Intracerebral Hemorrhage (ICH) Therapy: Current Status and Future directions

INTRODUCTION

Intracerebral hemorrhage (ICH) can be defined as acute spontaneous extravasation of blood into the brain parenchyma that can extend into ventricles or subarachnoid space. Intracerebral hemorrhage accounts for approximately 10% of all cases of strokes, and one of the leading cause of morbidity and mortality throughout the world. Worldwide incidence of intracerebral hemorrhage is 12 to 15 cases per 100,000 per year. Mortality in hemorrhagic stroke is higher than ischemic stroke. Mortality rate in ICH at one month is 30-40% and at one year, it is approximately 50%. Recent population based studies suggest that most patients present with small ICH are readily survivable with good medical care, so excellent and aggressive medical care has direct impact on ICH related morbidity and mortality.

As early deterioration is common in initial hours after ICH, rapid diagnosis and management of patients with ICH is crucial. More than 20% of patient will experience a decrease in the Glasgow coma scale score of >2 points between the prehospital emergency medical service assessment and the initial evaluation in the emergency department. As early deterioration is common in initial hours after ICH, rapid diagnosis and management of patients with ICH is crucial. More than 20% will experience a decrease in the Glasgow coma scale score of >2 points between the prehospital emergency medical service assessment and the initial evaluation in the emergency department.

CAUSES

Hypertension: is the most common cause of intracerebral haemorrhage and hypertension related ICH is also called primary ICH. In African Americans and Hispanics the incidence of stroke is directly proportional to high prevalence of hypertension. Uncontrolled hypertension leads to small vessel vasculopathy characterised by fragmentation, and degeneration of vessel wall, known as lipohyalinosis and false micro aneurysm formation (aneurysm of Charcot-Bouchard). Rupture of these micro aneurysm is proposed to be responsible for hypertensive intracerebral haemorrhage. Common sites of hypertensive cerebral haemorrhage in decreasing order are putamen (35%), lobar (25%), thalamus (10-15%), cerebellum (5-10%), pontine (5%), and caudate nucleus (5%).

Table I shows non-hypertensive causes of ICH: Intracranial aneurysm and arteriovenous malformation: Site of bleeding in intracranial aneurysm is usually subarachnoid space, intraparenchymal or rarely subdural space, whereas in arteriovenous malformation the site of bleeding is lobar, intraventricular or subarachnoid space. Annual risk of rupture for aneurysm less than 10 mm is 0.1% and for those larger than 10 mm risk of rupture is 0.5-1%. Rate of rupture in AV malformation is 2-4% per year.

Trauma: Primary sites for traumatic intracerebral haemorrhage are anterior temporal, basal frontal lobe, subarachnoid, subdural and epidural space. Acceleration-deceleration type of injury by a coup and contrecoup mechanism leads to multiple superficial brain Intracranial haemorrhages.

Tumours: Intracranial tumour bleed is an uncommon cause of ICH, but carries a very poor prognosis with a 30 day mortality of more than 90%. Common intracranial tumours that develop ICH are glioblastoma multiforme, and metastatic brain tumours with primary from lung carcinoma, renal cell carcinoma, malignant melanoma,
Choreocarcinoma, thyroid carcinoma and atrial myxoma. There are certain characteristic neuroimaging features that give suspicion of tumour related ICH and these are multiple sites ICH simultaneously, ICH in a site that is spared in primary ICH like corpus callosal bleed, papilledema on fundus examination, high density ring surrounding a low density centre on non contrast neuroimaging, and enhancing nodular lesion adjacent to haemorrhage in contrast CT scan or MRI.

**Coagulopathy, anticoagulants and fibrinolytic therapy:** Common haematological disorders causing ICH are congenital or acquired coagulation factor deficiency, quantitative or qualitative platelet dysfunction, aplastic anaemia, acute lymphocytic leukemia, and promyelocytic variety of acute myeloid leukemia. Coagulopathy related ICH can occur at any site in the brain, with a propensity for lobar and subdural region. In contrast to hypertensive ICH, coagulopathy related haemorrhage has slow progression over 24-48 hours.

