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A REVIEW ON CURRENT MANAGEMENT OF NON-TRAUMATIC SPONTANEOUS INTRACEREBRAL HAEMORRHAGE

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Abstract

Intracerebral haemorrhage is when blood suddenly bursts into brain tissue,causing damage to brain.Intracerebral haemorrhage is an important health problem leading to high rates of death and disability in adults. And it is the most devastating and disabling type of stroke. Uncontrolled hypertension is one of the most common causes for spontaneous intracerebral haemorrhage. Although the number of hospitals for admission for ICH has increased worldwide in past 10 years, mortality has not fallen. Significant treatment approaches include, early diagnosis and haemostasis, aggressive management of hypertension. Factors such as chronic hypertension; cerebral amyloid angiopathy and anticoagulation are commonly associated with intracerebral haemorrhage. Chronic arterial hypertension represents the major risk factor for bleeding. The incidence of hypertension related intracerebral haemorrhage is decreasing in some regions due to improvements of treatments in the chronic hypertension, anti-coagulant related ICH (vitamin-k antagonist and new oral coagulant drugs), represent an increase in the cause of ICH.

Key Words: Intracerebral hemorrhage,Uncontrolled hypertension**,** clinical management, Anti-coagulation**,** Cerebral amyloid angiopathy.

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INTRODUCTION

Non-traumatic intracerebral haemorrhage results from rupture of blood vessels in the parenchyma of the brain. It is amajor public health problem[1] it is the most sub-type of stroke, with an annual incidence of 10-30 per 100000 population[1,2] accounting for 2 million (10-15%)of about 15 millions strokes worldwide each yearprobably because of and increasing the use of anti-coagulants, thrombolytics and anti platelet agents, uncontrolled hypertension is the most common risk factor for spontaneous ICH. An incidence of ICH is higher in Asians, partly due to limited primary care for hypertension and non-compliance. Primary prevention with anti-hypertensive medication is likely the most effective strategy to reduce burden of ICH. Population based studies states that the majority of patients with small ICH are readily survivable with good Medicare. Whereas patients with large ICH, comprehensive multidisciplinary care is needed to minimize morbidity and mortality. Intra cerebral haemorrhage associated with the taking of oral anti-coagulants typically affects patients with vasculopathies related to chronic hypertension or cerebral amyloid angiopathy, which might represent the exacerbation of an existing risk of clinical and sub clinical disease.

CLASSIFICATION

- Spontaneous ICH can be classified as either primary or secondary based on the underlying cause.
- Primary intracranial haemorrhage caused due to spontaneous rupture of small vessels which damaged by hypertension or amyloid angiopathy. About ~70-80% of cases are observed due to this primary ICH.
- Primary intracranial haemorrhage is also classified by location as lobar versus non-lobar and supratentorial versus infratentorial.
- Lobar ICH is caused due to cerebral amyloid, angiopathy (CAA) [3], the most common locations of hypertensive ICH, are the putamen, thalamus, sub-cortical white matter, pons and cerebellum.
- Secondary ICH , occurred due to number of congenital and acquired conditions such as vascular malformations, tumor's, coagulation disorders, use of anti-coagulants and thrombolytic agents, cerebral vasculitis, drug abuse and cerebral venous thrombosis[4].

