Section A-Research paper

Brief Insight about Intracerebral hemorrhage

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Abstract

Background: the World Health Organization (WHO) defined stroke as "rapidly developing clinical signs of focal disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin". The pathology underlying strokes includes infarctions with its anatomical subdivisions [(Small vessel (lacunar) infarction, total or partial territorial infarction and border-zone infarction)], Intracerebral haemorrhage (ICH) with its anatomical subdivision (lobar, deep/basal ganglia and posterior fossa), Subarachnoid haemorrhage either aneurysmal or secondary to arteriovenous malformation (AVM) and Cerebral venous sinus thrombosis. The majority of strokes result from arterial pathology but a small proportion, less than 1%, results from cerebral venous thrombosis. Intracerebral hemorrhage (ICH) is the second most common type of stroke, after ischemic stroke with high morbidity and mortality. 30-day mortality for ICH is about 35–52 % with one-half of the deaths occuring during the acute phase, especially within the first 2 days. Intracerebral hemorrhage (ICH) is caused by bleeding, primarily into brain tissue parenchyma. Underlying pathologies are classified into arterial (small and large-vessel disease), venous disease, vascular malformation, hemostatic disorders and ICH due to other disorders.

Keywords: Intracerebral hemorrhage

Introduction

the World Health Organization (WHO) defined stroke as "rapidly developing clinical signs of focal disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin" **(Capildeo et al.,1978).**

Stroke affects approximately 16.9 million per year worldwide and is the second leading cause of death **(Feigin VL et al.,2014).**

The most important step in stroke classification is to differentiate ischemic versus hemorrhagic stroke. Ischemic stroke accounts for 80 % to 85 % of all strokes within the Western population. Although hemorrhagic stroke only account for 15 % to 20 % of all strokes, it has been associated with significantly higher morbidity and mortality rates compared to ischemic strokes **(Mehndiratta et al., 2015).**

The pathology underlying strokes includes infarctions with its anatomical subdivisions [(Small vessel (lacunar) infarction, total or partial territorial infarction and border-zone infarction)], Intracerebral haemorrhage (ICH) with its anatomical subdivision (lobar, deep/basal ganglia and posterior fossa), Subarachnoid haemorrhage either aneurysmal or secondary to arteriovenous malformation (AVM) and Cerebral venous sinus thrombosis. The majority of strokes result from arterial pathology but a small proportion, less than 1%, results from cerebral venous thrombosis **(Li et al., 2013).**

Intracerebral hemorrhage

Intracerebral hemorrhage (ICH) is the second most common type of stroke, after ischemic stroke with high morbidity and mortality. 30-day mortality for ICH is about 35–52 % with one-half of the deaths occuring during the acute phase, especially within the first 2 days **(Magistris et al., 2013)**.

Intracerebral hemorrhage (ICH) is caused by bleeding, primarily into brain tissue parenchyma. Underlying pathologies are classified into arterial (small and large-vessel disease), venous disease, vascular malformation, hemostatic disorders and ICH due to other disorders. **(Steiner et al, 2014)**

Table (1). Absolute Number of Women and Men with Stroke (in Millions) in the World by Stroke Type in 1990 and 2013 **(Feigin etal,2016).**

		Women		Men	
		1990	**2013**	**1990**	**2013**
Ischemic stroke	**Incident**	2.14	3.28	2.17	3.62
	Prevalent	4.86	8.66	5.18	9.65
Hemorrhagic stroke	**Incident**	0.86	1.53	1.03	1.84
	Prevalent	1.78	3.36	2.11	4.00

Intracerebral hemorrhage(ICH) results from two main sporadic cerebral small vessel diseases: hypertensive arteriopathy, which causes ICH in the territory of small perforating arteries of the deep grey nuclei, brainstem and white matter, including lobar areas; and cerebral amyloid angiopathy (CAA), which causes lobar ICH due to the superficial cortical and leptomeningeal small arteries rupture. It can also affect deep nuclei but extremely rare. Based on the presumed predominant underlying causal small vessel disease, Research categorises ICH into either "non-lobar (deep and infra-tentorial)" or "lobar", however this is an oversimplification, because hypertensive arteriopathy can cause both deep and lobar ICH. **(Charidimou et al, 2017)**

A. Epidemiology:

Globally, between 1990 and 2013, there were significant in-creases in prevalent cases, total deaths, and DALYs because of HS and IS in younger adults aged 20 to 64 years.

