absence of any functional disruption of the blood-brain barrier (as assessed by Evans blue dye injection), they concluded that the accumulation of serum proteins that were derived from the hematoma itself contributed to edema formation in the early period after an intracerebral hemorrhage. Although it has never been proven definitively in a clinical study, experience suggests that expansion of this perihematomal edema is responsible for the gradual deterioration and eventual decline of many patients who suffer a spontaneous intracerebral hemorrhage. Mayer et al,[32] in a prospective study of the factors contributing to secondary neurological deterioration in ICH, implicated worsening edema in nine of 15 patients (60%) who experienced deterioration.[32] Furthermore Del Bigio et al[33] correlated edema resolution with neurological improvement in a histopathological study of cerebral hemorrhage in rats. The mechanisms that contribute to edema formation are complex, but include the dissolution of serum proteins from the hematoma directly into the surrounding tissue (early phase), the liberation of coagulation factors – most notably thrombin and fibrinogen - from the hematoma (middle phase and, finally, blood-brain barrier breakdown (late phase).[26,29,31] Because of the major role the hemorrhage itself has in the generation of pathological edema, Wagner and colleagues[30] expanded on their initial work and studied the effect of early evacuation of the generated hematoma on the development of perihematomal edema and on blood-brain barrier integrity. They demonstrated a marked (i.e. >70%) reduction in hematoma volume and perihematomal edema, as well as a significant reduction in local cerebral tissue pressure (reflecting reduced mass effect) and blood-brain barrier preservation, in pigs whose hematomas were aspirated at three and a half hours post-induction, compared to those whose were not. These findings again suggest that early evacuation of an ICH, within hours of ictus, can reduce the pathophysiological impact of the hematoma (Figure 3), and potentially improve functional outcome.

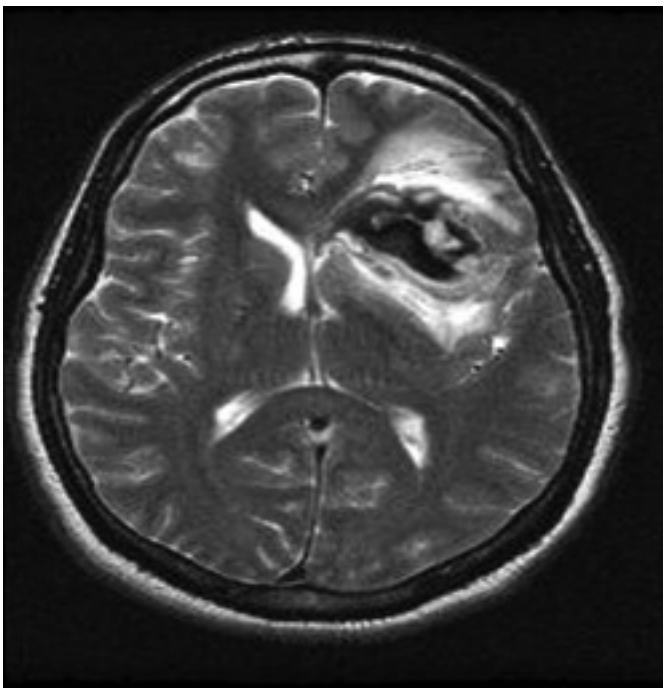

Figure 3: *Pathophysiology of sSICH. The T2 weighted MRI demonstrates a subacute deep intracerebral hemorrhage with surrounding "hyper intensity". Mechanisms leading to perihematomal neural injury and deficits include: mechanical disruption and compression, ischemia, edema, biochemical and inflammatory processes and hematoma expansion.*

Guidelines and Current Practices

In 1999, the American Heart Association published guidelines on the medical and surgical management of spontaneous intracerebral hemorrhage based on their analysis of four randomized studies (the only studies completed at that time).[17] Based primarily on the results of Auer's study, surgery was recommended only for those individuals suspected or shown to have an accessible and treatable structural lesion (and therefore not primary hemorrhage), and for relatively young patients with subcortical hemorrhages who were clinically deteriorating. Beyond this, further recommendations regarding sSICH were not (and could not) be made. It is therefore not surprising that the utilization of surgical treatment for sSICH varies widely between centres and across the world. There are numerous non-randomized and retrospective surgical series with enthusiastic conclusions, particularly related to early surgical evacuation.[34-39] While such results are surely influenced by the "confounding variable" of surgeon bias, this factor highlights the importance of patient selection. Recently there has been growing interest in minimally invasive techniques such as stereotactic hematoma fibrinolysis and aspiration.[40-44] This technique is usually applied beyond the 12 to 24 hour acute post hemorrhage time period, and evacuation accomplished gradually over several days. The single randomized clinical trial of stereotactic aspiration demonstrated clot evacuation was slow, incomplete and not associated with outcome benefit.[14] Conversely, mechanically facilitated stereotactic removal has been largely abandoned due to the higher procedure related bleeding risk.