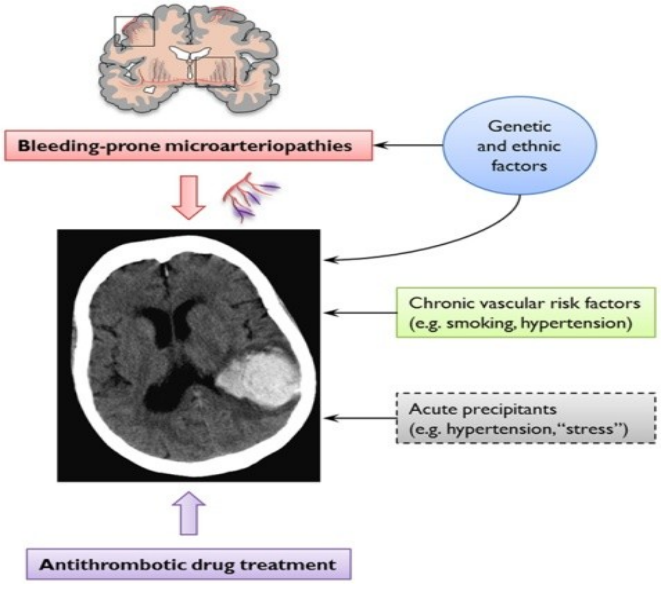
ETIOLOGY AND RISK FACTORS

The most important modifiable risk factor in spontaneous ICH is chronic arterial hypertension. The peripheral arteries in the pons, mid brain, thalamus, basal ganglia and deep cerebellar nuclei, chronically damaged by hypertension, are the most common locations for hypertensive bleeding.Besides hypertension, cerebral vascular amyloid deposition (i.e., cerebral amyloid angiopathy) is associated with ICH in older patients. The incidence significantly increases, they after and is almost always associated with a lobar haemorrhage. (i.e., the use of anti-thrombotic or thrombolytic agents) congenital or acquired factor deficiencies and systemic diseases such as thrombocytopenia, are possible causes of ICH. The use of oral anti-coagulants, especially vitamin-k inhibitors (i.e., warfarin) has increased coagulopathy associated ICH in recent years, acquiring for more than 15% of all cases[5] .Physiologically,

ethnic and economic factors place a role in the prelevance of cerebral haemorrhage. The identified risk factors for ICH include age (i.e., each decade from 50 years of age is associated with a twofold increases in the incidence of ICH).And an elevated alcohol intake . The most important considerable etiologies of ICH include: intra cranial aneurysms, (typically presenting as sub-arachnoid Haemorrhage, arteriovenous malformations, cerebral venous sinus thrombosis and venous infraction) brain tumors (>5% of all ICH cases) including cerebral metastasis (example; lung cancer,melanoma, renal cell carcinoma, thyroid carcinoma, chronic carcinoma and primary CNS tumors)and drugs of abuse (example: cocaine, amphetamine). Because of the differing etiologies of ICH, a rapid and accurate diagnosis of the underlying etiology of ICH is essential to direct appropriate management strategies[6].

PATHOGENESIS ICH

ICH consists of three distinct phases: 1.initial haemorrhage, 2.hematoma expansion, and 3.peri-hehematomaedema. The initial haemorrhage is caused by rupture of cerebral arteries influenced by the aforementioned risk factors. The disease outcome depends primarily on the latter two phases of progression. Haematoma expansion, occurring hours after initial symptom onset, involves an increase in intracranial pressure (ICP) that disrupts the integrity of the local tissue and the blood brain barrier. Additionally , obstructed venous outflow induces the release of tissue thromboplastin , resulting in local coagulopathy [2].In over a third of patients , haematoma expansion is associated with hyperglycemia hypertension and anticoagulation .The initial size of the haemorrhage and the rate of haematoma expansion are important prognostic variables in predicting neurologic detoriation . Hematoma size >30 ml is associated with greatly associated mortality .Following the expansion, cerebral edema forms around the blood brain barrier. This peri-hematoma edema is the primary etiology for neurological detoriation and develops over days following the initial insult. In up to 40% of ICH cases, the hemorrhage extends into the cerebral ventricles causing intraventricular hemorrhage (IVH).This is associated with acute obstructive hydrocephalus and substantially worsened prognosis .[7].ICH and accompanying edema may also disrupt or compress adjacent brain tissue, leading to neurological dysfunction. Substantia displacement of brain parenchyma may cause elevation of intracranial pressure with the potential outcome of fatal hemitation syndrome[8].