Oral anticoagulants are responsible for 12-14% of ICH. Advanced age, high prothrombin time, hypertension, previous ischemic stroke are the risk factors responsible for anticoagulant related ICH. **Hemorrhagic infarct:** Hemorrhagic infarction occurs commonly in embolic or venous occlusion, multiple petechial haemorrhages in the area of infarction are the hallmark feature.

**CNS vasculitis:** Primary (Granulomatous angiitis of CNS) and secondary CNS vasculitis especially PAN can lead to ischemic as well as hemorrhagic stroke.

**Cerebral amyloid angiopathy:** This is an important cause ICH in elderly. Histo-pathologically there is beta amyloid deposition occurs in media and adventitia of cerebral small and medium sized vessels as well as in the leptomeninges. Due to the superficial location of involved vessels in the cerebral cortex the amyloid angiopathy ICH is lobar in location. Hemorrhage in cerebral amyloid angiopathy occurs in succession and usually are multiple.

**Sympathomimetic drugs:** Sympathomimetic drugs like cocaine, amphetamime, and decongestants like phenylpropanolamine are associated with ICH. The common

<table>
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<tr>
<th>Table 1. Causes of Intracranial Haemorrhage</th>
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<tr>
<td><strong>Traumatic (Secondary to Head Injury)</strong></td>
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<tr>
<td>- Acute and Chronic Subdural Haematomas</td>
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<tr>
<td>- Acute Epidural Haemorrhage</td>
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<td>- Intracerebral Haemorrhage</td>
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<td>- Post Traumatic Delayed Apoplexy</td>
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<td><strong>Vascular (Diseases of cranial blood vessels)</strong></td>
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<tr>
<td>1. Primary i) Hypertensive Intracerebral Haemorrhage</td>
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<td>ii) Cerebral Amyloid Angiopathy</td>
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<tr>
<td>2. Secondary</td>
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<tr>
<td>- Ruptured Saccular Aneurysm</td>
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<td>- Ruptured AV Malformations</td>
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<tr>
<td>- Haemorrhagic Infarctions (Haemorrhagic Conversions, Venous and Cortical Venous Sinus Thrombosis)</td>
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<td>- Arterial Dissections (Vertebral or Carotid)</td>
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<td>- Cavernous Angiomas</td>
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<td>- Infectious Vasculitis (Mycotic Aneurysm, TB Meningitis, Herpes Simplex Encephalitis)</td>
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<tr>
<td>- Non-infectious Vasculitis (Acute Necrotizing Haemorrhagic Encephalitis, Cocaine)</td>
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<td>- Intracranial Tumours (Primary And Secondary) with Bleed</td>
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<td>- Moyan Moyan disease (in adults)</td>
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<td>- Pregnancy (Eclampsia and Cortical Venous Sinus Thrombosis)</td>
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<td><strong>Coagulopathies (Disorders of Blood haemostasis) (Also considered as Secondary ICH)</strong></td>
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<td>- Thrombocytopenia (leukemia, Aplastic Anaemia, Drug induced Pancytopenia or Thrombocytopenia, Idiopathic Thrombocytopenic Purpura, Arboviral diseases like Dengue Haemorrhagic Fever)</td>
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<tr>
<td>- Primary Coagulopathies (Haemophilia, Hypofibrinogenemia, Christmas Disease)</td>
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<tr>
<td>- Secondary Coagulopathies (Thrombolysis Induced ICH, Anticoagulant induced ICH, Liver disease)</td>
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locations for haemorrhage are lobar, subcortical white matter or subarachnoid space. Patients are usually young and non-hypertensive although transient blood pressure rise has been seen. Cocaine is responsible for parenchymal and subarachnoid bleed. ICH primarily involves subcortical white matter but deep hemispheric bleed can also occur.

**Cavernous angioma:** These vascular malformation usually occurs supratentorially and less commonly in infratentorial space where it predominates in pons. Most are solitary, but multiple lesions are seen in familial form. Cavernous angiomas are common in young female and manifest with ICH in 10-30% of cases. Site of bleed is usually lobar and subarachnoid space.