In 2013, in younger adults aged 20 to 64 years, the global prevalence of HS was 3.7 million cases [95% UI, 3.5–3.9] and IS was 7.3 million cases [95% UI, 7.0–7.6].

There were 1.5 million [95% UI, 1.3–1.7] stroke deaths globally among younger adults, but the number of deaths from HS (1.0 [95% UI, 0.9–1.2]) was significantly higher than the number of deaths from IS (0.4 million [0.4–0.5]).

The total DALYs from all strokes in 20 to 64 years old were 51.0 million. Globally, there was a 24.4% increase in total DALYs for this age group, with a 20% and 37.3% increase in HS and IS numbers.

There is also a difference in the incidence of both types of stroke between men and women with men having larger percent of ischemic stroke and although there has been a significant decline in the total burden of both types of stroke between 1990 and 2013 the relationship between sex and incidence has been preserved **(Feigin et al,2016).**

Recently, according to the global burden of disease study in 2010, the incidence of ICH in Egypt was estimated to be 49.9-61.2 patients per 100000 persons, at the year 2010. So, the incidence increased in comparison to what was estimated at 1990 (40.8-47.4 per 100000) **(Feigin et al, 2014).**

Etiology

Non-traumatic Intracerebral hemorrhage can be categorized into primary and secondary hemorrhage. Primary type accounts for 85% of all ICH and is related to chronic hypertension or amyloid angiopathy while secondary hemorrhage is considered to be related to bleeding diathesis (iatrogenic, congenital, acquired), vascular malformations, neoplasms, hemorrhagic conversion of an ischemic stroke, and drug abuse **(Flower and Smith, 2011).**

Primary intracerebral hemorrhage

Hypertensive vascular damage:

The diagnosis of a primary ICH is supported by a history of chronic hypertension, increased age, and location of the clot with exclusion of any other pathological or structural cause. In patients with chronic arterial hypertension, degenerative changes and lipo-hyalinosis of penetrating arterioles ocurr resulting in formation of Charcot-Bouchard aneurysms in the small arterial vessels supplying deep cerebral structures. More than 60% of primary ICH are related to hypertension, and these hematomas are mostly present in the basal ganglia, thalamus, posterior fossa and pons. **(Ziai and Carhuapoma, 2018).**

Cerebral amyloid angiopathy (CAA):

Lobar hemorrhages in elderly patients are characteristic feature of amyloid angiopathy which is a degenerative disease thought to be related to alleles of apolipoprotein E gene, causing increased deposition of amyloid within vessel walls. **(Aiyagari et al 2015)**

Secondary intracerebral hemorrhage:

Secondary ICH may be due to an underlying structural pathology, such as vascular anomalies including arteriovenous malformations, cavernous angiomas, cerebral aneurysms, and aorto-venous fistulae. Cerebral hematomas may also be due to a primary or metastatic lesion or caused by hemorrhagic conversion of a recent ischemic infarct **(Aiyagari et al 2015).**

Further, congenial and acquired bleeding diathesis is a common cause in ICH's, becoming more frequent with the increase in anticoagulant (i.e., warfarin) and antiplatelet (aspirin) therapy usage. **(Kawano-Castillo et al.,2014).**

C. Pathophysiology

Primary Injury:

The first pathological damage of ICH is the mechanical compression caused by hematoma resulting in elevation of intracranial pressure that subsequently increase the risk of brain herniatin **(Xi and Keep, 2012)**. Subsequently, brain edema and brain hernia cause secondary injury, which is associated with poor outcome and high mortality rates in ICH patients **(Yang et al, 2016)**.

Unfortunately, the available brain edema treatment such as steroids, mannitol, glycerol, and hyperventilation cannot decline intracranial pressure effectively or prevent secondary brain injury **(Bejot et al, 2018).**

Secondary Brain Injury

Inflammation

increasing evidences indicate that inflammatory mechanisms are associated with ICH-induced brain injury. Also microglia/macrophages activation, and polarization are thought to have vital pathophysiological roles **(Koh et al, 2018)**.