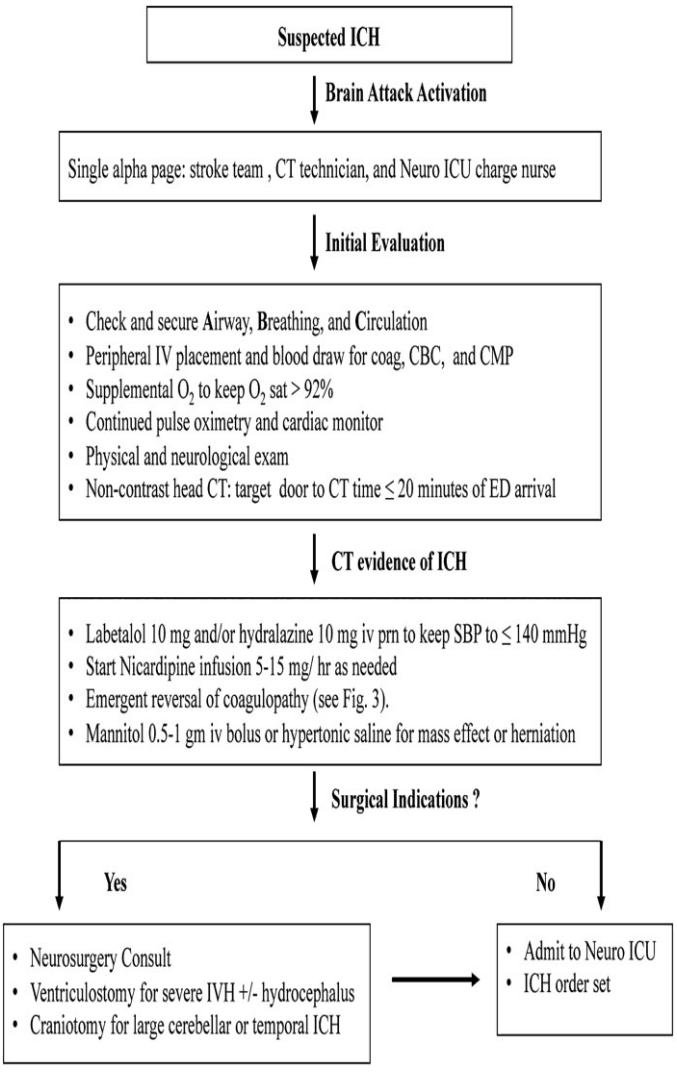


The pathogenesis of SICH involves interaction between an underlying bleeding-prone small vessel disease (example: cerebral amyloid angiopathy) and the use of oral anticoagulation treatments. This dynamic interplay is modified at various levels by genetic and ethnic factors and cardiovascular risk factors. Acute trigger factors for example, sudden increases in blood pressure or minor trauma may cause the rupture of these abnormally weak vessels. Anticoagulation may promote ICH by allowing an otherwise innocuous minor and self-limiting vessel leak to expand into a life- threatening hematoma.

DIAGNOSIS

CT scanning is the 1st line diagnostic approach; MRI with gradient echo can detect hyper acute intracerebral haemorrhage with equal sensitivity and overall accuracy and is more accurate to detect the microhaemorrhages. Perihematomal extravasion of intravenous contrast on CT-scan can detect ongoing bleeding. Cerebral angiography is needed to diagnose secondary causes of ICH such as aneurysm, arterio venous malformations, Dural venous thrombosis, and vasculitis[9,1]. MRI and magnetic resonance angiography can also identify secondary causes of ICH such cavemous malformations, although their sensitivity is not clear. A newer technique for hematoma expansion, the "leakage sign", has higher sensitivity and specificity for hematoma expansion than the spot sign and showed a significant association with poor outcomes.

Figure 2: The emergency department (ED) algorithm for early diagnosis and emergent intervention was shown[10].



CLINICAL FEATURES AND OUTCOMES

The classical presentation of SICH is sudden onset of focal neurological deficit progressing over hours with decreased consciousness and signs of brain stem dysfunction are related to the size and location of hematoma [1], neurological deficit accompanying headache, nausea, vomiting, altered consciousness and elevated blood pressure, supratentorial haemorrhage is commonly accompanied by vomiting and altered consciousness but is rarely seen in ischemic stroke.