**DIAGNOSIS**

Progression over minutes or hours, severe headache, vomiting, systolic blood pressure more than 220 mmHg, decreased level of consciousness or deep coma favours ICH although, no clinical characteristic can specifically differentiate ischemic versus hemorrhagic stroke. So neuroimaging is mandatory to differentiate ischemic from hemorrhagic stroke.

Non contrast CT scan is very sensitive to detect acute ICH and is considered gold standard. CT scan shows size and site of haemorrhage, ventricular extension, peri lesional edema, and tissue displacement due to mass effect. Gradient echo (GRE) and T2 susceptibility weighted MRI are also sensitive to identify acute and chronic ICH but time, cost, easy availability and patient convenience all favour CT scan as investigation of choice in acute ICH. Findings on CT scan or MRI that require angiographic studies are presence of subarachnoid haemorrhage, primary intraventricular haemorrhage, underlying calcification, or lobar haemorrhage in younger non-hypertensive patients. According to American Heart Association/American Stroke Association 2010 guidelines CT angiography and contrast enhanced CT may be considered to help identify patients at risk for hematoma expansion (class llb; level of evidence:B) and CT angiogram, CT venogram, contrast enhanced CT, contrast enhanced MRI, MR angiogram and MR venogram can be useful to evaluate for underlying structural lesions, including vascular malformation and tumours when there is clinical or radiological suspicion (class llb ;Level of evidence :B)(New recommendation). INTERACT (INTensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial) an open label, randomised controlled trial emphasised on intensive blood pressure control in ICH. It was a pilot study published in 2008 on 404 patients of ICH, out of which 203 were randomized to achieve a systolic blood pressure less than 140 mm Hg within 1 hour and maintained for at least the next 24 hours, Remaining 201 were randomized to a blood pressure target of 180 mm Hg as per previous AHA guideline. Lower absolute and relative hematoma volume from base line to 24 hours was shown in intensive blood pressure treatment group compared with control group. There were no difference of neurological deterioration, other adverse events, and clinical outcome including disability and quality of life between two groups.

Another study in support of INTERACT study is ATACH (Antihypertensive Treatment in Acute Cerebral Haemorrhage), which favours safety and feasibility of early intensive Blood pressure lowering in ICH, thus INTERACT and ATACH studies are best evidence regarding BP management in ICH.

American heart association (AHA) 2010 recommended the following guidelines about BP management in ICH.

1. (a) If SBP is >200 mm Hg or MAP is >150 mm Hg, then consider aggressive reduction of BP with continuous
2. Patients with ICH whose INR is elevated due to OACs
1. Patients with a severe coagulation factor deficiency or
given within 4 hours after ICH onset. AHA/ASA 2010
progression and better clinical outcomes when rFVIIa was
One phase 2 randomized trial showed decreased hematoma
not replenishes other Vitamin K dependent factors. Role
VIIa is another option in OACs related ICH, although it does
avoid volume overload. PCCs are being recommended as
rapidly correct INR, less allergic or infectious reactions and
complex concentrates contain factor II, IX, X, VII and it
correction are common drawbacks of FFP. Prothrombin
examine the patient every 15 minutes (class llb; level
Management of Coagulopathies and oral anticoagulants
(OACs) related ICH: As mentioned previously coagulopathies
and OACs are responsible for significant percentage of
total ICH. Patients with coagulation factor deficiency or
thrombocytopenia should be treated with coagulation factor
and platelets respectively. In OACs induced intracerebral
haemorrhage, INR should be rapidly corrected. Prothrombin
complex concentrates (PCCs) and recombinant factor VIIa
are newly emerged therapies beyond previously used vitamin
K and FFP in OACs related ICH. Therapeutic effect of Vitamin
K comes after hours, and allergic and infectious transfusion
reactions, processing time, and large volume required for
correction are common drawbacks of FFP. Prothrombin
complex concentrates contain factor II, IX, X, VII and it
rapidly correct INR, less allergic or infectious reactions and
avoid volume overload. PCCs are being recommended as
preferred therapy in OACs induced ICH. Recombinant factor
VIIa is another option in OACs related ICH, although it does
not replenishes other Vitamin K dependent factors. Role
of rFVIIa has also been tried in spontaneous non OACs ICH.
One phase 2 randomized trial showed decreased hematoma
progression and better clinical outcomes when rFVIIa was
given within 4 hours after ICH onset. AHA/ASA 2010
recommended following guidelines related to coagulopathies
and OACs related ICH.
1. Patients with a severe coagulation factor deficiency or
severe thrombocytopenia should receive appropriate
factor replacement therapy or platelets, respectively
(Class I; Level of Evidence: C). (New recommendation)
2. Patients with ICH whose INR is elevated due to OACs
should stop warfarin, and receive therapy to replace
vitamin K (Class I; Level of Evidence: C). Although
PCCs have not shown improved outcome compared
with FFP but due to fewer complications are reasonable
alternative to FFP (Class IIa; Level of Evidence: B). rFVIIa
does not replace all clotting factors, and although the
INR may be lowered, clotting may not be restored in vivo; therefore, rFVIIa is not routinely recommended as
a sole agent for OAC reversal in ICH (Class III; Level of
Evidence: C). (Revised from the previous guideline).
3. Although rFVIIa can limit the extent of hematoma
expansion in noncoagulopathic ICH patients due to
thromboembolic risk with rFVIIa it is not recommended in
unselected patients. (Class III; Level of Evidence: A).
(New recommendation)
4. The usefulness of platelet transfusions in ICH patients
with a history of antiplatelet use is not clear and is
considered investigational (Class IIb; Level of Evidence:
B). (New recommendation)