Under normal conditions, microglia/macrophages monitor the surrounding microenvironment and make sure that the stability of neurons ,matrix and blood–brain barrier (BBB) is maintained . When cerebral hemorrhage occurs, Excessive microglia/macrophages release a large number of inflammatory factors and induce inflammatory waterfall reaction resulting in pathological changes such as BBB injury, edema, cell death, and so on **(Bhatia et al, 2016)**.

After activation of microglia/macrophages, there are two types of cells, including classically activated microglia/macrophages (M1 phenotype) and alternative activated microglia/macrophages (M2 phenotype) **(Xiong et al, 2016)**.

To clear the hematoma,M1 express a large number of toll like receptor 4 (TLR4) and heme oxygenase 1 (HO-1), but they also produce pro-inflammatory mediators [interleukin (IL)-1β, IL-6, IL-12, IL-23, and tumor necrosis factor alpha (TNF-α)], iron content, and oxidative metabolites, which aggravate brain injury **(Varnum and Ikezu, 2012, Ponomarev et al, 2013, Scott et al, 2018)**.

M2 secrete IL-10 and transforming growth factor-β (TGF-β) to reduce inflammation and clear cell debris and are associated with tissue remodeling leading to improvement of brain recovery **(Pan et al, 2015, , Zheng et al, 2016, Zhang et al, 2018)**. Therefore, it is considered that promoting M2 phenotype and inhibiting M1 phenotype are beneficial to brain recovery after ICH.

Research show that pinocembrin can decrease the number of M1-like microglia without affecting M2-like microglia in the surrounding area **(Lan et al, 2017)**.

In experimental ICH, TLR4 blockage reduce neuronal loss and edema formation and improve neurological function **(Lin et al, 2012)**.

TNF-α produced by microglia/macrophages plays a central role in neuronal damage after brain injury **(Lambertsen et al, 2005, Rodriguez-Yanez and Castillo, 2008)**.

Another study showed that inhibitors ofTNF-α can reduce the degree of brain edema, inflammation, and neurologic impairment, but they do not alter hematoma volume **(Lei et al, 2013)**.

IL-1β produced by microglia/macrophages also is thought to be a key mediator of neuronal injury; some studies show that neuroprotection is associated with downregulation of IL-1β **(Wu et al, 2010, Bimpis et al, 2015)**.

Previous study found that misoprostol, an EP2/EP4 receptor agonist, can protect the brain from ICH damage **(Wu et al, 2015)**. In addition, the synthesis of PGE2 is catalyzed by cyclooxygenase (COX) and PGE2 synthase. Celecoxib is a selective inhibitor of COX-2 that can reduce ICH-induced brain damage **(Shao et al, 2019)**.

Oxidative Stress:

Oxidative stress (OS) is a condition in which there is an overproduction of free radicals, mainly reactive oxygen species (ROS). It is considered to be a contributing factor in secondary brain injury (SBI) following ICH as being involved in different important stages of pathophysiological response during ICH **(Aronowski and Zhao, 2011)**.

However The central nervous system consumes more oxygen, its endogenous antioxidant defense capacity is lower than other organs, making it more susceptible to OS **(Liu et al, 2019)**.

As a scavenger for oxygen free radicals, edaravone can reduce oxidative damage of neurons and inhibit lipid peroxidation in mice **(Lu et al, 2012; Wu et al, 2014)**.

In a published clinical trial, edaravone produce significant improvement improved the national institute of heart and stroke scale (NIHSS) in ICH patients after removal of hematoma with minimally invasive surgery **(Zhao and Liu, 2014)**.

Recently nicotinamide mononucleotide treatment reported to reduce brain edema, brain cell death, OS, intercellular adhesion molecule-1 expression, microglia activation, and neutrophil infiltration in brain hemorrhagic area by promoting the signaling pathway activation and OS inhibiting **(Wei et al, 2017)**.

PPARγ agonists also is considered to be an anti-oxidant by activating the antagonist pathway and increasing catalase and SOD **(Zhao et al, 2015**)

Cytotoxicity of Erythrocyte Lysates

Recently it has been reported that hemoglobin and iron release from the hematoma is a contributing factor to brain injury induced by ICH **(Zhang et al, 2017)**.

The mechanism of brain injury produced by erythrocyte lysates is multifactorial , and researchers have found that there are four main aspects: edema inflammation, oxidation and nitric oxide scavenging. Firstly, over-accumulation of iron is harmful to the brain. Also heme oxidase (HO)-1 will be expressed increasingly after ICH, which can exacerbate brain injury by promoting microglial activation and iron deposition **(Lin et al, 2012; Zhang et al, 2017)**.