The role for a nonsurgical approach is quite well defined for patients presenting at either extreme of the sSICH spectrum. Surgery is not generally indicated for those with good GCS and small ICH volume, or poor GCS and large ICH volume. The challenging patient subgroup are those presenting with moderate hematoma volume and neurosurgical deficits; these patients are expected to survive with significant neurological deficits. Experimental evidence suggests early clot removal may minimize secondary neural injury and improve outcome. Anecdotal experience supports this, while formal clinical trials

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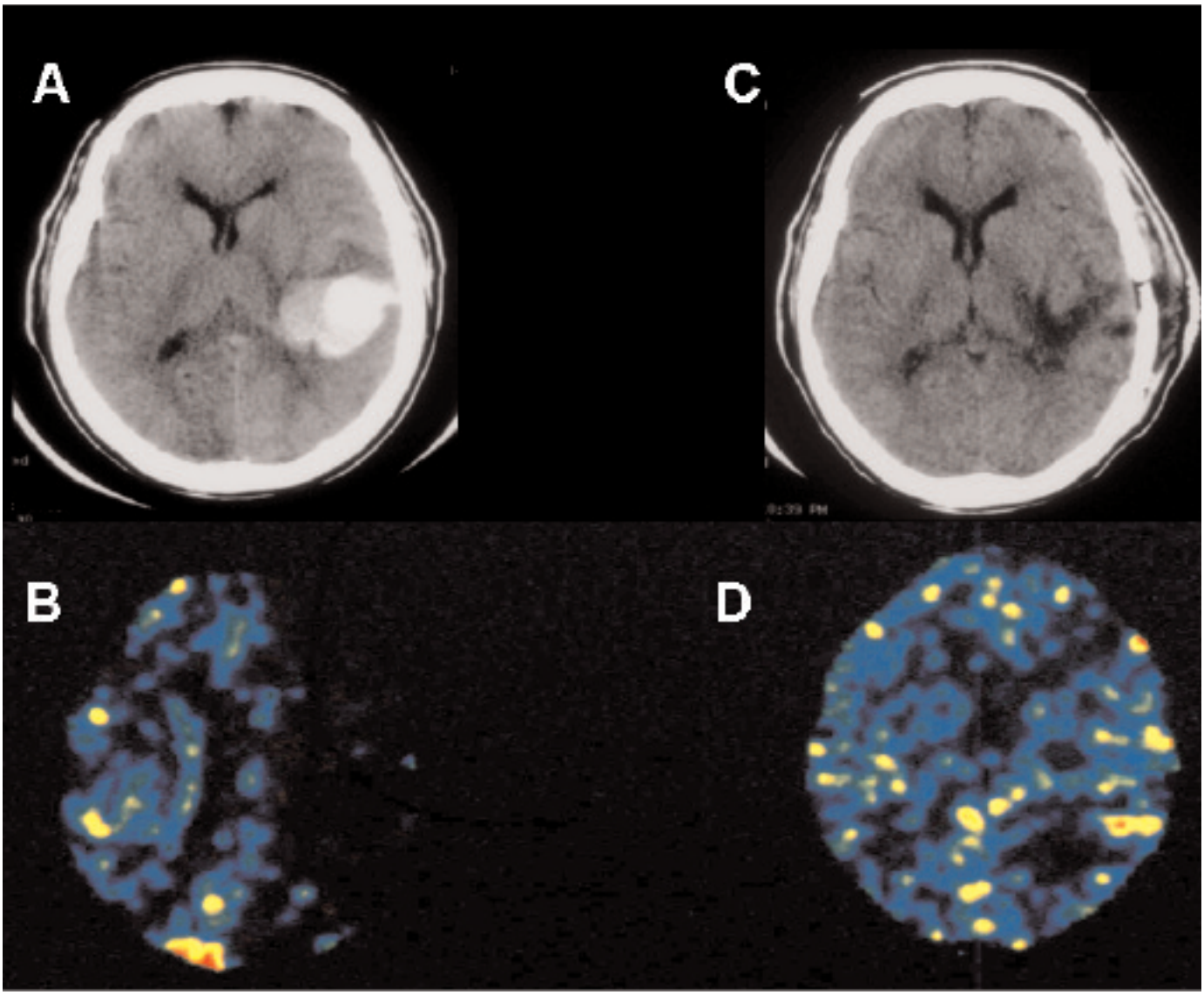

Figure 4: *Perihematomal ischemia and acute sSICH delineated on CT scan (A) is surrounded by an extensive area of hypoperfusion as demonstrated on a concurrent stable Xenon cerebral blood flow study (B) early clot evacuation (C) resulted in major neurologic improvement and correction of perihematomal ischemia (D) as documented 12 hours postoperatively.*

have not thoroughly evaluated this "aggressive" surgical approach. Examination of the recent randomized clinical trials, however, do demonstrate that surgery does not have a deleterious effect on outcome and therefore further study to define appropriate indications and techniques for surgery are warranted.

Future Directions

The clinical experience with sSICH derived from randomized clinical trials, case series and anecdotal reports suggests there exists some subgroups of patients who will benefit from early surgical evacuation. Current diagnostic imaging modalities accurately identify potential underlying structural lesions, and intraoperative localization techniques are becoming more widely available. Appropriate patient selection will remain a major and potentially contentious challenge. Perhaps physiological information derived from advanced diagnostic imaging tools may identify patients with significant perihematomal "penumbra" that may be successfully salvaged (Figure 4).