Deep vein thrombosis prophylaxis: Patients with ICH
especially female are prone to develop DVT. Combination of
intermittent pneumatic compression with elastic stockings
has shown better results in DVT prophylaxis as compared to
elastic stockings alone. Graduated compression stockings
alone are not effective in preventing DVT. AHA/ASA 2010
recommended that
- Intermittent pneumatic compression for prevention of
venous thromboembolism in addition to elastic stockings
(Class I; Level of Evidence: B).
- After cessation of bleeding, low dose subcutaneous low-
molecular-weight heparin or unfractionated heparin may
be considered for prevention of venous thromboembolism
in patients with lack of mobility after 1 to 4 days of onset
(Class IIb; Level of Evidence: B).

Management of Glucose: High blood sugar is an independent
poor prognostic factor in ICH irrespective of presence or
absence of diabetes. A randomized trial showing improved
outcome with tight glucose control (range 80 to 110 mg/
dL) using insulin infusions has increased the use of this
therapy. However, more recent studies have shown increased
incidence of systemic and cerebral hypoglycemic events
and even increased risk of mortality in patients treated
with this regimen. At present the optimal management of
hyperglycemia in ICH and the target glucose remains to be
clarified. Hypoglycemia should be avoided.

Temperature Management: Patients of ICH who survive
after 72 hours of admission the duration of fever is an
independent prognostic factor\textsuperscript{15}. So normothermia should be maintained in all patients with ICH.

**Seizures and Antiepileptic drugs:** Routine prophylactic use of antiepileptic in patients with ICH is not justifiable as there is only negligible risk of epilepsy in patients who did not have early seizures. Majority of seizures in ICH occurs at onset; with the incidence of clinical seizures within the first 2 weeks varied from 2.7\% to 17\%\textsuperscript{16}. Continuous EEG records have reported seizures in 28\% to 31\% of patients despite prophylactic anticonvulsants. AHA/ASA 2010 recommended that

- Clinical seizures should be treated with antiepileptic drugs (Class I; Level of Evidence: A) and Continuous EEG monitoring is probably indicated in ICH patients with depressed mental status out of proportion to the degree of brain injury (Class IIa; Level of Evidence: B).
- Patients with a change in mental status who are found to have electrographic seizures on EEG should be treated with antiepileptic drugs (Class I; Level of Evidence: C). Prophylactic anticonvulsant medication should not be used (Class III; Level of Evidence: B).