OUTCOMES

The 3-month mortality rate was 34% in a review of 586 patients with ICH from 30 centers,in other studies it was 31% at 7 days , 59% at 1 year, 82% at 10 years, subsequent risk of other cardiovascular events was 4% for ischemic stroke per patient per year ,effects of recurrent bleeding can be changed by antihypertensive treatment weather progressive functional impairments are equally treatable is unknown. The risk of poor outcome was predicted by GCS score, volume of hematoma, age, amount of alcohol consumed within 1 week before haemorrhage[12].

MANAGEMENT

There are several issues are made regarding medical and surgical management of ICH remain unanswered. Recent clinical trials examining hemostatic therapy, blood pressure control, and hematoma evacuation have advanced our understanding ICH management.

INITIAL EVALUATION AND CLINICAL STABILIZATION

According to the AHA/ASA guidelines and the emergency neurological life support protocols, spontaneous intracranial hemorrhage is a medical emergency and should be managed accordingly .The initial management should focus on the following principles:

1. ABC'S initial assessment and stabilization of airway patency, breathing, and circulation
2. Neuroimaging .Once clinical stability is achieved; an urgent imaging study for rapid and accurate diagnosis should be performed.
3. Standardized neurologic assessment to determine baseline severity.The National institutes of health strokes scales (NIHSS) [13],if the patient is awake or drowsy, or the Glasgow coma scale (GCS), if the patient is obtunded or comatose, should be performed and clearly documented.
4. Blood pressure management, reversal of coagulopathy, and evaluation of the need for early surgical intervention.

Frequent neurological examinations, at least every hour. , to detect early clinical deterioration and signs of increased intracranial pressure (ICP)should be part of the routine initial management algorithm[14].

AIR WAY

Patients with ICH are often unable to protect airway. Endotracheal intubation may be necessary but this should be balanced against the risk of losing the neurologic examination. Rapid sequence intubation is typically the preferred approach in the acute setting. Pretreatment with lidocaine may be considered as it may blunt a rise in intracranial pressure(ICP) associated with intubation. Paralytic agents include succinylcholine, rocuronium or Vecuronium , and for post intubation sedation, propofol is a reasonable choice given its short half-life[15].

BLOOD PRESSURE MANAGEMENT

Elevated blood pressure (BP) is common in the acute setting after an ICJH, and higher BP levels are seen with hematoma expansion and poor prognosis. However, it is not clear that reducing blood pressure improves outcomes·while lowering BP may reduce the risk of expansion; it may theoretically also reduce cerebral perfusion. One randomized clinical trial found that lowering SBP to 140mmHg compared to 180mmHg reduced the risk of hematoma expansion but had no effect on outcomes. A second trail found that rapid BP lowering using Nicardipine appears safe but again showed no difference in outcomes. Multiple clinical trials are currently ongoing to address the issues[16].Until these trails clarify the role of BP management on hematoma expansion, expert guidelines from the American Heart Association/American Stroke Association (AHA/AHS) recommended BP treatment as is The European Stroke Initiative (EUSI) guidelines are similar[17].

HEMOSTATIC THERAPY

It is tempting to consider that in a patient with ICH, acute hemostatic therapy will provide benfit. One phase III randomized trial in patients with no underlying coagulopathy found no clinical benefit from approach[18]. As a result, current approaches to hemostasis are focused on correcting the underlying coagulopathies.

ORAL ANTICOAGULATION

The most common class of agent used for oral anticoagulation is warfarin. Many authors believed that action to rapidly correct the coagulopathy may prevent continued bleeding[19]. A number of therapeutic options are available for warfarin reversal.As warfarin inhibits the vitamin k- dependent carboxylation of factors II, VII, IX, and X, vitamin k is a first line agent to restore these factors. Vitamin K given intravenously lowers the INR as early as 4 hours, but requires over 24 hours for full effect when used as monotherapy. Vitamin K infusion at a dose of 5-10 mg should be started promptly and given slowly over 30 minutes. Limitations include adverse events such as allergic reactions, potential transmission of infectious agents and transfusion-related acute lung injury (TRAIL)· There is also significant time needed for its administration in actual practice, including time spent ordering, matching, thawing, and delivering to the ED. The dose of FFP ranges from 10-20ml/kg of body weight. On average, the volume need to correct the INR varies from 800-3500 ml, which may impose a significant volume load. Early administration of coagulation factors maximizes the opportunity for early INR correction[20].