If surgical attempts are to be directed at earlier evacuation of sSICH, the safety of such a procedure will need to be addressed. As indicated by Morgenstern et al,[13] ultra-early craniotomy for hematoma evacuation may be complicated by a significant risk of rebleeding. However, efforts to alleviate this risk have already been initiated. To date, promising work has been presented

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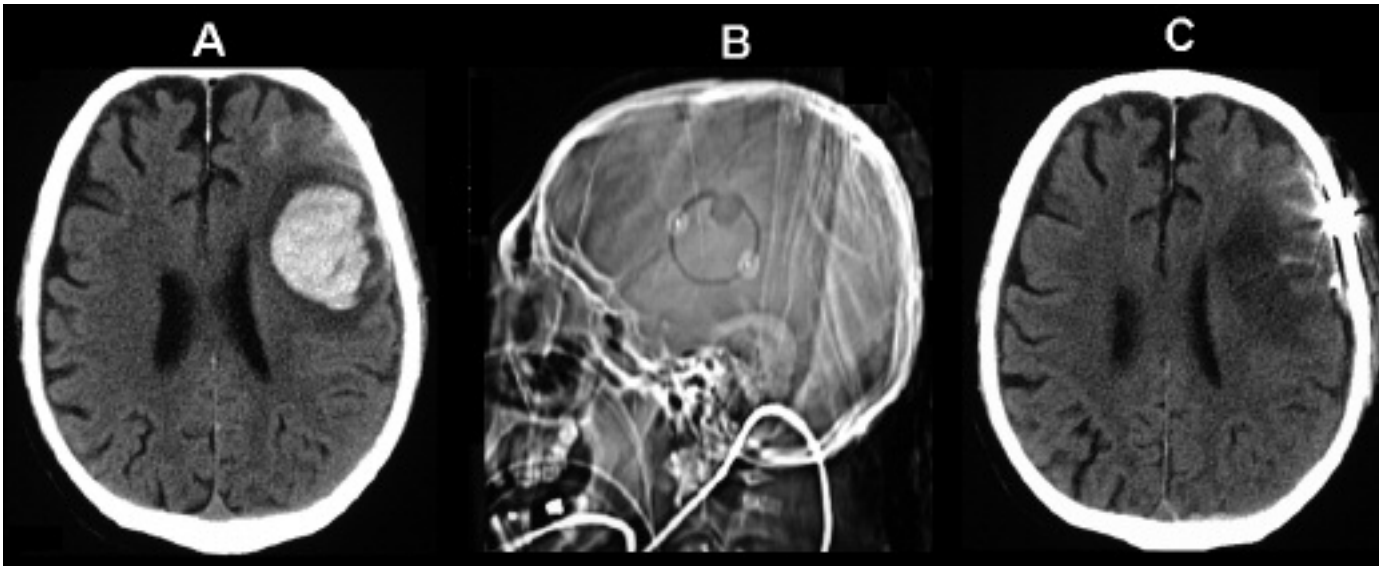

Figure 5: *Early sSICH evacuation and hemostasis. A left frontal, warfarin related sSICH (A) resulted in hemiparesis, aphasia and generalized seizures. Emergent hematoma evacuation was completed within 4 hours of stroke onset, through an ultrasound guided craniotomy and mini-corticectomy (B). Intra- and post-operative hemostasis was readily achieved with administration of vitamin K, FFP and rFVIIa (C).*

involving the use of potent site-specific hemostatic agents, to limit rebleeding and hematoma expansion. Recombinant activated factor VII (rFVIIa) has been successfully used to reverse warfarin-induced coagulopathies in neurosurgical cases.[45] In our own experience with a handful of cases, it seems to reduce intraoperative oozing or rebleeding following hematoma evacuation (Figure 5). While such an agent may have the potential to facilitate ultra early surgical hematoma evacuation by reducing the risks of perioperative bleeding, this has not yet been tested in clinical trials. A recent phase IIb randomized clinical trial, however, did demonstrate a single dose of rFVIIa infused within four hours of ICH did limit subsequent hematoma growth, reduce mortality and improve functional outcome at 90 days.[46]

Spontaneous ICH remains a common and vexing clinical problem. Although no randomized trial has shown a convincing benefit from surgery, the results of several studies suggest that a subgroup of patients – those with moderate-sized hematomas and modest neurological deficits – may profit from early evacuation. Recent experimental studies support early hematoma evacuation as a means of ameliorating the pathophysiological cascade of hematoma expansion, perihematomal ischaemia, and edema formation, that contribute to morbidity and mortality. If ultra early hematoma evacuation is to be pursued, efforts must be directed at achieving surgical safety and efficacy through proper patient selection, minimally invasive techniques, and pharmacological adjuncts that may limit edema and perioperative rebleeding.

Acknowledgments

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Conflicts of Interest

AMK has received honouraria from NovoNordisk Canada and has participated as a member of a NovoNordisk Canadian advisory board.