**Intracranial pressure (ICP) Monitoring and treatment in ICH:** ICP monitoring should be considered in patients with GCS score of less than 8, those with evidence of transtentorial herniation, significant IVH, or hydrocephalus. Cerebral perfusion pressure to be maintained of 50 to 70 mm Hg. Patients with hydrocephalus with altered consciousness should be treated with ventricular drainage

**Intraventricular haemorrhage; Role of t-PA:*** Intraventricular haemorrhage can be primary or secondary. Secondary ICH usually complicates basal ganglia and thalamic bleed, and seen in 45\% of spontaneous ICH. Ventricular catheter insertion is an option for drainage of IVH, although maintaining catheter patency is a problem. Thrombolytic agents including t-PA has been tried in clot lysis. Although intraventricular administration of recombinant tissue-type plasminogen activator in IVH appears to have a fairly low complication rate, efficacy and safety of this treatment is uncertain and is considered investigational (Class IIb; Level of Evidence: B).

**Surgical Treatment of ICH:** AHA 2010 recommended following guidelines for this

1. Patients with cerebellar haemorrhage who are deteriorating neurologically or who have brainstem

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**Suspected case of stroke arrives in the emergency room**

1. Clinical examination and confirmation
2. **C.T.SCAN AT THE EARLIEST**
   - Intracerebral Hemorrhage
     - Large
       - **Conservative**
     - Small
       - **Conservative**
   - Small Infarct
   - Large Infarct
   - No Infarct
     - **t-PA**
   - Treat Risk factors
   - Decongest
   - **ICP**

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Fig. 1: A 80 year old Female with a large Basal Ganglia Bleed with Intraventricular Extension on axial section CT scan. This location of bleed is characteristic of Hypertensive haemorrhage, associated cerebral atrophy can also be noted.

Fig. 2: CT Scan Of A 50 Year Male Showing Right Thalamic Bleed with midline shift, another Common Site for Hypertensive ICH.

Fig. 3: CT Scan of a 35 year Female Showing Cavernous Angioma Bleed In Midbrain.

Fig. 4: Angiogram of the patient with bleed in the frontal region showing the AV malformation responsible for the bleeding.

Fig. 5: CT Scan of A 30 Year Male With Cardioembolic Stroke who Developed Oral Anticoagulant Related ICH, Infarct with hemorrhagic Tranformation can be Noted.

compression and/or hydrocephalus from ventricular obstruction should undergo surgical removal of the haemorrhage as soon as possible (Class I; Level of Evidence: B). (Class III; Level of Evidence: C).

2. For patients presenting with lobar clots >30 mL and within 1 cm of the surface, evacuation of supratentorial ICH by standard craniotomy might be considered (Class IIb; Level of Evidence: B).

3. The effectiveness of minimally invasive clot evacuation utilizing either stereotactic or endoscopic aspiration with or without thrombolytic usage is uncertain and is considered investigational (Class IIb; Level of Evidence: B).

4. No clear evidence at present indicates that ultra-early removal of supratentorial ICH improves functional
outcome or mortality rate. Very early craniotomy may be harmful due to increased risk of recurrent bleeding (Class III; Level of Evidence:B)

Prevention of Recurrent ICH:
1. After the acute ICH period, absent medical contraindications, BP should be well controlled, particularly for patients with ICH location typical of hypertensive vasculopathy (Class I; Level of Evidence: A).
2. After the acute ICH period, a goal target of a normal BP of <140/90 (<130/80 if diabetes or chronic kidney disease) is reasonable (Class IIa; Level of Evidence: B).
3. Avoidance of heavy alcohol use can be beneficial (Class IIa; Level of Evidence: B). There is insufficient data to recommend restrictions on use of statin agents or physical or sexual activity (Class IIb; Level of Evidence: C).
4. Avoidance of nonvalvular atrial fibrillation as treatment for nonlobar ICH is recommended after spontaneous lobar ICH (Class IIa; Level of Evidence: A). Anticoagulation after nonlobar ICH and antiplatelet therapy after all ICH might be considered, particularly when there are definite indications for these agents (Class IIb; Level of Evidence:B).

REFERENCES