Prothrombin complex concentrates (PCCs) provide an alternative source of coagulation factors. The products regarding PCCs available in all countries except USA including, octaplex (octapharma) and beriplex (CSL Behring), which include clinically relevant amounts of all 4 vitamin K dependent factors, sometimes termed 4-factor PCCs to differentiate them from the other 3 factor PCCs[21]. PCC offers several advantages over FPP, including smaller infusion volume, faster time to INR correction, lack of need for blood type matching. Thromboembolic events are potential complications of the use of PCC, although it is not clear that this risk (approximately 1.9%) is any different with FPP.

HEPARINOIDS

Heparin- related ICH is relatively rare, and data is sparse regarding appropriate treatment. One reasonable approach would be to reverse heparin with IV protamine sulfate at a dose of 1 to 1.5 mg per 100 units of heparin with a maximum dose of 50mg[22].

PLATELET FUNCTION

The two major causes of platelet dysfunction are antiepileptic therapy and thrombocytopenia.Antiplatelet agents use prior to an ICH is associated with a small increase in mortality, suggesting an opportunity for intervention. The utility and safety of platelet transfusion is such patients are unknown, although some laboratory data suggest that such transfusions may improve platelet activity. Platelet transfusion is therefore considered investigational by the AHA and is not recommended

by EUSI. Additionally, it is not clear whether low platelets contribute to ongoing bleeding or worse outcome. Pending further data, current AHA recommendations are that patients with a severe thrombocytopenia should receive platelet transfusion[24]. A specific cutoff is not clarified; different groups use thresholds between 10,000 and 50,000 per microliter.

NOVEL ANTITHROMBOTICS

Recently, a number of new agents, such as factor Xa inhibitors Apixaban and Rivaroxaban and the direct thrombin inhibitor Dabigatran, have become available for stroke prevention[25]. There is no currently known antidote for reversal of these agents. Specific hemostatic agents such as rFVIIa and PCCs may be considered, though there is limited data on their use. For those cases related to Dabigatranuse, supportive and symptomatic treatment should be initiated and, due to its renal excretion, aggressive diuresis and potential dialysis could be considered.

INTRACRANIAL PRESSURE MANAGEMENT

An increase in the intracranial pressure (ICP) may araise from the presence of intraventricular haemorrhage (IVH) and subsequent hydrocephalus, or from mass effect of a large hematoma or perihematomal edema, currently, there are limited data regarding indications for ICP monitoring, current guidelines from the AHA/ASA suggest that patients with a GCS score of ≤8, those with clinical evidence of transtentorial herniation, or those with significant IVH or hydrocephalus should be considered for ICP monitoring and treatment. Cerebral perfusion pressure (CPP) can then monitored, and recommendations should maintain in between 50 to 70mHg[26]. The initial management of elevated ICP should comprise simple measures such as elevation of the head of the bed, analgesia, and sedation. Medical options for ICP treatment include Mannitol, hypertonic saline (3% -23.4%), and neuromuscular paralysis[12]. Barbituates can be considered in refractory intracranial hypertension. Although hyperventilation can produce a rapid decrease in the ICP, its effect is temporary, and its use has to be reversed for impending herniation while awaiting surgical decompression.

HYPERGLYCEMIA MANAGEMENT

Hyperglycemia measured at initial in the ED is associated with worse outcomes in the both non-diabetic and diabetic patients. Declining glucose values after ICH are associated with a decreased riskof hematoma expansion and poor outcome, suggesting that early glucose control may improve outcomes. Early evidence for this intervention comes from the QASC trail, in which patients with ICH and ischemic stroke was randomized to receive fever, hyperglycemia, and swallow screening, or not. The intervention (including glucose management) lowered mortality and improved outcome. This highlights the need for careful glycemic control in the early phase[27].