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Ultra-early Hemostatic Therapy for Primary Intracerebral Hemorrhage: A Review

Stephan A. Mayer

ABSTRACT: Stroke is a major health problem worldwide, causing high morbidity and mortality. Intracerebral hemorrhage (ICH) accounts for 10% of stroke cases in the United States and Europe and up to 30% in Asian populations. Intracerebral hemorrhage is less treatable than other forms of stroke and causes higher morbidity and disability. Data suggest that early hematoma growth is the principal cause of early neurological deterioration after ICH. Prospective and retrospective studies indicate that early hematoma growth occurs in 18–38% of patients scanned within three hours of ICH onset, and that hematoma volume is an important predictor of 30-day mortality. Recombinant activated factor VII (rFVIIa, NovoSeven®), a powerful initiator of hemostasis, is approved for the treatment of bleeding in patients with hemophilia and inhibitors, and can also promote hemostasis in patients with normal coagulation. A Phase-IIB randomized, double-blind, placebo-controlled, dose-ranging trial has been conducted in 399 patients with ICH to investigate the potential of rFVIIa as an ultra-early hemostatic therapy. A reduction in hematoma growth in non-coagulopathic ICH patients was evident with reduced mortality and improved clinical outcome at three months. The significance of these findings for neurocritical care is discussed.

RÉSUMÉ: Le traitement hémostatique très précoce de l'hémorragie cérébrale primitive : une revue. L'accident vasculaire cérébral (AVC) est un problème de santé majeur à travers le monde et cette pathologie entraîne une morbidité et une mortalité élevées. Aux États-Unis et en Europe, dix pour cent des cas d'AVC sont dus à une hémorragie cérébrale (HC) et ce taux est d'environ 30% dans les populations asiatiques. L'hémorragie cérébrale est moins traitable que les autres formes d'AVC et cause une morbidité et une invalidité plus élevées. Selon certaines données, l'expansion de l'hématome est la principale cause de la détérioration neurologique en phase précoce de l'HC. Des études prospectives et rétrospectives indiquent qu'une expansion de l'hématome survient chez 18 à 38% des patients chez qui on obtient un scan dans les trois premières heures de l'événement et que le volume de l'hématome est un facteur important pour prédire la mortalité à trente jours. Le facteur VII recombinant sous forme activée (rFVIIa, NovoSeven®), un déclencheur puissant de l'hémostase, est approuvé pour le traitement de saignements chez les patients hémophiles et chez les patients recevant des inhibiteurs de la coagulation. Il peut également promouvoir l'hémostase chez les patients dont la coagulation est normale. Un essai thérapeutique de phase IIb, randomisé, en double aveugle, contrôlé par placebo et étude de dose chez 399 patients atteints d'HC a été réalisé pour évaluer si le rFVIIa avait un potentiel thérapeutique comme agent hémostatique très précoce. Une diminution de l'expansion de l'hématome a été observée chez les patients sans coagulopathie atteints d'HC, ainsi qu'une diminution de la mortalité et une amélioration de l'issue clinique à trois mois. Nous discutons de la signification de ces observations dans l'optique de la réanimation neurologique.

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Stroke, comprising ischemic stroke, subarachnoid hemorrhage (SAH), and intracerebral hemorrhage (ICH), is the third most-common cause of death in the United States (US)[1] and the second most-common worldwide.[2,3] Moreover, stroke is the leading cause of chronic disability, particularly among elderly individuals.[4] As such, stroke is a major public health issue, due to the loss of patients from the workforce, extended hospitalization, and healthcare costs. Indeed, estimates of the annual cost of care for stroke patients exceed $50 billion in the US alone.[5] Accordingly, this devastating burden represents a prime target for therapeutic improvement.

Intracerebral hemorrhage is the least treatable form of stroke and is associated with higher morbidity and greater disability than ischemic stroke or SAH.[6] It is responsible for approximately 10% of stroke cases in the US and Europe and 20–30% in Asian

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populations.[3,6] Data for the US in 1997 indicated that of an estimated 37,000 patients presenting with ICH, 35–52% had died within one month, 10% were living independently after one month, and only 20% were independent at six months.[7,8]

The risk factor profile for ICH differs from that of other types of stroke. Hypertension, particularly untreated disease, is the most important risk factor for ICH,[4,9,10] being present in around 50–70% of cases.[11] In contrast, accepted risk factors for ischemic stroke, such as diabetes, ischemic heart disease, and prior transient ischemic attacks, appear to be less important in ICH. Advancing age is another important risk factor for ICH: incidence is low among individuals aged <45 years and increases dramatically in those aged >65 years.[12,6] Other risk factors include hypocholesterolemia, anticoagulant use, and excessive alcohol intake.[6]

Existing Management Strategies For ICH

In contrast to the successful therapeutic advances for ischemic stroke and SAH, there remains a lack of effective treatment for ICH. Existing therapy for ICH is primarily supportive in nature (control of blood pressure, intracranial pressure, fluid balance, body temperature, and prevention of seizures), and outcomes are generally poor. Although a small number of randomized clinical trials of surgical or medical interventions in ICH have been published,[7] no conclusive beneficial effects have been demonstrated. Interventions investigated have included surgical evacuation of the hematoma[13,14] and the use of dexamethasone or glycerol.[15] The recently-published International Surgical Trial in Intracerebral Hemorrhage (STICH) showed no effect on functional outcome or mortality with a policy of early surgery within 72 hours of onset compared with best medical management.[13] The current situation regarding therapy for ICH was summarized in a recent scientific statement from the American Heart Association: "Well-designed and well-executed treatment studies of ICH are urgently needed...We hypothesize that ultra-early treatment will be critical for patients with ICH." [7]

Early Hematoma Growth In ICH

Historically it was thought that the bleeding associated with ICH was completed within minutes of event onset, and that the neurological deterioration observed during the first day after the bleed was attributed to cerebral edema and mass effect around the hemorrhage.[16] More recently data from pathological studies, computed tomography (CT) analysis, and clinical observations suggest that early hematoma growth occurs as a result of "ultra-early rebleeding" into congested and damaged tissue around the hematoma.