Secondly, It is suggested that divalent iron ions can react with lipid to produce ROS and lipid ROS, leading to neurological damage and oxidative brain injury **(Katsu et al, 2010; Li et al, 2017)**.

Therefore, the iron chelator deferoxamine mesylate (DFX) is a promising candidate for ICH patients via generating a stable complex with ferric iron resulting in it reduction of free radicals production **(Yeatts et al, 2013; Zeng et al, 2018)**.

Thirdly, nitric oxide is depleted by hemoglobin rapidly , resulting in production of micro-thrombosis in cerebral vessels in SAH with further brain damage **(Bulters et al, 2018)**. Nitric oxide donors are thought to be beneficial for ICH and SAH **(Oldfield et al, 2013)**.

Neurotoxicity of Thrombin

Thrombin is an important component in the clotting cascade, and it is produced in the brain after ICH induction immediately **(Zheng et al, 2016)**. However, thrombin effect after ICH depends on its concentration **(Zhu et al, 2019)**. At very low concentrations, It may provide neuroprotective effects against OS and ischemic injury while direct infusion into the brain of large doses of thrombin causes infiltration of inflammatory cells to the brain, proliferation of mesenchymal cells, formation of scar tissue and brain edema, and seizures **(Xi et al, 2003)**.

Also, thrombin-induced injury to the BBB after ICH can be blocked by acute administration of hirudin (a direct peptide mimetic thrombin inhibitor) **(Liu et al, 2010)**.

Now ,it is clear that the balance between the hemostatic and pro-hemorrhagic actions of thrombin is likely dependent on multiple factors such as site (intra- or extravascular) and mode of action (activation of which type of receptor) and so on **(Cheng et al, 2014)**. Therefore, it is critical to block the neurotoxic effects of thrombin without inhibiting its hemostasis effect.

Clinical presentations

The most common location of ICH is the putamen, and clinical presentations differ with the size and site of ICH **(Ito et al,2005)**.

Common ICH symptoms are headache, nausea, and vomiting. Headache is more common in patients with large sized hematomas due to traction on meningeal pain fibers, increased intracranial pressure, or blood in the cerebrospinal fluid,while Small, deep hematomas are rarely associated with headache.

Vomiting is present in about half of patients with hemispheric ICH, and more common in patients with cerebellar hemorrhages. It is attributed to increased intracranial pressure. Patients with large ICH often have a decreased level of consciousness occur with increased intracranial pressure and compression of the thalamus and brainstem. Stupor or coma indicates large ICHs that involve the brainstem reticular activating system **(Steiner et al,2006)**.

signs of Meningeal irritation, such as neck stiffness, Brudzinski sign or Kernig sign indicate the presence of blood in the subarachnoid space or irritating pain-sensitive leptomeninges. Patients with caudate, thalamic, or cerebellar hematoma have are more susceptible for having meningeal irritation signs as these hematomas often rupture into the ventricles due to their close proximity to the ventricle systems nearby **(Ko et al., 2012)**.

Seizures occur in about 10% of patients with ICH , its risk increased up to 50% of patients with lobar hematoma . Seizures classically occur at the onset of bleeding or within the first 24 hours **(Vespa et al,2003)**.

Neurological deterioration is common before and during hospital admission and usually indicate early hematoma expansion or worsening of edema **(Qureshi et al,2009).**

Patients with a supratentorial ICH involving the basal ganglia or thalamus have contralateral sensorimotor deficits, Lobar hematoma may present with symptoms of a higher cortical dysfunction such as aphasia, neglect, hemianopia and gaze deviation, while patients with an infratentorial ICH, signs of brainstem dysfunction occur such as ocular motor or other cranial nerve abnormalities, and contralateral motor deficits **(Qureshi et al,2001).**

Putaminal hemorrhage - Spread of hemorrhage into the putamen most commonly occurs along white matter fiber tracts, causing hemiplegia, hemisensory loss, homonymous hemianopsia, gaze palsy, stupor, and coma. Internal capsule hemorrhage - Small hemorrhages restricted to the internal capsule may cause mild dysarthria, contralateral hemiparesis and sensory deficit. **(Chung et al,2003).**