TEMPERATURE

The presence of fever is a common finding in patients with ICH, especially in those with IVH. Again, data from the QASC trail suggests lower mortality and improved outcome in those patients receiving fever control as part of a multidisciplinary approach. Those with fever should undergo a thorough investigation to find any source is possible[28].

ANEMIA

The presence of anemia is common in patients with ICH. It is present up to 25% of cases at admission and is associated with larger hematoma volumes. It is also frequently develops during hospital stay Although current guidelines do not address this issues, a recent study found that packed red blood cell (PRBC) transfusion in these patients was associated with improved survival at 30 days[29]. Therefore, transfusion can be considered in such patients, although the ideal target hemoglobin level has not been determined.

ANTI-EPILEPTICS

Patients with ICH are at an increased risk of developing seizures; however, most of these events are subclinical electroencephalographic findings. Seizures are more common in lobar ICH and during the first 72 hoursafter admission. The majority of patients develop a single episode of seizure during hospitalization, suggesting that those episodes are related to the pathophysiological processes that occur early after an ICH. The use of prophylactic antiepileptic drugs (AEDs) in patient with ICH is a common practice, although it is not clear that the presence of seizures and/or the use of prophylactic AEDs affect short or long-term outcome[30]. The continuous electroencephalography (EEG) monitoring should be considered in those patients with depressed mental status out of proportion to the degree of brain injury.

SURGICAL INTERVENTIONS

EXTERNAL VENTRICULAR DRAIN PLACEMENT

As described previously, some patients may benefit from ICP monitoring. External ventricular drain (EVD) placement not only provides the ability to monitor ICP but has the advantage of allowing therapeutic drainage of the CSF, which is valuable in patients with hydrocephalus. The AHA recommends that ICP was monitoring and treatment be considered in patients with a GCS score ≤8, those with clinical evidence of transtentornial herniation, or those with significant IVH or hydrocephalus.

INTRAVENTRICULAR THROMBOLYSIS

IVH occurs when ICH extends into the ventricles. It occurs in approximately 45% of ICH, more frequently in relatively large and deeply located haemorrhages. The presence and the volume of IVH are correlated with poor prognosis in patients with ICH. Although evacuation of an intraventricular clot is currently not routinely recommended, a recent study comparing the use of intraventricularrtPA to placebo showed that the use of rtPA was notonly feasible and safe, but also showed a significantly greater rate of blood clot resolution[31]. In addition, a recent meta-analysis found that adding intraventricular fibrinolysis to EVD placement is associated with better functional outcome. Although no prospective randomized trial has evaluated this.

HEMATOMA EVACUVATION

The role of surgical evacuation is to detect and decrease mass effect related to the presence of blood, as well as to minimize secondary injury. The only clear recommendation for immediate surgical intervention is in patients with cerebellar hemorrhages with neurological deterioration, brainstem compression, and hydrocephalus from ventricular obstruction. For these patients, emergency neurosurgical consultation should be obtained[32]. However, it is less clear whether patients with supratentorial ICH will benefit. One large phase III clinical trial, the STICH trial, compared early hematoma evacuation with initial conservative treatment for patients with

spontaneous supratentorial ICH this study showed no difference in outcome, suggesting that surgical evacuation provided no benefit. This possibility is being evaluated in the ongoing STICH II trial[33].

MINIMALLY INVASIVE SURGERY

The development of less invasive surgical techniques may decrease the risk of surgical complications. These techniques are showing promising results, particularly in deep hemorrhages where conventional surgery showed no benefit in the past. Minimally invasive stereotactic puncture is reported to be safe and feasible and may lead to better long-term outcome and fewer complications when compared with conventional craniotomy and conventional medical treatment [34].

CONCLUSION

Spontaneous ICH is a neurological emergency associated with high mortality and morbidity, key management issues include prompt etiological diagnosis, reversal of anti-coagulation, consideration of surgical management, and control of blood pressure. Recent advances in early diagnosis and neurocritical care have contributed to improved survival. Continued research into prevention and effective therapy is pivotal in reducing disease burden and improve functional recovery.

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