Neurological deterioration associated with early hematoma growth

In the late 1980s, retrospective analyses of repeated CT scans in small numbers of patients without coagulopathy illustrated early hematoma growth.[17,18] These studies were the first to describe the phenomenon of early hematoma growth, highlighting it as a possible target for intervention. More recently, a series of retrospective studies and a single prospective study involving larger patient numbers (*n* ranging from 103 to 627 patients) provided further support for the occurrence of early hematoma growth.[19-22] These studies, involving patients scanned within three hours of onset of ICH, showed that early hematoma growth, as documented by subsequent CT scans, occurs in 18–38% of individuals (Table 1). Of note, the highest rate of early hematoma growth (38%) was documented by the sole prospective study, and these investigators concluded that the true frequency of hematoma growth must be higher than this rate because clinical deterioration and immediate surgical intervention precluded the performance of the follow-up scans in some patients.[21] In this prospective study, early hematoma growth occurred in 26% of patients within one hour of the baseline scan, and in an additional 12% between one and 20 hours.[21]

The occurrence of early hematoma growth is associated with poor clinical outcome.[21–24] Significantly greater reductions in Glasgow Coma Scale scores and increases in National Institutes of Health Stroke Scale scores have been reported among patients

Table 1: Hematoma growth (%) in patients with ICH: data from one prospective and three retrospective studies

Interval from ICH onset to CT (h)	Prospective	Retrospective		
	Brott et al 1997[21] (n=103)	Fujitsu et al 1990[19] (n=107)	Fujii & Tanaka 1998[22] (n=627)	Kazui et al 1996[20] (n=204)
0–3	38	NA	18	36
3.1–6.0	NA	NA	8	16
0–6	NA	21	17	29
6.1–24.0	NA	NA	2	10

NA: not available. Adapted from reference 35 (Mayer SA: Ultra-early hemostatic therapy for intracerebral hemorrhage. Stroke 2003; 34; 224-229.), with permission.

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with documented growth on one hour follow-up scans, compared to those without growth.[21] Moreover, larger retrospective studies have reported significantly higher mortality rates in patients with hematoma expansion, compared to those without growth.[20,22]

Pathophysiology of early hematoma growth in ICH

One of the key requisites for developing effective therapy for ICH is an understanding of the pathophysiology of early hematoma growth. However, this has proved to be a difficult task, as no animal model exists that accurately mimics the dynamic processes involved in human ICH. Nonetheless, the notion that ultra-early rebleeding continues at the site of a single ruptured lenticulostriate artery or arteriole has been contested. Evidence from studies employing histopathology, CT analysis, single-photon emission computed tomography (SPECT), and both conventional and CT angiography suggests that it is more likely that secondary multifocal bleeding into tissue at the periphery of an existing clot occurs in cases of early hematoma enlargement.

Histopathological analyses of brain tissue have indicated the presence of micro- and macroscopic bleeds in the area peripheral to fatal hemorrhage, perhaps representing ruptured arterioles or venules.[25] Simultaneous CT and SPECT analyses have shown that in some cases, early ICH growth relates to secondary bleeding in the periphery of the existing clot into ischemic, congested, perilesional tissue (Figure 1).[26] Moreover, an association has been reported between early hematoma growth and irregular clot morphology, which may reflect multifocal bleeding.[22,23] In these studies, the incidence of hematoma growth was greater in patients with irregularly shaped hematomas compared with those with round hematomas, and it was postulated that the irregular shape indicated bleeding from multiple arterioles.[23] The CTA performed immediately after ICH demonstrates active contrast extravasation into the hematoma in 30–46% of patients, and has been associated with subsequent hematoma enlargement[27] and increased mortality.[28] Finally, bleeding from multiple lenticulostriate arteries has been demonstrated angiographically immediately after ICH.[29,30]

The evidence provided by these observations suggests that early hematoma growth occurs because of bleeding into a necrotic layer of tissue that forms acutely at the margin of the hematoma.[31] Possible contributing factors include increased local tissue pressure leading to mechanical injury, reduced cerebral blood flow, plasma protease induction, and secondary inflammation related to clotting proteins; however, the relative importance of these factors in the early hours after ICH is unclear.[32-34] Most probably, a form of 'congestive' ischemia occurs in the brain tissue surrounding the hematoma, similar to the venous infarction associated with dural sinus thrombosis, with an increase in vascular congestion and local tissue pressure. Intravascular hydrostatic pressure may cause secondary bleeding from venules and arterioles, and bleeding may continue due to regional mechanical and ischemic tissue damage. Alternatively, it is possible that a local coagulopathic environment enhances bleeding. Plasma infiltrates into peripheral brain tissue very quickly,[33] and may hinder the process of hemostasis in adjacent brain tissue through inhibition of thrombin, platelet aggregation, and clotting factor degradation.