Thalamic hemorrhage - a thalamic hemorrhage may extend in a transverse direction to the posterior limb of the internal capsule, downward to put pressure on the tectum of the midbrain or may rupture into the third ventricle. Symptoms include hemisensory loss, hemiparesis and occasionally transient homonymous hemianopsia. There may also be an upgaze palsy with miotic pupils that are unreactive, peering at the tip of the nose, skewed, or “wrong way eyes” toward the weak side (in contrast to hemispheric cortical injury in which the eyes are deviated away from the hemiparesis). Aphasia may occur

if the bleed affects the dominant hemisphere, while neglect may develop if the bleed affects the nondominant hemisphere. **(Celikbilek et al,2013).**

Lobar hemorrhage - Lobar hemorrhages differ in their neurologic signs depending on location. They most often affect the parietal and occipital lobes. These bleeds are associated with a higher incidence of seizures. Occipital hemorrhages frequently present with a very dense contralateral homonymous hemianopsia. Hemorrhages in the frontal region will produce contralateral plague or paresis of the leg with relative sparing of the arm **(Hu et al,2013).**

Cerebellar hemorrhage - Cerebellar hemorrhage usually originates in the dentate nucleus, extends into the hemisphere and fourth ventricle, and possibly into the pontine tegmentum. These bleeds cause imbalance with an inability to walk , headache, vomiting, neck stiffness, gaze palsy, and facial weakness without hemiparesis **(Qureshi et al,2001)**.

Pontine hemorrhage - Pontine hemorrhage is characterized by a medial hemorrhage that extends into the base of the pons. These often lead to deep coma within the first few minutes following the hemorrhage, probably due to affection of the reticular activating system. The motor examination is characterized by total paralysis. The pupils are pinpoint and react to a strong light source. Horizontal eye movements are absent, and there may be ocular bobbing, facial palsy, deafness, and dysarthria when the patient is awake **(Almutawa et al,2012).**

D. Complications

Re-bleeding

According to studies, the survivor of 1.3- 7.4% and up to 18.8% of ICH patient experience recurrence within a years and five years respectly. In the other study primary ICH recurrence occurred in 9.8% of cases **(Poon et al,2014) (Schmidt et al,2016).**

Seizures

Seizures in the first days after ICH occur approximately 15 percent of patients; they are more common in lobar hemorrhages (affecting cortical tissue) than in deep or cerebellar ICH **(Kuramatsu et al,2015).**

Cardiac abnormalities

Cardiac abnormalities are frequently associated with spontaneous ICH. The most common associated electrocardiographic (ECG) changes are prolonged QT interval and ST-T wave changes. These changes may represent catecholamine induced cardiac ischemia, which is most likely due to a centrally mediated release of excessive catecholamines caused by elevated intracranial pressure or disturbance autonomic functions **(El-Menyar et al, 2017).**

E. Diagnosis

Evaluation and Diagnosis ICH is a medical and neurological emergency as it is associated with increased risk of ongoing bleeding, progressive clinical deterioration, permanent disability, and death.

ICH diagnosis require Neuroimaging with brain CT or MRI to confirm it and to exclude ischemic stroke and stroke mimics as possible causes . Once acute ICH is identified by imaging, the etiology must be determined based on clinical and imaging findings . The main considerations are patient age, associated risk factors (mainly hypertension), and hematoma location (lobar versus non lobar) **(Ahangar et al,2019)**.

Recommended laboratory tests for patients with ICH

1. Complete blood count, blood urea nitrogen, creatinine, and blood glucose level
2. Prothrombin time (with INR) and activated partial thromboplastin time for all patients; thrombin clotting time for patients taking direct oral anticoagulants
3. Cardiac-specific troponin
4. Toxicology screen to detect cocaine and other sympathomimetic drugs
5. Urinalysis and urine culture.
6. Pregnancy test in a woman of childbearing age **(Hemphill et al, 2015).**

Brain imaging

1.Non contrast head Computed tomography (NCCT)

CT is an easy method in acutely ill patients who may be neurologically or hemodynamically unstable, intubated or confused. It is available in most emergency rooms and hospitals around the clock and a head CT takes a short time. For these reasons, head CT is considered the modality of choice **(Morgenstern et al., 2010).**

Computed tomography (CT) can determine the size and site of the hemorrhage. It also provides information about the surrounding edema, midline shift and the presence of intravencular extension or not. Hyperacute blood will appear as hyperdense area except in patients with sever anemia in which it appears as isodense Over weeks, the blood will become isodense and Chronically, the blood is hypodense **(Ahangar et al,2019)**.