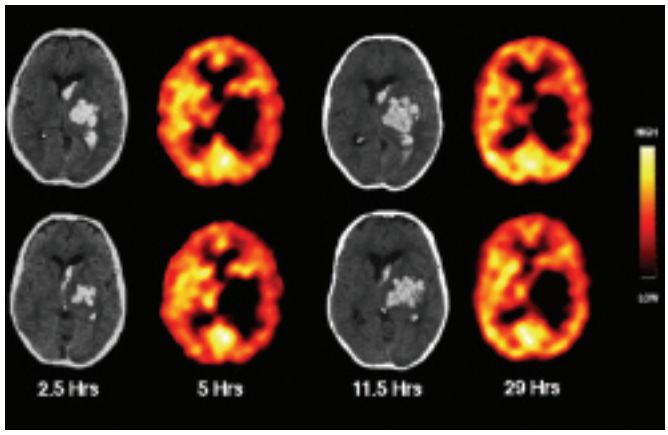

Figure 1: *Early hematoma growth in a 71-year-old woman with left putaminal hemorrhage. The ICH volume increased by 80%, from 15 mL at 2.5 hours to 26 mL at 11.5 hours. Concurrent SPECT images indicate that that the enlargement resulted from the addition of discrete hemorrhages within the no-flow zone around the existing clot. Reproduced from reference 26, with permission (Mayer SA, Lignelli A, Fink ME et al. Perilesional blood flow and edema formation in acute intracerebral hemorrhage: a SPECT study. Stroke 1998; 29: 1791-8).*

A New Therapeutic Approach to ICH

Ultra-early hemostatic therapy

To be effective, hematostatic therapy must be given as soon as possible after the onset of symptoms of ICH.[35] By extrapolating prospective data of patients scanned within three hours of onset,[21] if one assumes that ultra-early rebleeding occurs somewhere between a linear and exponential rate during the first 60 minutes after scanning, even if the intervention is completely effective, hematoma enlargement would be expected in 10%, 17% or 22% of patients after a 15-, 30-, or 45-minute treatment delay following the baseline scan (Figure 2). Underlying this principle is the fact that the only consistently identified predictor of early hematoma growth is the interval from the onset of symptoms to CT: the earlier the first scan is obtained, the more likely subsequent bleeding will be detected on a follow-up scan.[20,23] As a corollary, hematoma growth occurs in only five percent of patients who are initially scanned beyond six hours of symptom onset.[20,23]

Ultra-early hemostatic therapy may have the potential to halt early deterioration by preventing hematoma growth and also late deterioration (≥12 h after ICH onset), occurring as a result of perihematomal edema and mass effect. The importance of preventing late neurological deterioration is emphasized by a study involving 46 patients with ICH in which approximately 33% experienced late neurological deterioration and its occurrence was predicted by ICH volume.[36] These observations led to the hypothesis that perilesional edema related to large established hemorrhages is the main cause of late neurological deterioration post-ICH.

The use of ultra-early hemostatic therapy is a novel approach to treating ICH. Administered alone or in conjunction with

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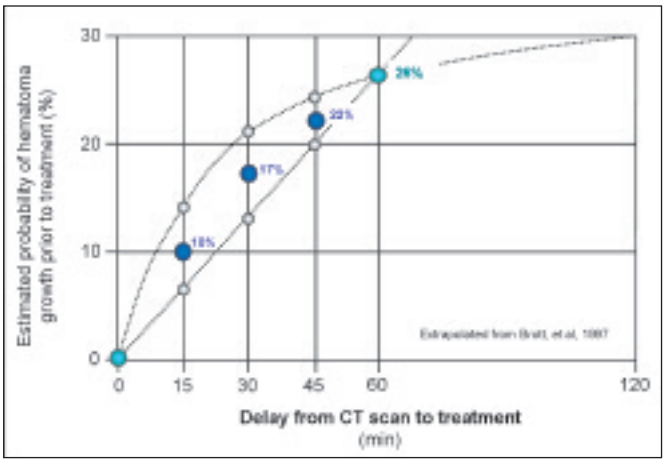

Figure 2: *Estimated effect of the interval between CT scan and treatment on the probability of interval hematoma expansion when the initial CT scan is performed within three hours of onset of ICH. Reproduced from reference 35, with permission (Mayer SA: Ultra-early hemostatic therapy for intracerebral hemorrhage. Stroke 2003; 34; 224-229).*

surgical or neuroprotective intervention, ultra-early hemostatic therapy may have the potential to become the standard care for ICH and revolutionize its treatment in the emergency room and intensive care setting. If found to be effective, it may become the counterpart to tissue plasminogen activator in the management of acute ischemic stroke.

Potential agents for ultra-early hemostatic therapy

An ideal ultra-early hemostatic agent for use in ICH patients would be one that inhibits fibrinolysis and activates coagulation locally, allowing fast and effective hemostasis without causing systemic adverse events. Several agents may potentially be used for this purpose.

Aminocaproic acid and tranexamic acid

Aminocaproic acid and tranexamic acid are synthetic derivatives of the amino acid lysine and have proven antifibrinolytic activity in humans.[37] These agents bind reversibly to plasminogen, which blocks its activation by fibrin and prevents its conversion to plasmin. Tranexamic acid has a longer half-life than aminocaproic acid and is much more potent. Both agents inhibit fibrinolysis and act as effective clot stabilizers, but they do not activate coagulation, thrombin generation, or clot formation. They are effective in treating bleeding disorders, including primary menorrhagia,[38] upper gastrointestinal bleeding,[39] and mucosal bleeding in patients with thrombocytopenia or other coagulation disorders.[40] Prolonged antifibrinolytic therapy reduces aneurysm rebleeding after subarachnoid hemorrhage, but at the expense of an increase in secondary infarction from vasospasm, resulting in no net benefit on mortality.[41]

Aprotinin

Aprotinin is an inhibitor of serine proteases such as trypsin, chymotrypsin, plasmin, and kallikrein. Its action against kallikrein indirectly inhibits factor XII formation, which disrupts coagulation. Aprotinin interferes with both fibrinolysis and coagulation when blood comes into contact with a foreign surface, but has no effect on platelet function. Aprotinin has been demonstrated to reduce blood loss during surgical procedures, including cardiac surgery[42] and orthotopic liver transplantation.[43]

Recombinant activated Factor VII (rFVIIa)

Coagulation factor VII is a naturally occurring initiator of hemostasis, and its activated form, recombinant activated factor VII (rFVIIa, NovoSeven®; Novo Nordisk, Bagsvaerd, Denmark) was developed for the treatment of spontaneous and surgical bleeding in patients with hemophilia A or B and inhibitors to factors VIII or IX, respectively.[44] Recombinant activated Factor VII (rFVIIa) binds to the surface of activated platelets where it generates activated Factor X allowing partial restoration of platelet surface thrombin generation.[45] Through its action of enhancing local hemostasis after binding to exposed tissue factors, rFVIIa has been shown recently to be an effective initiator of hemostasis in patients with a normal coagulation system.[46,47] Moreover, its efficacy has been reported in promoting hemostasis in central nervous system bleeding in patients with hemophilia.[48] Cessation of bleeding occurred in 84% of central nervous system bleeding episodes after administration of rFVIIa 80–100 µg/kg. One patient died, and there were no adverse events related to rFVIIa administration.[48] The lack of systemic adverse events associated with the use of rFVIIa, together with its rapid action at the site of bleeding and short half-life of two and one half hours suggest that rFVIIa may be an ideal agent for use during the high-risk stage of ICH. Given this potential and the lack of effective treatments for ICH, evaluation of the efficacy and safety of rFVIIa as an ultra-early hemostatic intervention in ICH is warranted. Recently, a randomized, placebo-controlled, dose-ranging study has been conducted with rFVIIa in non-coagulopathic patients with ICH. A summary of this study, the outcomes observed and their significance are presented and discussed below.

The NovoSeven® ICH trial

The results of the NovoSeven® ICH trial, an international, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study, have recently been published. The main objective of the study was to determine if rFVIIa could limit ongoing bleeding and effectively reduce hematoma growth in acute ICH, and thereby improve outcome. The study compared the efficacy of three, randomly assigned, single doses of rFVIIa (40, 80 and 160 µg/kg) to placebo, administered intravenously over one-two minutes. Patients with spontaneous ICH diagnosed by CT scan within three hours of symptom onset were enrolled. Their allocated treatment was then administered within an hour of the baseline CT scan.

The primary outcome measure was the mean percentage change in ICH volume between baseline and 24 hours as determined by CT scan. In addition, clinical outcomes at three months were determined using the following assessment

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instruments: the modified Rankin Scale (mRS), the Barthel Index, the Extended Glasgow Outcome Scale, and the National Institutes of Health Stroke Scale. The main safety outcome measure was the frequency of thromboembolic serious adverse events (SAEs) at day 90.

In total, 399 patients (61% male, mean age 66 years and predominantly white) were randomized to treatment: placebo (n=96), rFVIIa 40 µg/kg (n=108), 80 µg/kg (n=92), 160 µg/kg (n=103). The ICH volume at baseline (mean 24 mL, range: 0.4 to 153 mL) was similar in each treatment group. The mean interval from symptom onset to baseline CT scan was 114 ± 35 minutes; the mean interval from CT scan to treatment was 54 ± 21 minutes, and mean onset-to-needle time was 167 ± 32 minutes. Approximately 12% of all ICH patients treated at the study centers during the trial period were enrolled and randomized.

The mean percentage increase in ICH volume was 29% following placebo treatment, compared with 16%, 14% and 11% in the rFVIIa 40, 80 and 160 µg/kg groups, respectively (Table 2; combined treatment effect, P=0.01). The comparison between the rFVIIa 160 µg/kg and placebo groups was statistically significant (P=0.02). A similar pattern emerged for the absolute mean change in ICH volume from baseline to 24 hours, which was significantly reduced with rFVIIa treatment compared with placebo (P=0.01). Mean absolute growth in ICH volume was reduced by 3.3, 4.5 and 5.8 mL with rFVIIa 40 µg/kg (P=0.13), rFVIIa 80 µg/kg (P=0.04) and rFVIIa 160 µg/kg (P=0.008), respectively, compared with placebo.

Notably, the hemostatic effect of rFVIIa treatment was more pronounced when administered within three hours of symptom onset. In the subset of patients where this criterion was met (n=269), the mean percentage increase in ICH volume was 34% in the placebo group compared with 13% for rFVIIa-treated patients (P=0.004). The absolute increase in ICH volume was 10.7 mL and 4.4 mL for placebo- and rFVIIa-treated patients, respectively (P=0.009).