2. Brain MRI Hemorrhage appearance:

Hyper-acute parenchymal hemorrhage can be detected using MRI with T2-sensitive pulse sequences such as gradient echo (GRE). These sequences are very sensitive to the non-uniform static magnetic fields produced by paramagnetic molecules such as de-oxyhemoglobin. This property of paramagnetic molecules is called the magnetic susceptibility effect; it results in rapid dephasing of proton spins causing signal loss (darkening or hypo-intensity that is best seen in T2*-weighted images **(Ahangar et al,2019)**.

The addition of diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) map to conventional MRI study with its multiple sequences is helpful for the differentiation of ICH with its various stages from acute infarction and for the further characterization of intracranial hemorrhagic lesion **(Attia et al., 2007).**

Predicting hemorrhage expansion:

A. Spot sign: The spot sign describes the appearance of small focal or multifocal areas of contrast enhancement within a hemorrhage on CT angiography (CTA) source images. The spot sign has been related to hematoma expansion and poor outcomes in many studies **(Wada et al, 2007).**

B. Swirl sign: The swirl sign describes the appearance on non-enhanced CT of rounded, linear, or irregular regions that are hypo-dense or iso-dense (compared with normal brain parenchyma) within the region of hyper-density that represents the hemorrhage. Limited data suggest that the swirl sign is associated with hematoma expansion, poor outcome, and high mortality rate **(Wagemans et al,2016).**

3- ***Computed tomography angiography (CTA) or magnetic resonance angiography*** of the intracranial circulation are helpful screening tests for aneurysms ,vascular malformations and moyamoya vessels **(Abid et al,2013)**.

H. Management

Prehospital Care:

The main target of prehospital management of ICH is to provide airway and cardiovascular support to unstable patients, along with careful determination of time of symptom onset, medical history and current medications. Also , early notification decrease the time to non- contrast computed tomography (NCCT) scan in the emergency department (ED) aiming at faster diagnosis of ICH . **(Hemphill et al, 2015)**.

Airway protection

Patients with ICH are often unable to protect the airway due to reduced level of consciousness, therefore Endotracheal intubation may be needed , but this decision should be balanced against the risk of losing the neurologic examination. Pretreatment with lidocaine may be recommended as it may blunt intracranial pressure (ICP) rise associated with intubation **(Salhi et al, 2007).**

Blood pressure management:

Blood pressure variability (BPV) during the hyperacute first minutes and hours after intracerebral hemorrhage onset was independently associated with poor prognosis. Stabilization of BPV in the pre-hospital and early emergency department course, is a potential therapeutic target **(Chung et al, 2018).**

According to a combined analysis of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trials 1 and 2 (INTERACT), Intensive BP reduction (target BP < 140 mm Hg systolic) early in the management of patients with intracerebral hemorrhage appears to decrease the absolute growth of hematomas, especially in patients who have received previous antithrombotic drugs **(Song et al,2016).**

A 2017 joint practice guideline from the American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP) calls for physicians to initiate treatment for patients who have persistent systolic blood pressure at or above 150 mm Hg to reach a target of less than 150 mm Hg to decline risk for stroke, cardiac events, and death **(Qaseem et al, 2017)**.

The most robust data on BP management comes from INTERACT2 study, a clinical trial randomizing patients to one of two different blood pressure control strategies (SBP<140mmHg vs. SBP<180mmHg for the first 24 hours).it failed to prove improved outcome with intensive BP treatment (SBP<140mmHg) **(Anderson et al,2013).**

Hemostatic treatment:

- Platelet function: The utility and safety of platelet transfusion in ICH patients taking antiplatelet medications still unclear and there is no enough evidence to support application of a reversal strategy to improve platelet function **(Hemphill et al, 2015).**
- Platelet transfusion is indicated in patients with severe thrombocytopenia with suggested thresholds between 50.000 and 100.000 platelets per microliter **(Hunt et al, 2014)**.
- Warfarin-associated coagulopathy: OAT is associated with higher baseline ICH volume, increased risk of hematoma expansion and poor outcome. Coagulopathy correction is aimed at preventing continued bleeding. Warfarin discontinuation and IV administration of vitamin K are the first therapeutic steps. Vitamin K should be infused slowly (over 10 minutes), at the dose of 10 mg with close monitoring of vital signs given the rare but not negligible risk of anaphylaxis (1/10.000) **(Aguilar and Freeman, 2010)**.