At three months, mortality in the placebo group was 29% compared with 18% in the rFVIIa treatment groups combined. Furthermore, all four global outcome scale assessments at three months showed more favorable outcomes following intervention with rFVIIa compared with placebo. Comparisons for all dose levels of rFVIIa were significant, versus placebo, for the mRS and National Institutes of Health Stroke Scale assessments, whilst comparisons were significantly in favor of rFVIIa 80 and 160 µg/kg, versus placebo, for the Barthel Index. These results indicate that treatment with rFVIIa more than doubled patients' odds of improving by one level on the mRS, and decreased the proportion of patients who died or became disabled from 69% in the placebo group to 53% with rFVIIa treatment.

Thromboembolic SAEs occurred in 2% of patients receiving placebo compared with 6%, 4%, and 10% receiving rFVIIa 40, 80 and 160 µg/kg, respectively. The difference between active treatments and placebo was not significant (P=0.12). There were no arterial thromboembolic SAEs in the placebo group compared with frequencies of 6%, 2% and 8% in the rFVIIa 40, 80 and 160 µg/kg groups, respectively (overall P=0.01). These SAEs

Table 2: ICH volumes from the NovoSeven® ICH trial

ICH volume	Placebo (n=96)	rFVIIa			
		40 µg/kg (n=108)	80 µg/kg (n=92)	160 µg/kg (n=103)	Combined (n=303)
At baseline (mL)	24 ± 22	22 ± 22	23 ± 24	26 ± 30	24 ± 26
At 24 hours (mL)	32 ± 29	26 ± 29	28 ± 31	28 ± 32	27 ± 30
Estimated mean relative increase from baseline, % (98.3% CI)	29 (16–44)	16 (4–28)	14 (2–27)	11 (0–23)	14 (7–21)
P value, vs placebo	–	0.07	0.05	0.02†	0.01†
Estimated mean absolute increase from baseline, mL (98.3% CI)	8.7 (4.9–12.4)	5.4 (1.7–9.0)	4.2 (0.3–8.0)	2.9 (-0.8–6.6)	4.2 (2.0–6.3)
P value, vs placebo	–	0.13	0.04	0.008†	0.01†

Plus–minus values are means ± standard deviation (SD). For estimated mean differences, 98.3% confidence intervals (CIs) are derived from a generalized linear mixed model with the patient and the reader as random effects and baseline intracranial hemorrhage (ICH) volume, time from onset to CT, and time from CT to treatment as fixed effects. †The comparison was statistically significant according to the prespecified Bonferroni-corrected threshold of P=0.0167. Reproduced with permission from reference 49 (Mayer SA, Brun NC, Begtrup K, et al. Recombinant activated factor VII for acute intracerebral hemorrhage. N Engl J Med 2005; 352: 777-785).

included seven myocardial ischemic events and nine cases of cerebral infarction that occurred within three days of dosing. However, fatal or disabling thromboembolic SAEs that were considered possibly or probably related to treatment occurred in 2% of patients receiving placebo and in 2% of rFVIIa-treated patients.

This study demonstrates the feasibility of ultra-early hemostatic therapy with rFVIIa. When administered within four hours of ICH onset, rFVIIa significantly reduced subsequent hemorrhage growth and improved patients' clinical outcome, despite a non-significant increase in the frequency of thromboembolic adverse events. Mortality was reduced by 38% with rFVIIa treatment (P=0.025). Compared with placebo, a reduction in ICH volume of approximately 5 mL was evident 24 hours after rFVIIa treatment; this translated to an 11 mL reduction in total lesion volume at 72 hours, and a 16% absolute reduction in the risk of death or severe disability at three months as assessed by the mRS. A dose-response effect was evident for reduction of hemorrhage growth; the smallest effect occurred with rFVIIa 40 µg/kg and the most substantial effect with 160 µg/kg. Timing of administration appears to be critical; treatment within three hours of symptom onset provided the best outcomes. These results are supportive of ultra-early hemostatic therapy with rFVIIa; they are also consistent with the view that active bleeding occurs in a large proportion of patients within the first few hours of ICH onset, but this rapidly diminishes over time.

The results obtained with rFVIIa treatment in this study are encouraging and may offer improved prospects for patients in need of acute neurocritical care. However, further research is needed to identify those patients at risk of thromboembolic complications, to define the optimal therapeutic window, and to assess rFVIIa for coagulopathic ICH.[50] A large phase III trial (Factor Seven for Acute Hemorrhagic Stroke Treatment, the FAST Trial) is now underway.

Summary

Intracerebral hemorrhage is the cause of significant morbidity and mortality worldwide and, as a result, inflicts a heavy burden on society. In the absence of effective management strategies, new approaches to ICH treatment are needed. The use of ultra-early hemostatic therapy in the emergency setting to limit ongoing bleeding and minimize ICH volume is biologically plausible and its clinical feasibility has been confirmed in a Phase IIB randomized clinical trial with rFVIIa.

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Conflicts of Interest

SAM has received honouraria from NovoNordisk and has participated as a member of a NovoNordisk International advisory board. SAM was the principal investigator for the randomized clinical trial examining the efficacy rFVIIa for the treatment of intracerebral hemorrhage.

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