Intracranial pressure management:

The most common causes of increased intracranial pressure (ICP) in ICH patients are mass effect from the hematoma and surrounding edema and IVH with secondary hydrocephalus. Current AHA/ASA guidelines suggest ICP monitoring in patients with coma, significant IVH with hydrocephalus and evidence of trans-tentorial herniation, with a cerebral perfusion pressure (CPP) target of 50 to 70 mmHg **(Hemphill et al, 2015)**.

ICP can be measured with parenchymal or ventricular devices. The latter (an external ventricular drain, or EVD) might be preferred in hydrocephalus as it allows cerebrospinal fluid (CSF) drainage. Elevation of the head to 30 degrees, adequate sedation, and avoidance of hyponatremia are mainstays of therapy; hyperosmolar therapy with mannitol or hypertonic saline can be considered in patients at risk of trans-tentorial herniation **(Hemphill et al, 2015)**.

Seizures and antiepileptic treatment:

seizures occur in up to 14% of patients with ICH in the early course of the disease **(De Herdt et al, 2011)**. The main risk factors for early seizures are cortical location of the ICH and occurrence of medical complications **(De Herdt et al, 2011; Pezzini et al, 2013)**.

Prophylactic administration of AED therapy is not recommended and only patients with clinical or electroencephalographic (EEG) evidence of seizures should receive antiepileptic drugs. Continuous EEG monitoring is recommended in patients with impaired mental status that is disproportionate to the degree of brain damage **(Hemphill et al, 2015)**.

Blood glucose management:

Hyperglycemia has been shown to be associated with poor outcome in ICH **(Stead et al, 2010)** and decreasing values of glucose appear to be associated with lower risk of hematoma expansion **(Qureshi et al, 2011)**.

The AHA/ASA guidelines suggest to avoid both hyperglycemia and hypoglycemia although a specific blood glucose target level is not provided **(Hemphill et al, 2015)**.

Temperature management:

Fever is a common finding in ICH patients, especially in extensive IVH and appears to be independently associated with unfavorable outcome **(Middleton et al, 2011)**.

Therefore, Treatment of fever appears reasonable, however the optimal temperature management is still unclear **(Hemphill et al, 2015)**. Therapeutic normothermia failed to improve outcome in one trial **(Lord et al, 2014)** although treatment of fever did improve outcome in another **(Middleton et al, 2011).**

Surgical treatment:

a-**Intraventricular hemorrhage (IVH) management:** in patients with hydrocephalus, coma and significant IVH, External ventricular drain (EVD) placement is recommended in order to drain blood and CSF and avoid significant elevation of ICP **(Hemphill et al, 2015)**.

b- **Surgical hematoma evacuation:** Two large randomized controlled trials, the surgical treatment of intracerebral hemorrhage (STICH) I and II trials, investigated the role of surgical hematoma evacuation, compared to conservative treatment in patients with supra-tentorial ICH **(Mendelow et al, 2005; Mendelow et al, 2013)**.

c- **Decompressive craniotomy** with or without hematoma evacuation: Decompressive craniotomy may be associated with better outcome in a subset of patients with supra-tentorial ICH **(Fung et al, 2012; Hayes et al, 2013)**. This subset includes those with coma, large hematoma with significant midline shift, or elevated ICP not controlled by optimal medical therapy **(Hemphill et al, 2015)**.

d- **Minimally invasive surgery(MIS):** The development of less invasive techniques might allow hematoma evacuation with less damage to viable brain tissue and reduce the rate of secondary complications compared to traditional craniotomy **(Dey et al, 2014; Barnes et al, 2014)**. Several MIS techniques have been available , ranging from endoscopic treatment of IVH to parenchymal hematoma evacuation with or without combined administration of rtPA **(Barnes et al, 2014; Beynon et al, 2015)**. The clinical efficacy of all these MIS approaches is still uncertain and clinical trials are ongoing.

Conflicts of Interest: The authors declare no conflict of interest.

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